FIFTY-FIVE YEARS (1955-2010) OF THE COAGULATION SECTION AT LABORATORY OF HEMATOLOGY, SESTRE MILOSRDNICE UNIVERSITY HOSPITAL, AND ITS FOUNDER, HEMATOLOGIST LJUBOMIR POPOVIĆ

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SUMMARY – The Coagulation section at Laboratory of Hematology, Sestre milosrdnice University Hospital, Zagreb, was founded in 1955 by Ljubomir Popović, hematologist and assistant at School of Medicine, University of Zagreb, in cooperation with hard-working laboratory technicians. Apart from papers on hematologic neoplasms, plasmacytoma and lymphoma, Ljubomir Popović published a number of papers in the field of anticoagulant therapy with heparin and oral anticoagulants, some of which are also in use today. After Ljubomir Popović left the Hospital in 1964, the Laboratory was run by Professor Nedjeljko Milić, head of the newly founded Division of Hematology. In 1968, the management of the Laboratory of Hematology was taken over by Biserka Raić, MS, medical biochemist, until her retirement in 2007. Great development in morphological and cytometric studies of blood and blood cells has been paralleled by continuous progress and almost dominating activities in the diagnosis of hemostasis disorders. In the 1970s, Marko Koprčina, hematologist, and Biserka Raić introduced the then latest tests in practice at all Hospital departments. In that golden age of the Coagulation section, M. Koprčina, B. Raić and their associates transferred their knowledge to all colleagues in the Hospital. Through that collaboration, high standards in the diagnosis of hemostasis disorders were achieved, from which the currently high level of clinical knowledge about coagulation disorders and their treatment has derived, making Sestre milosrdnice University Hospital one of the leading hospitals in this field in the country. By describing development of the Coagulation Section and the life of its founder Ljubomir Popović, the authors tried to provide an answer to the following question: can today’s clinicians still have a deciding role in laboratory development, considering that assessments of different phenomena are always initiated by an interested clinician who is trying to interpret and understand the nature of the disorder? This means that the clinician’s place may still be in the laboratory, or else, it will become clear that the laboratory, as well as knowledge in general, has undergone such an expansion that the clinician is no longer able to run it by himself. It is our belief that the answer will assert itself through the survey of the history of the Coagulation Section at Laboratory of Hematology, Division of Hematology, and the lives of its founders and beneficiaries.

Key words: Hospital departments – history – Croatia; Laboratories, hospital – history – Croatia; Hematology – history – Croatia; Blood coagulation disorders

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Received April 20, 2010, accepted September 14, 2011
Introduction

The Coagulation Section at Laboratory of Hematology was founded 55 years ago, in 1955, and for half a century, until 2005, it functioned as part of the Division of Hematology, University Department of Medicine, Sestre milosrdnice University Hospital, in Zagreb, Croatia. In 2005, the Coagulation Section, together with another part of the Laboratory of Hematology, was separated from the Division of Hematology and annexed to the Division of Clinical Chemistry, Sestre milosrdnice University Hospital.

This 55th anniversary (1955-2010) deserves both respect and analysis. In the historical account of the beginnings and development of the Coagulation Laboratory within the Section and thereafter Division of Hematology, University Department of Medicine, we will describe the role of clinicians internists in the foundation, development and scientific progress of the Laboratory and their contribution to its work, as well as the contributions of individual technicians and medical biochemists. Thus, we try to keep their names from falling into oblivion and inspire the present-day generations of doctors and medical biochemists with their enthusiasm and approach.

The Foundation of the Laboratory of Hematology

The Internal Section of the then Hospital of St. Vincent de Paul Sisters of Charity was opened and began working on July 15, 1894, the founder and the first manager of the Section being chief physician Ivan Kosirnik, who was in charge until 1914. Chief physician Franjo Gutschi was head of the Section until 1921 and his successor was Professor Lujo Thaller.

