Davor Solter Interview

Damjanov, Ivan; Pećina, Marko

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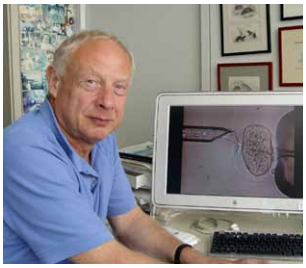

Davor Solter, MD,PhD
Emeritus Member and Director
Max-Planck Institute of
Immunbiology and Epigenetics
Emeritus Research Director
Institute of Medical Biology,
A*STAR, Singapore
Visiting International Professor
Siriraj Center of Excellence for
Stem Cell Research
Mahidol University, Bangkok

Email: davorsolter@mac.com

1. Your mother and your uncle were physicians. Was it almost inevitable for you to enter medicine, or did you have other interests as well?

Who knows why somebody decides to study medicine. I recently read somewhere that the majority of physicians in the USA decided on a medical career due to the feeling of power and status associated with it. I doubt that that was a motive for many in our time or now in Croatia. It is true that my family was rather medically oriented and I heard many interesting medical stories at the dinner table. I also read several classics that influence people to pick up medical studies like *Eleven Blue Men* and *Microbe Hunters*, also others, not so common, such as *Not as a Stranger* and *Arrowsmith*. However I was much more impressed by books like Gamow's *One Two Three….Infinity* and seriously considered studying mathematics. However, I soon realized that, although I could handle high school mathematics with ease, I was certainly not born with a "real feel" for mathematics. It seemed to me there is very little purpose in being an "average" mathematician, while, with proper application one could become a good physician. You have to realize how difficult is to remember the mental state and decision-making process of a teenager sixty years later, but it seems to me that my decision was made on the basis of a rational evaluation of my abilities. Or I like to think it was.

Figure 1. Annual Meeting of Yugoslav Medical Students in Rijeka 1964. From left to right: Pavao Rudan, Ivan Damjanov, Ana Jo, Vlatko Grnja, Davor Solter, Jasenka Pravdić, Jaroslav Soudyl, Nada Dabić

2. Any fond memories of your medical school days?

Once there I liked to go to the lectures and missed very few during five years of study. Not so much because I believed I could learn something better this way instead of reading it in a textbook, but I liked to see how different people presented their subject and knowledge. In one aspect my medical studies were somewhat unusual and were more like medical studies must have been long ago, when a young apprentice was attached to a physician and learned by watching and doing. Since my mother and uncle were, respectively, a senior and respected internist and a surgeon, I was able to profit from this close association. After the first year I spent every summer working in my mother's ward at Vinogradska Hospital and every Saturday and Saturday night in the Traumatology Hospital. As you can imagine after the first year of medical school, I did not know anything so in the beginning I just followed people around and listened and did simple chores. As the time progressed I did more and more, so after five years I had a lot of practical experience in dealing with patients, something which was very useful when I had to be an independent physician during my army service.

3. After two years of medicine you became a teaching assistant in Anatomy, spending for the next three years most of your afternoons dissecting cadavers and teaching medical students classical anatomy. What did you learn from this teaching stint?

Indeed, after my second year of medical school I did became a student assistant (demonstrator) in the Anatomy Department and a year later, a teaching assistant guiding and examining students during dissection. Anatomy class is the first tone in which medical students do something "medical" and they are usually quite interested. We also tried to make anatomy more relevant by indicating how important an anatomical fact could be in understanding and treating specific diseases. It is also the first class in which medical students realize how much memorization of facts is important in medicine. It is true that you can always look it up, but it would be a poor surgeon who would stop in the middle of an operation to consult an anatomy textbook. This period was important to me as I learned how to teach, I started doing research I also wrote my first research paper. One could say that, unknowingly, I started to choose my future career.

