EVEN VISITING SCIENTISTS COULD MAKE DISCOVERIES IN MONTREAL

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MÉG A VENDÉGTUDÓSOK IS TEHETTEK FELFEDEZÉSEKET MONTREALBAN
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This publication summarizes the scientific adventure with Professor Selye, and focuses on the specific effect of rare metal salts on reticuloendothelial functions. Rare earth metal ions markedly affect the functions of cells involved in inflammatory and immunological phenomena. The Kupffer cell blockade induced by GdCl3 is a generally accepted method for investigation of the physiological and pathophysiological roles of Kupffer cells. Potential beneficial effects of macrophage blockade have been demonstrated in different shock states, liver injury and obstructive jaundice.

Keywords: *Dr. Hans Selye; Kupffer cells, macrophage blockade, obstructive jaundice*

Közleményemben összefoglalom Selye Jánossal kapcsolatos tudományos élményeimet, kiemelten a ritka fémsóknak a reticuloendothelialis funkciókra kifejtett specifikus hatásával kapcsolatos ismeretekre. A ritka földfémek ionjai jelentős hatást fejtenek ki a gyulladásos és immunjelenségekben részt vevő sejtek funkciójára. A GdCl3 által kiváltott Kupffer-sejt-blokád a Kupffer-sejtek élettani és kórélettani szerepével kapcsolatos kutatások általánosan elfogadott módszere. Különböző sokkállapotokban, májkárosodásban és obstrukciós sárgaságban kimutattuk a macrophagblokád potenciális előnyös hatásait.

Kulcsszavak: *Selye János; Kupffer-sejtek, macrophag-blokád, obstrukciós sárgaság*

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One of my early dreams as a young scientist engaged in biomedical research was to meet professor Selye and to visit the famous Institute of *Professor Hans Selye* in Montreal, and even work with Selye professor. Although, I did not know him personally, for me he was the scientist who incarnated creativity and originality. I knew his basic discoveries and his concept of stress, the exhaustion of the organism, pluricausal diseases, and the adaptation syndrome[1-5]. I was particularly excited because the focus of my interest was very close to that of the research topics in Selye Institute.

When I received an invitation from professor Selye in 1967, we had described that a rare earth metal complex, *"Phlogodym"* with anticoagulant and antiphlogistic properties, aggravates the intravascular coagulation during different forms of shock[6].

At the same time it was demonstrated in the Institute of Professor Hans Selye that the rare earth metals, which exhibited an anticoagulant property, sensitize the organism to the development of a thrombo-haemorrhagic phenomenon induced by catecholamine administration[7]. The thrombo- hemorrhagic phenomenon was therefore the bridge that led me to Montreal. Even the four-year-delay before I received my exit permit is vivid in my memory.

I was always afraid that Professor Selye would become weary of waiting for me and his invitation would not be valid forever. When I wrote a letter to Professor Selye in 1971 saying that it seems I would finally make it within two months, Professor Selye reply was the following, and here I quote from his letter:

"I was very glad to learn that you will now be able to come about two months. During the summer months the life somewhat less stressful at our

Institute, it would be most appropriate time for you to arrive. Looking forward to pleasure of meeting you soon here on Canadian soil." Szívélyes üdvözlettel: János bátyád. Professor Selye would never miss writing couple of sentence Hungarian at the bottom of his letter written in English or French.

Nevertheless, finally I was there. When I arrived in Montreal late afternoon in September, Professor Selye received me in his office. At this first meeting Professor Selye already presented me with the research options.

"I gladly join in the research work of the Institute- I replied- yet I believe I will have enough time to realize my own research plans as well."

Hans Selye demonstrated that stress from a variety of sources causes adrenal enlargement and thymus atrophy. The idea that stress alters the immune function gained notable interest among clinicians and scientist and has led to the development of the modern concept of psychoneuroimmunology.

My research conducted in Selye's institute became the basis of my later research and has proved that the macrophages are the "alarm" cells of the organism, which play a key role in the immune system and the cytokines, the mediators produced by macrophages may start off unwanted reactions damaging the organism similarly to the reactions elements of chronic shock.

Effect of rare metal salts on reticuloendothelial activity

One of my first papers published from Selye institute reported that the rare earth metal salts, among the gadolinium chloride, depress the reticuloendothelial activity[8-10], and selectively interfere with the function of the Kupffer cells[11].

These works became determinant in my further scientific work. How is our research work related to the stress concept? Macrophages are the body's "alarm" cells that synthesize and excrete highly reactive materials. The biological active materials are very important in killing bacteria and tumor cells. However, macrophages not only act as a first line of defense and have pivotal role in regulating immune response.