In 1938, Lujo Thaller expanded Internal Section and according to the statements made by Professor Mladen Sekso, a small Laboratory of Hematology and Biochemistry was set up in 1938, and Laboratory of Cardiology in 1947. As Professor Sekso wrote, "hematological and cardiological laboratories were the core of the hematological and cardiological service during the following years". In 1951, two separate laboratories were formed out of the joint Laboratory of Hematology and Biochemistry, i.e. Laboratory of Biochemistry (which remained on the first floor of the annexed pavilion) and Laboratory of Hematology, situated on the third floor of the Internal Section pavilion. From April 29, 1945 to September 1, 1946, Primarius Halle was also head of the First Internal Section, so new hematologic tests were slowly introduced in practice. In 1946, Professor Dinko Sučić, PhD, who had previously worked at Department of pediatrician Emil Najman, who was closely associated with the very beginnings of pediatric hematology. For a number of years, Professor Najman worked at Pediatric Department of our Hospital and the Imerslund-Najman-Graesbeck syndrome has, among others, been named after him because he was one of the first to describe congenital megaloblastic anemia in children caused by deficiency of the receptor for intrinsic factor in terminal ileum.

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Internal Medicine, Rebro Hospital, became new head of the Internal Section and supplied new instruments for Laboratory of Biochemistry and Hematology. In 1948, on the first floor of the Internal Section, now Section of Cytology at Division of Hematology, Laboratories of Hematology and of Biochemistry were situated in two rooms each.

In 1948, Laboratory of Hematology was headed by internist Ljubomir Popović, who was employed at the Hospital in the same year, while Professor Dušanka Mikac-Dević, PhD, a biochemist, was head of the Laboratory of Biochemistry.

During 1949, 40296 tests were performed at Laboratory of Hematology, 2675 less than the year before because “three of six laboratory technicians left the laboratory”. In the same year, prothrombin time assessment by Quick’s method was introduced at Laboratory of Hematology and 110 blood transfusions were administered with the help of laboratory technicians, since there was no transfusion service at that time.

Figure 2 shows specification of blood tests performed at Laboratory of Hematology in 1949, most of them related to red blood cell, hemoglobin and leucocyte differentiation.

In the same year, Ljubomir Popović, assistant at the Zagreb School of Medicine, was already working at Section IIIIC, ran Laboratory of Hematology, worked as doctor on call, held practical classes for undergraduate students and worked as social insurance doctor for Hospital employees. Out of three papers submitted for publication that year from the Hospital, one was written by Ljubomir Popović and entitled Reticuloendothelioses. In 1950-1951, due to an increased volume of work, the Laboratory of Hematology was moved to the third floor of today’s old building of the University Department of Medicine.

In 1955, Ljubomir Popović established Coagulation Section within the Laboratory of Hematology. In addition to coagulation tests, Dr Popović also performed sternal puncture as well as bone marrow and peripheral blood smear analyses. Blood typing and Coombs test needed for blood transfusion were performed at the Laboratory.

“For the measurement of prothrombin time (PT), laboratory employees prepared reagents by themselves: thrombokinase, coagulation factors V and VII. For the preparation of thrombokinase, technicians took brain cortex from a cadaver at Pathology Department, washed it out in acetone, crushed it, dried it at room temperature and then by extraction in water bath (reagent plus saline) obtained thromboplastin, a reagent for PT measurement. In order to get the standard curve, a minimum of five normal plasma samples were needed at 100%, 50%, 40%, 30%, 20% and 10% dilution, the mean value of five specifications with 100% and 10% was calculated, thus obtaining the standard curve for reading off the percentage of PT in patient plasma. The procedure was as follows: PT=0.1 mL...
of plasma + 0.1 mL of thromboplastin + 0.1 CaCl₂ = turn on the stopwatch and at 37 degrees Celsius keep an eye on thrombus formation. Reagents for coagulation factors V and VII were made from cow blood, which was obtained from the Sljeme Slaughterhouse. Blood was filtered through the Saisor filter vacuum system and then the standard curve was determined.