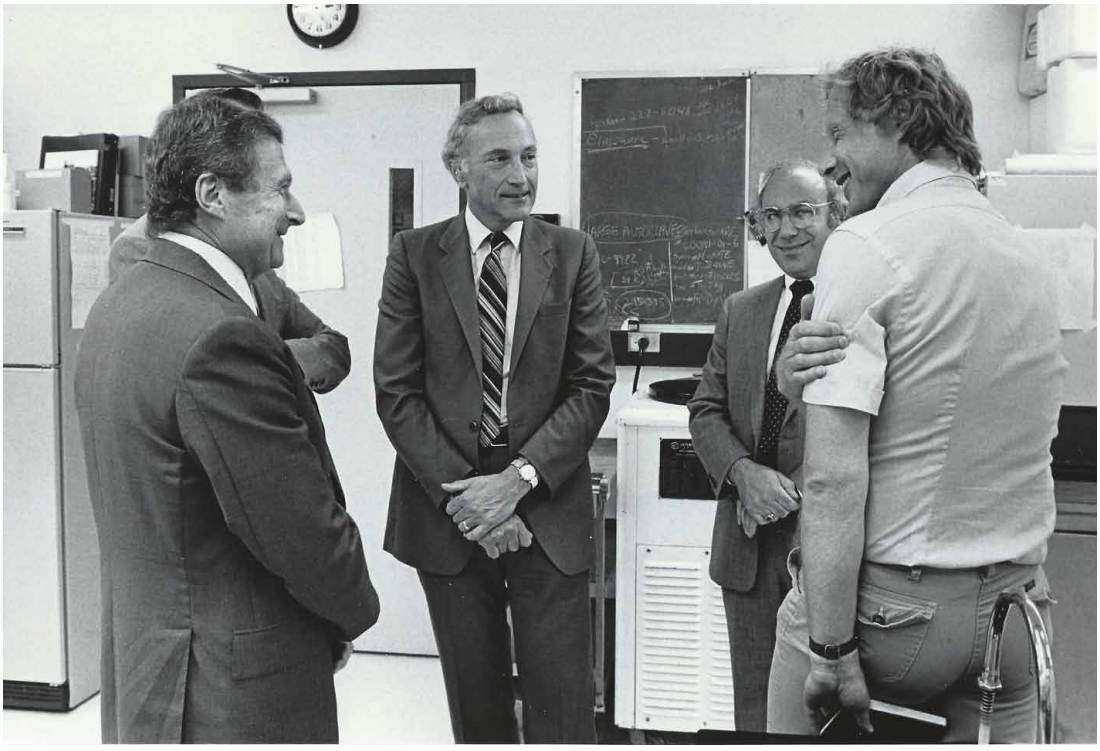

Figure 2. The Wistar Institute 1983. The Honorable Richard S. Schweiker, U.S. Secretary of Health and Human Services visited Solter's laboratory to hear about nuclear transfer and imprinting. From left to right: Hilary Koprowski, Richard S Schweiker, NN, Davor Solter

4. After graduation did you have clear plans for your professional development?

I don't think so. It seems to me now that what happened to me after medical school and my one year of army service was a mixture of vague planning and serendipity. I only knew that I didn't want to become a clinician. (my family blamed this on the amount of time I spent working with patients during medical school). So, I decided to specialize in pathology and started to work in the Pathology Department in the Vinogradska Hospital. Fate intervened and after several events too boring to recapitulate I ended up two years later as an Assistant Professor back at the Anatomy Department, and more or less decided on an academic research career.

5. You ended up working in the Department of Biology under professor Nikola Skreb. How important was Nikola Skreb for you and your future scientific career?

