

The contribution of Professor Karel Opatrný Jr., MD, DSc. (1954-2006) to nephrology



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ABSTRACT

Karel Opatrný Jr., finished his medical studies at the Charles University in Pilsen in 1979. After graduation he began to work at the 1st Department of Internal Medicine at then part of the District Health Authority, and Charles University School of Medicine in Pilsen until the end of 1989. From 1990 to 1992 he worked as an assistant professor in the Department of Internal Medicine at Strahov in Prague. During 1992-1994 he was the Head of this department. In 1994 he returned to Pilsen and became the Head of the 1st Department of Internal Medicine, Charles University Medical School and Teaching Hospital. He worked in this position until his premature death in 2006. The principal subjects of his scientific contributions were: hemostatic disorders in hemodialysis patients; biocompatibility of dialysis membranes; and the novel field of proteomics. He published more than 300 scientific papers, most of them in international journals, and delivered more than 280 lectures.

KEY WORDS: nephrology, Karel Opatrný Jr., uremia, biocompatibility of dialysis membrane, hemostatic disorders, proteomics

Introduction

Professor Karel Opatrný Jr., MD, DSc., was born on July 4, 1954 in Prague and died on March 9, 2006 in Pilsen at the age of 51 (Figure 1).



Figure 1 - Professor Karel Opatrný Jr, MD, DSc.

Karel Opatrný Jr. graduated from the Medical Faculty of Charles University in Pilsen in 1979. He started his medical career at the 1st Department of Internal Medicine at then part of the District Health Authority, and Charles University School of Medicine in Pilsen. In 1985 he defended his doctoral thesis on "Haemostatic disorders in hemodialysis patients" at the Faculty of Medicine in Prague. In 1988 he passed the nephrology attestation, and in 1991 he was habilitated as an associate professor in internal medicine.

The topic of his habilitation thesis was "Chronic Kidney Failure and Haemostatic Disorders". He was appointed full Professor of Internal Medicine by President Václav Havel in 2000. He defended his academic title of "Doctor of Medical Sciences" at the Medical Faculty of Comenius University in Bratislava on the topic of "Biocompatibility of dialysis membranes" in 2002.

Professor Opatrný Jr., began working as an assistant professor at the Department of Internal Medicine at Strahov in Prague at the invitation of Professor Albert Válek, MD, DSc., in January 1990. From 1992 to 1994 he was the Head of this department. He returned to Pilsen in 1994 to take up the position of Head of the 1st Department of Internal Medicine, Charles University Medical School and Teaching Hospital replacing his father, Professor Karel Opatrný Sen, MD, DSc., after his retirement. He worked in this position until his premature death in 2006.

Professor Karel Opatrný Jr. scientific activity was manifested in more than 300 published papers, most of them in international journals, and over 280 lectures delivered various congresses around the world, especially in Europe, the USA, and Japan, often as an invited speaker. He held many positions at the university, faculty, international societies and other institutions; for example he was a Vice Dean for Science, Education and International Relations of Charles University in Prague; a Vice President of the Czech Nephrological Society; a Member of the Editorial Boards of international journals such as Blood Purification, Kidney and Blood Pressure Research and Nieren-und Hochdruckkrankheiten. In 1995 he was a founder and editor in chief of the journal "Aktuality v nefrologii" (News in Nephrology) issued at his initiative that continues to be

published to this day. For his outstanding research activities and achievements in the field of nephrology he received several awards, notably the "International Distinguished Medal" of the American National Kidney Foundation.

His scientific interests and the most important results of his research studies were as follows: At the beginning of the 1980s, K. Opatrný Jr. started his scientific work in the Laboratory for Hemostasis and Thrombosis Research at the 1st Department of Internal Medicine at then part of the District Health Authority, and Charles University School of Medicine in Pilsen, together with J. Dvorak, MD and later L. Vit MD, under the guidance of Professor Cepelak.

Diligent as he was, K. Opatrný studied the platelet adhesion and aggregation induced by adenosine diphosphate (ADP) and collagen, as well as the anticoagulatory activity of heparin and heparinoids (predecessors of today's low molecular weight heparins) *in vitro* and *in vivo*. *In vivo* research was conducted in healthy volunteers and in patients with end-stage renal failure, who showed persistent strong inhibition of the collagen-induced platelet aggregation activity after administration of heparin even on days without hemodialysis (1).

