 Prague Medical Report / Vol. 106 (2005) No. 4, p. 428–434

Remembrance of Professor Milan Hašek, MD., DSc.

Svoboda J.[1], Holáň V.[2], Kinský R.
[1]Group of Cellular and Viral Genetics of the Institute of Molecular Genetics of the Academy of Sciences CR, Czech Republic;
[2]Group of Transplant Immunology of the Institute of Molecular Genetics of the Academy of Sciences CR, Czech Republic;

Received October 12, 2005, Accepted November 10, 2005

Mailing Addresses: Prof. Jan Svoboda, MSc., DSc., Institute of Molecular Genetics of the Czech Academy of Sciences, Flemingovo nám. 2, 166 37 Prague 6, Czech Republic, Phone: +420 220 183 532, e-mail: svoboda@img.cas.cz; Assoc. Prof. Vladimír Holáň, MSc., DSc., Institute of Molecular Genetics of the Czech Academy of Sciences, Flemingovo nám. 2, 166 37 Prague 6, Czech Republic, Phone: +420 220 183 226, e-mail: holan@img.cas.cz; Radoslav Kinský, DVM., MSc., Castle, 591 02 Žďár nad Sázavou, Czech Republic

Hašek's Immune Tolerance

Hašek's discovery of immune tolerance emanated from his interest in organism development mechanisms and mutual influence of developing embryos. He chose a developing hen egg as a model, joined two eggs together by removing shell membranes and he placed the blastoderm of another embryo between the openings. In this way he connected blood circulations of both eggs, which resulted in an exchange of blood elements. The conspicuous consequence of these blood anastomoses during embryogenesis was that it was possible to transfer skin grafts between individuals with interconnected blood circulations without problems.

On the other hand future Nobel Prize laureates for immune tolerance had major problems because of inadequacy of some of their experiment techniques. Therefore Sir Macfarlane Burnet was not able to induce immune tolerance against the influenza virus. Sir Peter Medawar induced immune tolerance in mice by inoculation with mature spleen cells but the mature cells reacted with the host tissue (graft versus host reaction) and caused high mortality of inoculated newborn

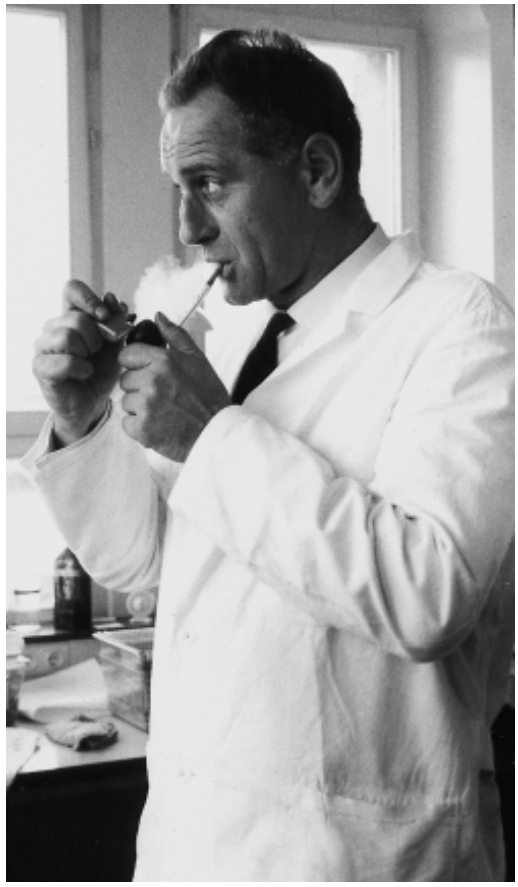

Figure 1 – Professor Milan Hašek, MD., DSc., was born on October 4, 1925, died on November 14, 1984.

mice. From this point of view Hašek's experimental methods exceeded all approaches at that time.

Hašek soon understood the importance of embryo bone marrow for transplants and mainly for treatment of irradiation disease. I remember when he advised Alena Lengerová, who was working in that area, to use embryo bone marrow for treating consequences of this disease. Thus a series of similar experiments started. Hašek was also interested in cases of natural connection of blood circulations between placentas (placental anastomoses), which should lead to immune tolerance. He used two sheep for this purpose and he performed transplants on them for testing the tolerance. The animals were kept at a farm in Kolč. I remember when Milan asked about the transplanted sheep but the farmers told him that they had been killed by dogs. Hašek realized what had happened and responded promptly: "If you don't have the sheeps bring me at least their skin." And then he looked with satisfaction at the healed grafts that survived the skinning.