While working in the Anatomy Department I started postgraduate studies (the MS degree was conditional for PhD studies) at the Faculty of Arts and Sciences at the Zagreb University . I did not wish to choose an anatomical subject so my friend, and current interviewer, suggested I ask Professor Nikola Skreb in Department of Biology if I could work there studying mammalian development, a subject I knew nothing about. Professor Skreb said yes and that was that. I certainly did not know at that time that my life work had been decided. I moved to the Biology Department, finished my PhD and started planning to go abroad for postdoctoral work. Nikola Skreb was a wonderful mentor, able to adjust his approach to the needs and abilities of his mentees. In my case, Nikola suggested a subject for my Master's degree research project, which took me six months to figure out that it would not work; but by that time I read enough to come with an alternative theme which he approved. Early mammalian development was a perfect subject for our conditions in Zageb at this time. Not much work had been done on this subject in the global scientific community and several months of reading were sufficient to cover the whole field (today one would never be able to catch up with the published papers in the field; they are now coming faster than one can read). In addition, quite a lot could be done with very simple and readily available techniques.

6. How did you enter the international scene?

During the four years I spent at the Biology Department I collaborated with my friend Ivan Damjanov, in the Department of Pathology. We both worked for our PhDs together and split our collaborative results into two themes. One of the interesting and unexpected results was the finding that if one transfers a gastrulating mouse embryo under the kidney capsule of another mouse, it will develop into a tumor containing mature tissues, a teratoma (which had been described before) but also containing undifferentiated malignant cells, a teratocarcinoma. Finding that the mouse embryo contains undifferentiated cells, which during normal development differentiate into adult tissues, but that can also persist in the undifferentiated state forever and give rise to malignant tumor, was novel enough to publish in Nature (1). This and other papers published in international journals established both Ivan and me as researchers in the field of mammalian development and embryonic stem cells.

7. You moved to Wistar Institute, affiliated with the University of Pennsylvania, Philadelphia in 1973, and worked there for almost 20 years. Why did you choose that institute?

Going abroad for postdoctoral studies was always a rite of passage and in my opinion an essential part of the education of a scientist. I applied to three different laboratories in USA and received an encouraging response from the Wistar Institute in Philadelphia. Director, Hilary Koprowski, asked me to apply for a Damon Runyon Cancer Foundation Fellowship which I did and was lucky enough to receive, so in January of 1973 I started working at The Wistar Institute. I was planning to stay there two, maybe three years, little did I know that I will spend next eighteen years in Philadelphia. The funny part was that I went there expecting to find a great place to learn mammalian development, but they accepted me because they needed somebody who could work with mammalian embryos. In the end one of us was right.

8. At that time the Head of the Wistar Institute was Hilary Koprowski, an internationally known virologist and immunologist . How much did he help you establish yourself as an independent scientist?

Hilary Koprowski was a great scientist and an excellent institute Director who had turned the Wistar Institute from rather a sleepy place into a leading scientific center. In the beginning he was rather interested in my work, but then other subjects drew his attention, and I was left to proceed on my own. The greatest advantage of being there was the quality of the scientists which Hilary managed to recruit was excellent and most of them were collegial and willing to collaborate and help. The diversity of interest was such that it was very likely that any technical or scientific problem one had, could be answered, or at least discussed by another researcher next door or one floor away.

9. At Wistar you met Barbara B. Knowles. Very soon thereafter you started collaborating with her and her name began appearing on some of your most important papers. There is a saying: Behind a successful man there is often an even more successful woman. Was Barbara that woman in your life?

Barbara was also part of the loosely structured Koprowski group. When I arrived, she was working on somatic cell hybrids and immunology. Wistar was undergoing major construction and the animal colony was moved into an old building rented from the University of Pennsylvania a couple of miles from The Wistar Institute. Barbara and I, and several other scientists working with mice moved there. Barbara and I each had a small group so we decided to join forces and avoid duplication of facilities in the small quarters assigned to us. This led to work on joint projects and the most successful and enduring collaboration of my life. Barbara is a much more serious and studious scientist than I and she taught me how to be very critical and suspicious of easy explanations and incomplete data. Since that time, we lived and worked together, although we always had both joint and individual projects and students and postdoctoral fellows. So, the short answer is yes.