At that time, patients were taking oral anticoagulants, 100 mg dicumarol tablets, 3 mg marcoumar tablets and 30 mg Thromexan tablets, and the lowest PT therapy value was 20%. Heparin treatment was controlled by coagulation time on a small laboratory glass plate and by using the stopwatch. In case of Bürger's disease, technicians applied treatment with malaria. The attenuated and pretreated Plasmodium was obtained from Rome, from the laboratory of Professor Corelli senior, Doctor Popović's longtime associate. In the treatment of post-thrombotic syndrome, subcutaneous application of oxygen was used” (memories of Mrs. Jasna Kainc, employee and chief technician, who spent all her active life working at Laboratory of Hematology, Sestre milosrdnice University Hospital) (Figs. 3-5).

On June 13, 1964, the Internal Section became Department of Internal Medicine, a teaching unit of the School of Medicine, University of Zagreb, and on September 30, 1964, Doctor Popović left the Hospital. Perhaps the reason was his disappointment with unjustly postponed academic advancement at the School of Medicine, or his desire for better working conditions that would enable him further professional rise, but also because of his temperament, and partly due to the lack of understanding of his associates and of support from the superior Hospital board. Maybe it was announced to him that centralization of the Hospital Laboratory would come about and he could not come to terms with it. The survey of his career shows how important laboratory work was to him as a clinician, who was looking for answers both at patient bedside and in the laboratory.

In these nine years of work of the Coagulation Section at Laboratory of Hematology, from 1955 to 1964, through his dedicated work chief physician Popović showed that the scientific approach of an excellent clinician raising right questions to the laboratory gave impetus to the laboratory progress, as well as to the progress of the clinical thought and patient treatment.

Several years later, owing to similar initiatives by Professor Mladen Sekso and later by Krešimir Bano-vac, MD, a modern endocrinology laboratory was founded at the Section of Endocrinology, in which Josip Rešetić and Marijan Petek introduced the then latest methods of assessment of hormone concentrations in blood using the radioimmunoassay (RIA) method. Josip Rešetić received further education at Karolinska Hospital in Stockholm, at the laboratory of Professor Suad Efendić (previously resident at our Hospital), and used his knowledge in the work of endocrinology laboratory.

In these years, the third specialized laboratory arose at University Department of Medicine.
Samoščanec, a young chief of Nephrology Department, founded the new specialized laboratory for analysis of kidney function. Samoščanec’s knowledge, together with the huge clinical experience and curiosity, resulted in great improvement in the diagnosis and treatment of kidney diseases.

Primarius Popović sought for similar experiences at laboratories abroad and, among others, actively collaborated with Professor Corelli senior from a well-known hematology department in Rome. It was from Corelli’s laboratory that he was obtaining pyrogenic substances on the basis of *Plasmodium malariae*, with which he, in association with a young cardiologist Josip Gjurović, treated patients suffering from Bürg er’s disease. Doctor Popović’s associates were always pointing out his medical erudition, working capacity and his skills as a clinician. As an excellent hematologist, he took part in medical treatment of Cardinal Alojzije Stepinac and attended doctors’ consultation in the village of Krašić, where Stepinac was imprisoned by the order of the communist authorities. A group photograph shows chief physician Popović and members of the doctors’ consultation with Professor Ante Šercer at the head and Cardinal Stepinac at consultation held in Krašić in 195310,11 (Fig. 6).