In his continued research, he hypothesized improvement of the efficacy of 4 times re-used dialyzers (plate dialyzers Gambro Lundia) through administration of the antiplatelet drug ticlodipin (Ticlid) during hemodialysis alongside the standard heparin anticoagulation. The additional administration of 500 mg ticlodipin 2 times/day showed increased dialyzer urea and creatinine clearance. This was a placebo controlled study, i.e. a high-quality randomized controlled trial – especially considering it having taken place in the 1980s' Czechoslovakia during the communist era (2).

In subsequent studies he examined the relation between hemodialysis efficacy and hemostasis from a different point of view. It was a prospective study in ESRD patients on long-term maintenance hemodialysis treatment, as then was usually twice a week for 7 hours on a coil dialyzer with an effective surface area of 1 m². Surviving patients were checked after three and a half and after five years. The study revealed serious defects of thrombocyte functions which deteriorated further during prolonged hemodialysis treatment. He concluded that the applied dialytic therapy was not adequate enough from the aspect of hemostasis and stressed the necessity to alter the technique and prescription the used in the country (3). Later, collaborating with Professors K. Šebeková and R. Džurík, they described the retention of a uremic toxin, 5- hydroxyindole-acetic-acid, in ESRD and its effect on platelet aggregation (4).

Subsequently he extended his studies to fibrinolysis, specifically on derangements of fibrinolytic activity in ESRD patients on maintenance hemodialysis or on conservative treatment as compared to healthy volunteers; after a standard fibrinolytic stimulus of i.v. administration of 1-deamino-8- D-arginine-vasopressin (DDAVP). There was a significant reduction of the fibrinolytic activity in hemodialysis patients, which was considered significant in relation to the frequent incidence and an early onset of atherosclerosis in this patient population (5).

Opatrný Jr. continued to study this issue after joining the team of Professor Albert Válek in the Department of Internal Medicine in Strahov, Prague. With the availability of more sensitive and specific methods, which were far from easy to obtain then in Czechoslovakia, he was able to demonstrate that the decreased fibrinolytic response to DDAVP administration in dialysis patients is caused by inadequate rise in the plasma concentrations of tissue-type plasminogen

activator (t- PA) released from vessel wall (6).

In subsequent studies, he tried to identify factors contributing to the changes in tissue-type plasminogen activator during haemodialysis (7). The design of this study was very complex and resulted in the finding that t-PA is released from vessel walls during hemodialysis. Thus the extracorporeal circulation system of hemodialysis apparatus was shown to be a contributory factor.

In the 1990s, erythropoietin (EPO) gradually became available to ESRD patients in the Czech Republic. By then, it was still administered in high doses and the treatment was not free of cardiovascular complications including tendency to arteriovenous fistula thrombosis and to blood clotting in the extracorporeal circuit. Karel Opatrný Jr., and his team sought to assess, by means of the changes in thrombin-antithrombin III complex (TAT III), the effect of EPO on coagulation activation during hemodialysis. Surprisingly enough, there was no increase in predialytic nor intradialytic TAT III concentrations (8, 9). Subsequent studies confirmed that EPO therapy does not enhance coagulation activation during hemodialysis, does not have an effect on thrombocyte activation, and does not influence complement activation, provided the hematocrit does not exceed a value of 31% (10). Even when sensitive and specific fibrinolysis markers were used, he did not find fibrinolysis changes during EPO treatment, again when increasing the hematocrit slowly to values not higher than 34% (10). Later he demonstrated a dependence between the severity of anemia and the effectiveness of blood purification in peritoneal dialysis patients as assessed by the Kt/V index, whereas correlation between the renal component of Kt/V was much closer and at a higher level of significance than peritoneal component of Kt/V (11).

In vitro studies had shown that some dialysis membranes significantly adsorb EPO, a fact that might have an effect on anemia in long-term hemodialysis patients and on anemia treatment with recombinant human EPO. In a study designed to determine whether the ability of adsorption demonstrated *in vitro* also has an effect on EPO concentrations *in vivo*, he showed that under clinical conditions, AN69 and Cuprophan membranes do not differ in their effects on plasma EPO concentration (12).