10. After twenty years at Wistar you moved to the Max Planck Institute in Freiburg, Germany. Why? Was it easy?

It was time for me to move on, but this led to a quest to find the right place. At a small, excellent research institute like the Wistar you either had to grow or die. Wistar was not a very well-endowed institute and everything, including your salary, came from the grant money that you raised to support yourself. By early nineties Barbara's and my labs were operating with a yearly budget of close to two million dollars and I had the impression that I was doing nothing but writing grant applications, progress and final reports. Also, I was involved in the NIH grant machinery, evaluating grant and program projects in various Study Sections and Councils. It became a struggle to find time to go to the lab and do some work. Just at that time my friend and colleague, Rolf Kemler, came up with the suggestion that I come to the Max-Planck Institute of Immunbiology in Freiburg. This Institute was initially devoted to immunology but Rolf came there to work on embryonic stem cells and mammalian developmental biology and he needed a colleague with similar interests. It seemed like an ideal solution, stable, no grant writing and I could help young scientists develop into independent researchers. A year later Barbara left Wistar to become the Director for Research at The Jackson Laboratory in Bar Harbor. She was very busy with organizational problems and with many projects she initiated but we continued a transatlantic life and collaboration, mostly on the molecular biology of early mouse development. It was pioneering and technically very demanding work and I think we did very well in identifying the scope of the preimplantation mouse embryo transcriptome and in characterizing several developmentally important genes.

Figure 3. The Congress in Dubrovnik 1986. From left to right: Draško Šerman, Ivan Damjanov, Nikola Škreb, Davor Soloter, Anton Švajger

Figure 4. New Orleans 1998. Davor Solter receives March of Dimes Prize in Developmental Biology. Anna Eleanor Roosevelt, granddaughter of March of Dimes founder President Franklin Delano Roosevelt, Davor Solter, Barbara B. Knowles

11. Following your retirement from Germany, you spent a few years in Singapore and then some time in Bangkok. How do these experiences compare with your years in Philadelphia and Freiburg?

Barbara and I retired more or less at the same time, debating what to do next, when the opportunity arose to join the newly established Institute of Medical Biology (IMB) at A*STAR, in Singapore. A*STAR was and is a very ambitious project started by the Singapore Government to establish the scientific base upon which to build the new economy of Singapore. Singapore was quite good in physical and chemical sciences but needed to develop breadth and depth in biology and biomedicine. To do so they established a massive conglomerate of several independent research institutes and imported scientists from all over the world to establish the necessary science. When we joined IMB our duties/tasks were to do the best possible research, to publish in the most prominent journals and to train young Singaporean scientists. The five years we spent there were in a way returning to our early days at Wistar when we were most productive and effective. Barbara and I never stopped working at the bench but other duties at the Max-Plank Institute and at The Jackson Laboratory often interfered. In Singapore we had no other duties, we assembled a small group of postdoctoral fellows from Singapore and other countries, and we made it clear that the lab would close in five years, so we had better get going. With everybody working on their individual but interconnected projects we were quite efficient and published several breakthrough papers in Science (2, 3) and many more in other high-quality journals. Even more importantly we succeeded in getting every postdoctoral fellow well established, published and successfully employed. I think we were very lucky to finish our career in such a place and in such a manner.

12. During your long scientific career, you made quite a few important observations and discoveries. What are your three most important contributions to science?

It is interesting that each of my "important" contributions were a combination of technical development which made subsequent discoveries possible. In the late seventies we worked on the role of cell surface molecules in early mammalian development. This was at the time when hybridoma technology was just being developed and we were able to adapt this technology to preimplantation mouse embryos. Working with these early mouse embryonic stages the issue of quantity is always crucial. One can easily immunize with millions and millions of cells but collecting even a thousand embryos is always a problem. Nevertheless, we were able to collect sufficient numbers of embryos, use them as immunogen and produce and characterize several monoclonal