In the second period of work, the Laboratory of Hematology and Coagulation developed further within the Section of Hematology, until 1965. At that time, the Section was run by Professor Nedjeljko Milić. Professor Milić, as a French student, had also obtained broad education and excellent theoretical knowledge of clinical hematology. He habilitated after earning his doctoral dissertation on the morphology of plasmacytomic cells, his thesis advisors and professors being Beata Brausil, cytologist, and Erik Hauptman, hematologist. Despite all his knowledge and erudition, Professor Milić failed to restore relations with the Coagulation Laboratory at the level achieved in the time of chief physician Popović. Maybe he lacked courage to apply the insights found by laboratory procedures in practice, maybe he lacked interest in laboratory work, or preferred academic career, which he was building persistently, or maybe it was due to the fact that after a year, the laboratory was taken from his authority and centralized, so there was no time for him to accomplish his goals. Nevertheless, he was genuinely glad of the new insights of his associates and colleagues at the Section (Sonja Handl, PhD, Marko Koprčina, MD, Željko Pečanić, MD, Vladimir Stančić, PhD), Cytology Section (Željka Znidarčić, PhD) and Hematology Laboratory (Biserka Raić, MS, Biserka Getaldić, MS), dealing with clarification of abstruse clinical presentations. “Kupidus rerum novarum” is the title he had proudly given to the author of these lines, as a reward for having successfully solved a complicated case of Wilson’s disease.

Although Professor Milić’s relations with his colleagues-associates and laboratory staff at Coagulation Laboratory and later Cytology Laboratory were not always the best possible, the progress of the Coagulation and Hematology Laboratory, as well as of the entire Division of Hematology was uncontainable.

In 1965, the Hospital laboratory service was centralized for the first time (the second centralization was implemented forty years later), so Department of Internal Medicine lost its laboratories. Marking the 150th anniversary of the Hospital work, Professor Sekso wrote in the same article: “… since this reorganization did not yield the desired results, in 1971 the laboratories were returned to the Department of Internal Medicine. However, in the mid-1970s, the Biochemistry Laboratory was separated from the Department and was constituted as an independent division”. The causes of repeated decentralization of the laboratories in 1971 were probably multiple, but the main one doubtlessly was (as it was twenty years before when chief physician Popović made efforts to establish a laboratory of hematology-coagulation) at-
tempts of the clinicians, now primarily Professor Sekso, to take part in establishing a new one (endocrinology laboratory and cytology laboratory), as well as in guidance and improvement of the methods and work in the already established laboratories (hematology). This centralization and then again decentralization of the laboratory service in the Hospital supports the thesis that in university hospitals the clinicians are the ones who should have greatest influence on creating laboratory service and on its development. The reason is that by being near the patient, they are continuously exposed to the issues of optimal disease diagnosis and have to decide on the best laboratory procedure. It goes without saying that such a clinician, along with the basic knowledge of internal medicine, should also possess other necessary basic knowledge of chemistry and physics as well as instrumental procedures. Today, the number of such clinicians is in decline, but they still can be found.

In 1968, Biserka Raić, a young medical biochemist, was employed at Hematology Laboratory. In 1971, Hematology Laboratory was incorporated again into the Division of Hematology, followed by an explosive growth of medical science and progress in the diagnosis of thromboembolic disease and fibrinolytic treatment.

The 1980s were golden years in the work of the Coagulation Laboratory, in which, through collaboration between Biserka Raić and the newly employed hematologist Marko Kopčina, the diagnosis and interpretation of laboratory results gained a fresh impetus. The new tests were introduced and the overall knowledge was transferred to other Hospital departments, where there was the need for monitoring changes in hemostasis system, especially to surgeons and anesthesiologists. The prophylaxis of thromboembolic disease in surgical patients was advanced and the Coagulation Laboratory gained reputation as one of the best coagulation laboratories and internal medicine institutions, in which the latest achievements in the diagnosis and treatment of hemostasis disorder were applied. Some of today’s reputable clinicians in other institutions, specialists in coagulation disorders, are Doctor Kopčina’s students, to whom he generously transferred his immense knowledge. This brilliant progress was occasionally disrupted by differences between Professor Milić, head of Hematology Section, and Marko Kopčina as a gifted hematologist and clinician. These difficulties were the reason why the present status of Coagulation Laboratory at Division of Hematology is not even better.