Nowadays the Kupffer cell blockade induced by $GdCl_3$ became a generally accepted method for investigation of the physiological and pathophysiological roles of Kupffer cells **(Figure 1.)**. Mac - rophage blockade has the theoretical advantage of abrogating inflammatory responses at an earlier stage of disease and in a specific fashion. It has also been reported that $GdCl_3$ inhibits the secretion of

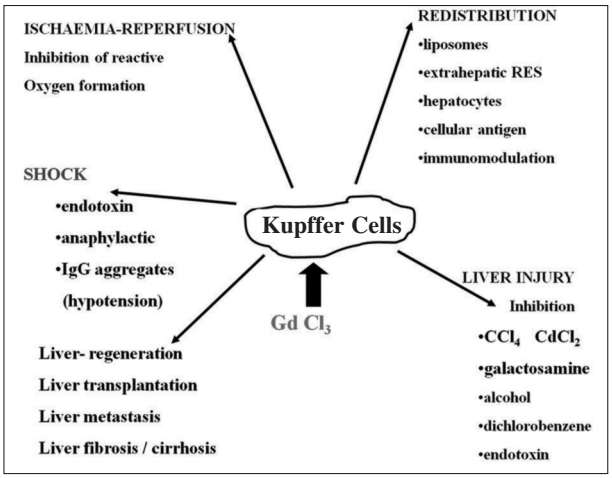

Figure 1. *The physiological and pathophysiological roles of Kupffer cells*

biologically active substances from the liver Kupffer cells, and decreases the liver-damaging effects of hepatotoxins[12], ischemia-reperfusion[13]. Furthermore the ablation of the functions of the liver's macrophages inhibits the development of anaphylaxis[14], lethal septic[15] and endotoxin shock[16, 17]. $GdCl_3$ also influences the hypotension induced by immunoglobulin aggregates[18], and prolongs the survival of a human insulinoma cell xenograft in the liver[19].

Pathophysiological rules of Kupffer cells in obstructive jaundice

Despite advances of intensive care, survival of critically ill patients with obstructive jaundice did not improve over the last decades - and septic complications are still the leading cause of mortality[20, 21]. The Kupffer cell functions are changing after biliary obstruction as well[22-24] and Kupffer cell-dependent immune modulation may lead to divergent outcomes[25-28]. Defects in crucial elements of RES function after cholestasis are leading to hypersensitivity to bacterial endotoxin with high rate of septic complications in the long run. However, it has been demonstrated that attenuation of Kupffer cell activity with $GdCl_3$ might decrease endotoxin-induced lethality and morbidity in obstructive jaundice[29-30].

Previously it has been shown that biliary obstruction enhances the inflammatory and microvascular response of the liver to endotoxemia[29, 31]. Our recent observation clearly demonstrates that hepatic microcirculatory dysfunction is significantly exaggerated if obstructive jaundice is

followed by endotoxin administration[32]. The results also show that hepatic Kupffer cells have a pivotal role in this process. Our results that the inhibition of a Kupffer cell-dependent inflammatory response reduces the endotoxin-induced lethality and organ injury in obstructive jaundice suggest a novel application for this experimental treatment modality.

Conclusions

In his book "From dream to discovery" Selye states that timing makes a huge difference, and as far as he was concerned he was fresh and active, and most optimistic especially in the morning. Indeed, Selye arrived at the institute at 6 a.m. before any of employees usually after an early swimming or cycling. The picture shows Selye professor returning cycling around the university campus **(Figure 2.)**. From 6 to 8.30 a.m. he was the most intensive and focused work of writing various papers ensued. His productivity is proved by numbers publications, more than 30 books and nearly 2000 articles. Our offices of Sándor Szabó and me were closed to each other. And Professor Selye very frequently visited us in our offices for a short conversation. He very frequently said "Only the Hungarians know the hard-working Hungarian farmers, who start work every day early in the morning when the day is just breaking and stopped at exactly six o'clock in the evening." At 3 p.m. Selye would start his autopsy meeting, during which he would analyze the results of experiments with his characteristic magnifying glass and head lamp. Usually, these times Professor Selye was invited to deliver a lecture about his experiments concerning the stress. He asked us, Sanyi, Gyuri do you want to accompany me? And we willingly went with him to hear his excellent lectures.

Figure 2. *Professor Selye returning from cycling*

During one year scholarship 15 relevant own papers were prepared in Montreal In Selye's Institute. After this fruitful scientific year I returned home and continued my work at home with my co-workers.

My work in Montreal has determined my scientific carrier and has been motivated continuously. When I try to recall our life in the company of Hans Selye, my feeling is always that time has stopped and we are young again, full of energy and ambition as we were so many years ago in the old Selye Institute.

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