Professor Milan Hašek had interpreted his experiments differently in different stages which is fully understandable since as described further he dealt with a very complex and not yet solved issue. First he spoke about vegetative hybridization then about immune identification and finally he adopted Medawar's terminology – immune tolerance. Based on his own experience Milan Hašek understood that immune tolerance is a multifaceted phenomenon that cannot be interpreted in a simplified way. This approach attracted scientists from abroad, e.g. French professor Voisen, since Hašek gave them freedom in interpretation and left space even for confrontation opinions. The understanding of immune tolerance has

Figure 2 – Professor Hašek during his lecture in U. S. A in the late of sixties.

changed several times. Originally it was postulated as an adaptive phenomenon, later as a selective one and finally it was stressed that it also includes anergization of immunologically competent cells. In line with Hašek's approach there came discoveries of regulatory T cells (T regs) able to actively inhibit immune response. This mechanism is also implicated as a part of phenomenon leading to immune tolerance.

Milan Hašek established a distinctive school based on immune tolerance that later expanded to related disciplines such as cell genetics, virology and others. We can say that he was the founder of modern experimental biology. He was very foresighted and he described exactly what dramas were going to happen in the area of cell biology, today called molecular cell biology.

I would like to stress yet another characteristic of Milan Hašek. His positive approach to his colleagues and students, irony-free, full of willingness to understand and advice. I think this is the maximum we can expect from a teacher. There are fewer and fewer of us, who were close to Milan. On our behalf and on behalf of myself I would like to thank Milan Hašek once again for what he had done for world science and for us.

Milan Hašek in the Memories of His Last Student

The history of every science discipline has outstanding personalities arising above the horizon of hundreds of other researchers that have left a significant imprint and moved science forward. One of those who stood out of the crowd thanks to his contribution and ideas was professor Milan Hašek. His life had been far from slowly elapsing in a quiet and straightforward way like that of many others; he had gone through many ups and downs that severely affected his fate. Nevertheless Milan Hašek contributed to science with new knowledge and ideas, educated many excellent immunologists and then unexpectedly and prematurely he left all his students and friends without saying goodbye.

I was very lucky since I was the last student writing a dissertation under his tutorship, then his postgraduate student and later on his closest colleague. When I entered Hašek's office in the then Prague Institute of Experimental Biology and Genetics in 1972 as a 3rd year student at the Faculty of Sciences of the Charles University admiring the success of prof. Ch. Barnard who had carried out the first heart transplants in the world; and outlined my visions explaining to him what I would like to do, I soon understood that we would find common language. I wanted to do research in the area of transplants because it was research close to the needs of people. I remember very well when prof. Hašek, a doctor carrying out research in that area, clapped me on the back and said: "This is what we need". Immediately he took me to the adjacent laboratory to doctor Jitka Chutná, his closest colleague at that time, and together they provided conditions for my research. Since then Hašek and Chutná had been directing and correcting my work and it was mainly Milan Hašek, who always came with original ideas and was

glad that there was someone willing to carry them out. We spent a lot of time in the laboratory and I felt that Hašek rejoiced every successful experiment. I remember how we were washing and boiling test-tubes in a borrowed big pot so that they were ideally clean and usable for measuring macrophage adherence. Together we celebrated the results. They came soon and our first publication issued in Cellular Immunology in 1974 was later according to SCI among ten most quoted works of Czech authors for the period between 1973 and 1988. Our further works that appeared in the most prestigious publications, such as Nature (2×), Transplantation, Immunology and others reflected magnitude and originality of Hašek's ideas.

With Milan Hašek as my tutor I successfully defended my dissertation and started to work in his group. As his student I found open door everywhere and in a short period of time I was able to visit a number of prominent research institutes in the United States and present our results there. Thanks to Hašek and his reputation I was also able to do a fellowship at the London University, the laboratory of Hašek's friend Prof. Avrion Mitchison, where I continued in our work. By then I understood how important it is for a young beginning scientist to be in the right place at the right moment. And I was lucky in that respect since I came to Milan Hašek's laboratory. Later on, I met the leading scientists of transplant immunology at that time. I became aware of this fact mainly in 1982, when we went with Milan to the World Transplant Congress to the UK and he introduced me to a number of top transplantologists including his friend and Nobel Prize laureate for the discovery of immune tolerance, Prof. P. B. Medawar. I will never forget Milan's words when we were leaving the congress – he was returning back to Prague and I was staying for my one-year fellowship and we discussed whether I would return afterwards. He told me sincerely: "If you decide to stay abroad, we will miss you a lot, but believe me no-one is irreplaceable". It was a said departure at that time but I knew I would go back. I would miss him as much as I would miss my home. I knew very well that he had never had easy life as everyone who stood out of the crowd and he was well known and welcomed in every foreign country and could have stayed abroad easily. He nevertheless always returned home and never regretted his decision. He used to say that it was necessary to fight from the inside as well. He started as a postgraduate and gradually took different positions and even became the Director of the Institute of Experimental Biology and Genetics of the Czechoslovak Academy of Sciences but later he was tolerated only as a leader of a small working group. However he was always surrounded by people that loved, valued and respected him and were willing to sacrifice themselves for him.