In spite of the problems, the Section of Hematology at Sestre milosrdnice University Hospital, with the doctors working there at that time had the first physicians, internists hematologists, who, apart from other hematologic diseases, intensively dealt with the problems of hemostasis-coagulation. This emphasis on the internist approach in monitoring the disorders and in the interpretation of laboratory results, which goes beyond the average knowledge of an internist hematologist, is visible even today in the physicians’ work at Division of Hematology. It may be said that already the fifth generation of clinicians has matured, from Halle, Popović, Milić and Kopčina to Stančić, Gaćina and associates, who have gone through the same “school” and have implemented the acquired knowledge in collaboration with the laboratory.

For such a unique approach to patients suffering from hemostasis disorder, five generations of internists are not enough. What is also needed is continuous collaboration with biochemists and laboratory technicians, especially at coagulation laboratory because the obtained results require fast interpretation and treatment has to be adjusted to the new condition.

For years, until her retirement in 2007, the Coagulation Section and the entire Hematology Laboratory was run by Biserka Raić, MS, biochemist. She managed the laboratory very devotedly, keeping up to date with progress in the professional field, introducing new tests and discussing the results with clinicians on a daily basis. Benefits from better comprehension and more accurate interpretation of blood coagulation test results were mutual, both for the clinician and the biochemist, but the patient was the one who profited most because he could get optimum diagnosis and treatment. The model in this two-way Hematology Laboratory communication with clinicians is not only Coagulation Section, but also Section of General Hematology, run for years by Biserka Getaldić, biochemist. Both biochemists Raić and Getaldić have for years regularly attended professional weekly meetings at Division of Hematology and actively participated by reporting on different cases. From this communication, we all have learned how to interpret the results obtained, keeping up with the development of blood analyzers.
Accordingly, by writing on the history of the Coagulation Section at Hematology Laboratory we also write on the history and work of several generations of internists hematologists, who were or still are working at Division of Hematology. It may be that this sentence conceals the answer to the question posed at the beginning of this survey: should the permeation of physicians’ work at patient bedside with their work in the laboratory be favored, following the example of chief physician Popović’s work, or should, on the other hand, lead to separation-disintegration? Even though this disintegration may seem only formal, it definitely happened on June 1, 2005, and after five years we may say that communication between clinicians and laboratory is declining.

The clinicians who currently use the services of Coagulation Laboratory will not have an opportunity to listen to discussions and interpretations by a coagulation specialist, a hematologist and a biochemist; they will be deprived of stimulating thoughts on the analysis of the most complex homeostatic system in the human body. On the other hand, they will be more self-satisfied in an unjustified perception that they understand all secrets in the interpretation of the results obtained. I believe that both chief physician Popović and Professor Milić would agree with this, as well as with, I presume, the most inquisitive researcher of humoral medicine Paracelsus, although I did not know him in person.