antibodies reactive with stage specific antigens on the surface of preimplantation mouse embryos (4, 5). Interestingly these reagents also proved crucial in isolating and establishing lines of human embryonic stem cells. We took a similar approach to establish expression libraries of preimplantation embryos. In the late eighties preparing cDNA libraries presumed the availability of mRNA in milligram quantities which would imply collecting hundreds of thousands if not millions of early mouse embryos, a clearly impractical, if not impossible task. In 1987/88 Barbara and I spent a sabbatical year at Cold Spring Harbor Laboratory and managed to improve cDNA library construction to the point that twenty thousand preimplantation stage embryos were sufficient. Admittedly, still a high number but possible. We were able to construct several cDNA libraries representing full grown oocytes and different stages of preimplantation development. We used these libraries to analyze the changes in gene expression during preimplantation development and to describe mechanisms which regulate gene expression (6). We also for the first time described the role of endogenous retroviruses in activating expression of specific genes during early development of the mouse embryos (7). Finally, we developed the first reliable and successful method of nuclear transfer in the mouse zygote (8). Using this method, we were able to demonstrate for the first time that maternal and paternal genomes in male and female gametes are functionally not identical and both have to be present in the zygote to insure normal development (9). The process which makes genomes functionally different occurs during gametogenesis, it is called genomic imprinting and its discovery, in early eighties, initiated the conceptualization of epigenetics.

13. Your contributions to developmental biology were widely recognized by your peers and you received some of the most prestigious scientific awards. Could you list some of your most important awards?

I received the March of Dimes Prize in Developmental Biology in 1998 of which I am especially proud as this award specifically honors contributions to developmental biology. In 2007