I hope Milan Hašek had a happy life, he always believed in the good of human spirit and was convinced that human reason will eventually win. Even in the most difficult situations when relations were poor and the truth was suffering he

used to say to me: "Let it be it will turn out somehow". And he was always right. He loved life and knew how to enjoy it. I remember the transplant congress in Brighton in 1982 with several thousand participants; when the music started to play at the final cocktail party Milan Hašek was the first to go to dance and I had to follow. It was great school of life for me. Milan liked everything beautiful I remember how he admired masters' works in galleries, regularly went to concerts and liked culture. He loved and admired beautiful women; was fond of nature and his science. Despite all misfortunes he remained a convinced optimist and occasional blue moods that everyone with a demanding job sometimes has, did not prevent him from coming with new experiments, searching for new opportunities of cooperation and linkages of basic research with clinical practice. Behind the basic research he had always seen people that can benefit from science. He knew very well that new knowledge in the area of transplants can save the worthiest thing a man has – his life, or at least improve significantly its quality.

Milan Hašek had many plans and ideas. Many times he was too original he was not understood, he was ahead of his time and stood out from the social stereotype, carried out what the others did not even plan to do. Transplants were only beginning but Milan foresaw future lack of donated organs and tissues and therefore we started research in the area of xenotransplants, i.e. transplants of tissues and organs between different animal kinds. He worked to the last moments of his life, was planning travels abroad and other long-term perspective experiments. Not long before his death we started to write a textbook on immunology, because he wanted to leave something here.

Therefore it was a great shock for us when we heard the news that came out of the blue saying that Milan Hašek deceased November 14, 1984. I was working in a sterile box with cells from mice tolerating skin transplants carrying out one of our joint experiments. I will never forget the moment when our laboratory technician Erika Knížková knocked on the door and came in with tears in her eyes saying just: "Milan is dead". The experiment remained unfinished as well as Milan's life. And as other experiments followed our last joint experiment his students followed the work and life of Milan Hašek spreading his name, the name of his school and of our country all over the world. And we, Hašek's students, found open door everywhere. If it had not been thanks to Milan Hašek Czech immunology and many of his students would not have gone as far what they did and experienced so many good things in science. Milan had always said optimistically that no-one was irreplaceable, we would only miss someone more, someone less. And we have been missing Milan Hašek a lot for a long time. He could have lived longer with us. He was the man we will never forget.

A Man of Science but Primarily a Man

Hašek's scientific work is a legacy for world immunology and for next generations of scientists that could be represented on hundreds of pages. A significant legacy

was also education of tens of students and colleagues for whom they created extraordinary environment together with Věra Hašková, with space for intellectual development contrasting with recession in many other economic and cultural areas in Czechoslovakia of those days.

After many years of manual work and only private education I found coming to Hašek's laboratory thanks to the intervention of prof. Ivan Málek and a few reasonable people as my rebirth and as a haven after sailing on a stormy sea.

Hašek's closest colleagues were excellent scientists such as Marta Vojtíšková, Alena Lengerová, Milena Rychlíková, Jitka Chutná, Tomáš Hraba, Jan Svoboda, Ivan Hilgert, Grozdanovič, Majer, Jan Hort and many others. Another big change for me was that at a colloquium in Liblice, fellowships and conferences organized by the Academy of Sciences where I usually worked as a simultaneous interpreter in the time when English was not a common language in the scientific sphere yet, I was again able to communicate with people from abroad. Most of those people and personalities during their visits to the Czechoslovak Socialist Republic saw only our privileged environment described above comparable to the department of Jaroslav Šterzl from the intellectual perspective.

Only because of that, frequent positive comments on the situation in our country spread in the West by the visitors of scientific congresses and fellow-associates in our research institutes can be explained. Thanks to Hašek's help in the autumn 1958 I was able to meet my parents after ten years, and my siblings and especially Tamara who I married several months later. I have always regarded Hašek's colleagues as members of a foster family that adopted me and thus frustrated plans of some ultra Marxists trying to make the descendant of a noble family to become intellectually stunted not knowing anything else than drag and dung. Of course one of the closest colleagues after my departure from Prague was Ivan Hilgert, with whom we have a number of joint publications. He was one of the first Hašek's students and a close colleague of Alena Lengerová.

Hašek visited us several times in Paris and I am convinced that he felt with us as in his own family. The misfortunate occupation of our country in 1968 was the beginning of scientific recession and departure of more than twenty Hašek's former students to Western countries where nearly all of them were successful in prestigious research institutes and universities. It was the merit of the then young Hašek's colleague Vladimír Holáň that he took care of his teacher and made it possible for him to continue in his work despite his health problems.

Of course there are also critics of Hašek's work and lifestyle. However I am convinced that without personalities like Milan's our Republic would have suffered much more than it did during those unfortunate 40 years when Western world left us to our fate. The return to the group of developed European countries would have been even more difficult. All honour to his memory!