Based on his original results from methodical and elaborate work, Karel Opatrný Jr. was invited to collaborate on testing biocompatibility of dialysis membranes developed by the AKZO company, when it became possible to cooperate with Western Europe again. These were well designed methodically challenging, flawlessly conducted and comprehensive trials whose outcome laid the foundation for composition changes of the dialysis membranes under development. These complex trials included activation testing of complement, platelets and fibrinolysis (13). This cooperation resulted not only in a professional collaboration, but also in a lifelong friendship with J. Vienken, of whom Karel Opatrný Jr. thought very highly. The procedures already established were extended and enriched with others, which were used in further studies testing high-flux membranes (14), where, among others, C5a (complement 5a) transfer into dialysate was described.

Another international team Karel Opatrný Jr. started a cooperation with was based at Grosshadern Clinic in Munich, Germany, under the leadership of Prof. Gurland and S. Mujais from Northwestern University in Chicago. Together, they examined the influence of polyacrylonitrile (PAN) membrane modification on its biocompatibility. Modification of this

membrane was necessary, as otherwise, it led to disturbing interaction with bradykinin generation system particularly in the presence of angiotensin converting enzyme inhibitors (15).

In another study, K. Opatrný Jr. proved that heparin used to rinse polysulphone dialyzers before hemodialysis (HD) had no effect on blood coagulation or on the need for heparin during the procedure (16).

Professor Opatrný Jr. considered it an honour to be able, together with prof. H. Klinkmann and D. Falkenhagen, to edit a monograph titled "Blood-material interaction" released in 1998 and to contribute to it a chapter on "The fibrinolytic system in blood/material interaction" (17).

In science, there is considerable need for the exchange of information. To that end, Professor K. Opatrný Jr. started organizing high quality scientific meetings in Pilsen, focused predominantly on uremic toxicity and subsequent metabolic abnormalities in chronic kidney disease. On this occasions, he collaborated not only with above mentioned colleagues, but also with Professors M. Mydlík and K. Derzsiová from Kosice, Slovakia, Professors N.G. De Santo, G. Bellinghieri, V. Bonomini from Italy, Professors Grabensee, Debussmann, Ostenand from Germany, Professor Kokot from Poland, Professors Shaul G. Massry, JD Kopple, G. Eknoyan from the United States as well as many others.

The scientific work of Professor Opatrný Jr. and his team included also the field of peritoneal dialysis, continuous renal replacement therapies and plasmapheresis (18). Further detailed analysis of his contribution to this field would however exceed this article's framehold.

As a next step, alongside with new technological developments, Professor K. Opatrný Jr. intended to advance

his biocompatibility research to the next level through proteomics. Thanks to his scientific work, his enthusiasm and determination and the prospect of introducing proteomics in Pilsen, he succeeded in obtaining a large grant, for *The Main Research Project (No MSM 0021620819)*, of almost 12 millions Euros (approximately 300 millions Czech crowns) for the School of Medicine in Pilsen. He studied proteomics at the Department of Nephrology (head: Professor John Klein) at the Louisville University, Kentucky. During his stay of several months, he collaborated especially with Prof. Visith Thongboonkerd, whom he enjoyed greatly and with Prof. Thongboonkerd, whom he held in high esteem. Regrettably, the unfortunate premature death of Professor Opatrný Jr. put a sad end to all these plans.

However, Prof. Thongboonkerd proved to be not only a brilliant scientist but also an outstanding friend, who helped the Pilsner School of Medicine to introduce and develop proteomic methods even after Prof. Opatrný's death. This has moved this department to a different level not only within the Charles University and the Czech Republic, but also at the international level. For a whole next generation of scientists in Pilsen, the hard and tremendously diligent work of Professor Karel Opatrný Jr., MD, DSc., thereby became a spring board to work under entirely new and never-thought-of possible circumstances.

In the death of Professor Opatrný the Medical Society in Pilsen as well as the whole Czech Society of Nephrology as well as the International Society of Nephrology have lost a professionally outstanding personality.

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