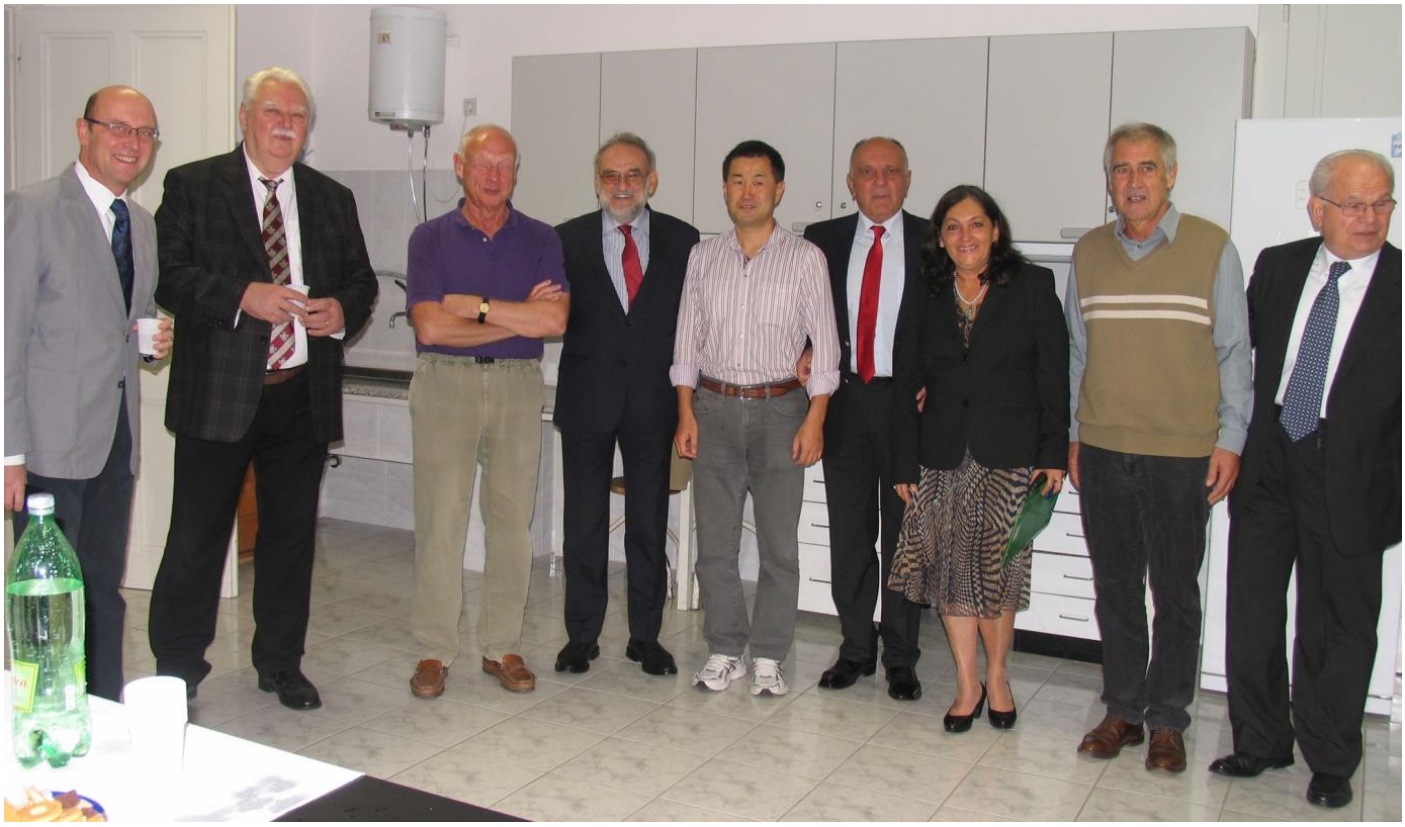

Figure 5. Zagreb 2013, Nikola Škreb Symposium: Development and stem cells at the beginning of new millennium. In the Laboratory in the Department of Biology from left to right: Davor Ježek, Mladen Belicza, Davor Solter, Pavao Rudan, Takashi Hiiragi, Marko Pećina, Floriana Bulić-Jakuš, Rolf Kemler and Draško Šerman

Figure 6. Toronto 2018, Davor Solter receives Canada Gairdner International Award. From left to right: Janet Rossant, President Gairdner Foundation, Davor Solter, Lorne Tyrrell, Chair of the Board of Directors of the Gairdner Foundation and Her Excellency Marica Matković, The Ambassador of the Republic of Croatia to Canada

Figure 7. Zagreb 2018. Davor Solter lectures at the HAZU. From left to right: Slobodan Vukičević, Pavao Rudan, Davor Solter, Marko Pećina, Ivica Kostović, Ivan Damjanov and Vlatko Silobrčić

I received Rosenstiel Award for Distinguished Work in Basic Medical Research from Brandeis University and in 2018 the Canada Gairdner International Award. These were all awarded for discovery of imprinting.

14. Over all these years since you left Zagreb, did you keep in touch with your Croatian colleagues?

As much as possible. During my time in The Wistar Institute several Croatian scientists came to work as postdoctoral fellows and visiting scientists. In addition, young scientists came to do the laboratory work necessary for their master's and doctoral degree and when they finished, they defended their theses in Zagreb. Their work resulted in each case in several publications in the first-class international journals. Same things happened while I was in Max-Plank Institute in Freiburg. I also participated in organizing the international scientific meetings in Croatia: in Dubrovnik 1986 and in Zagreb 2013 and 2018. In addition, during most of my visits to Croatia I gave lectures at the Medical School, Institute Ruđer Bošković or HAZU.

In 2018 Barbara Knowles and I spent one month at the Department of Biology, of the Medical School in Zagreb as part of Scientific Center of Excellence for Reproductive and Regenerative Medicine (CERRM) which was established by the Ministry of Science, Education and Sport of Croatia and funded by the European Union. During that time, we discussed with the members of CERRM various scientific projects and made plans with them for future collaboration. We devoted most of our time to interacting with PhD students in the Department of Biology and to helped several of them in designing their research projects. At the same time we organized the Second Nikola Škreb Symposium entitled "New platforms in developmental biology-toward the clinical application

15. If you were not a scientist, what would you have done with your life?

This is hard question to answer. I cannot think of an alternative. All the things I might have liked to do require talents that I didn't have . Science sometimes seems nothing but routine, you

Figure 8. Zagreb 2018. Nikola Škreb Symposium: New platforms in developmental biology-toward the clinical application. Ivan Damjanov, Barbara Knowles and Davor Solter sit behind Davor Ježek in the new Čačković Hall auditorium together with the number of students

go to the lab, you do experiments, they sometimes work and sometimes they do not. Data accumulate and sometimes they mean something and sometimes, very rarely, they open a new vista. The hope is always there that if you are good and lucky you will one day know something that, for a moment, nobody else in the world knows. When they asked Al Hershey, a Nobel laurate in 1969 for his idea of scientific happiness, he answered: "To have one experiment that works and keep doing it all the time". This was called "Hershey heaven" and I sometimes think, he may have had something.

16. In preparation for this interview I was looking at some of your old emails and found one on ligamentum teres capiti femoris Bertini. Do you think that today›s medical students even know who was Doctor Bertin?

Maybe they do, let us be optimistic. I always liked eponyms; they gave medical terms a personal flavor. However, I am also glad that I am not in the medical school today, the number of syndromes named after a multitude of discoverers is incredible. I must slightly correct you, Bertin's ligament is actually the *ligamentum ileofemorale* not the *ligamentum teres capitis femoris*. L. ileofemorale Bertini is the strongest ligament in the human body, and I used to tell my students in anatomy classes that, in the medieval punishment of quartering, the femur would break before the ligament. For some reason I assumed that Bertin observed this during the execution of Damiens who attempted to kill Louis XV and whose public execution was terribly botched (see Foucault's *Surveiller et Punir*). I am probably wrong since I cannot find any evidence for that, another urban legend. There is another interesting thing about the iliofemoral ligament that I call "eponym nationalism". Bertin described it in mid-eighteen century, but in the USA the ligament is known as the ligament of Bigelow, named after the Civil War surgeon Bigelow who described the ligament a hundred years later. You may wonder why I know all this trivia but they were part of my first scientific work which dealt with the variations in the vascularization of the head and neck of the femur and the role of ligaments and joint capsule in providing vascularization (10). Like a first child, one's first paper is always special.

17. In another email of yours I see that we were discussing Horace and his line Non sum qualis eram. We agreed that it is quite factual and refers to both of us. Nothing to add or subtract were it not for the fact that it prompted you to quote another verse of Horace, used by Ernest Dowson as a title of a short poem of his. You wrote that Dowson is one of your favorite British poets. I will reprint that poem here and ask you to end this interview with two three short sentences telling our readers why did you like that poem.

Vita summa brevis spem nos vetat incohare longam

They are not long, the weeping and the laughter,
Love and desire and hate:
I think they have no portion in us after
We pass the gate

They are not long, the days of wine and roses
Out of a misty dream
Our path emerges for a while, then closes
Within a dream

The movie *Gone with the Wind* was seen by more than two hundred million people and the book was printed in more than thirty million copies. Yet I wonder if one in a thousand of these viewers and readers knew that the title came from the poem written by Ernest Dowson or even knew who Ernest Dowson, poet and decadent (as one of his biographers titled him) was. Dowson was a "minor" English poet who died young in the first year of twentieth century, yet he was admired by and influenced poets like T. S. Eliot, Ezra Pound and Rupert Brooke. His command of language was exceptional, and nobody found words to convey the quiet desperation as Dowson. "Gone with the wind", "the hollow lands", "the end of all songs", "the days of wine and roses" will remain forever in the treasure chest of the English language as will the last line of his last poem: "O pray the earth enfold our life-sick hearts and turn them into dust". Today I probably appreciate intellectual poets like Eliot more, but I always return and reread *The Complete Poems of Ernest Dowson*, which he dedicated, fitting to his troubled life, to his only true and fruitless love, the twelve-year-old Adelaide (Missie), daughter of the owner of a small Soho restaurant Poland which Dowson frequented. Regardless of the esteem and position of Dowson in the world literature I certainly agree with the final worlds of his biographer, Jad Adams: "Life presented him with suffering, and he returned it as beauty".

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