Chief physician Ljubomir Popović was born on October 1, 1922 in Zagreb. His father Milko was professor and his mother Marija, maiden name Tomek, a housewife. He completed elementary school and Third Male High School in Zagreb, which he finished in 1941. In 1946, he graduated from the Zagreb University School of Medicine and in 1947 participated in a campaign against spotted fever in Bosnia (Fig. 7). In 1948, he was employed at Internal Section, Dr Mladen Stojanović Hospital in Vinogradarska cesta and was appointed assistant at School of Medicine and Professor Dinko Sučić’s associate. Besides his dedicated work with patients at Hematology Section, Popović was also frequently on call and acted as a senior doctor for the Hospital employees. He left the Hospital on September 30, 1964, continuing his career in a German town Koblenz, where he was chief physician in Kemperhof town hospital. After that, he worked at the town hospital in Weiden as Oberarzt (head of section). He returned to his homeland in 1972 and was head of the Internal Section at Bračak Hospital until 1982, when he died in Zagreb from prostate cancer. He published the following research papers: 1. Popović Lj. Prilog novim istraživanjima o značenju mijeloma. Liječnički vjesnik, offprint 1949;2:1-10; 2. Žikić M, Popović Lj, Postružnik S. Prevencija i terapija tromboza u opstetriciji i ginekologiji. JAZU, offprint, Zbornik radova i. naučnog sastanka ginekologa, Zagreb, 1952:269-76; 3. Popović Lj, Postružnik S. Naša iskustva s dicumarolom. Saopćenja, Pliva 1954;1:1-4; 4. Popović Lj, Heparin. Saopćenja, Pliva, offprint 1954;1:1-4; Popović Lj. Terapija antikoagulansima. Liječnički vjesnik, offprint 1955;5-7:239-51; 5. Popović Lj. O nekim problemima doktrine i organizacije terapije antikoagulansima. Radovi Medicinskog fakulteta u Zagrebu 1958;2:185-94; 6. Popović Lj. Kombinirane Anwendung von Prednison und Zytostatika bzw. Roentgenbestrahlung in der Behandlung der chronischen Lymphadenosen und Lymphgranulomatosen. Folia Haematol. Neue Folge

The enlisted papers show extraordinary scientific and clinical sharp-wittedness of chief physician Popović, some of them being up to date in their originality and approach even today. The quality of papers in the field of anticoagulant treatment and scientific approach in clinical practice support the fact that chief physician Popović indeed was the first internist specialized in coagulation at Sestre milosrdnice University Hospital. His work was pioneering, his approach strictly scientific and the clinical applicability of his research papers first-rate. Apart from brilliant clinical laboratory coagulation research, he also managed to be concerned with the challenges of diagnosis and treatment of different diseases covering the whole area of hematological interest, from myeloma and lymphoma to leukemia. Popović also reported on his studies at various foreign symposia and conferences, which was never easy for our physicians. Finding work in a foreign country at forty-two years of age posed an almost insurmountable problem for an average physician specialized in a certain field coming from our country. The main reason for this was the language barrier and the need to prove oneself and earn recognition in the new surroundings, the difficulties which chief physician Popović successfully overcame as Oberarzt in a German town hospital (Fig. 8).

In his last ten years of employment, working as head of the Internal Section at Bračak Hospital, he educated highly competent associates and set a high level of internal medicine practice. He came back from Germany, where it was a practice (the author of this paper witnessed it, too, while staying in UKH Eppendorf, Hamburg) for experienced heads of sections to go to other towns and hospitals and advance the work of the institutions they visit by their qual-
ity and knowledge. Unfortunately, it did not happen in the biography of chief physician Popović. We may assume that his knowledge and experience, matured and confirmed in a setting where medical development was at a much higher level than it was in our country, could be of better purpose if used to promote the work of one of the more prominent departments of internal medicine in Zagreb than it was the one in Bračak (with all due respect for the Bračak Hospital). There are multiple reasons for this and it is to be expected that only the exchange of ideas, knowledge and people in the anticipated European Union will enable an optimal circulation of competent people, clinicians and scholars like Ljubomir Popović, who returned to his native country (as did the famous modernist Croatian writer A. G. Matoš) some thirty, maybe even forty years too early.

Acknowledgments

I thank Mrs. Popović, widow of chief physician Ljubo Popović, for handing me over a number of photographs and facsimiles as well as a short biography of her husband. I would also like to express my gratitude to Mrs. Jasna Krainc for having invested her time and enthusiasm while describing events and work in the Laboratory, to Mrs. Biserka Raić, MS, for her support and gathering documentation for this paper, and to Mrs. Tanja Sušec, BA, for all information and articles on the history of the Sestre milosrdnice University Hospital. I am also thankful to Professor Vlado Oberiter for the review of this paper and inspiring conversations we conducted regarding his friendship with Doctor Ljubo Popović. And the last but not the least, I am indebted to my wife Nevenka for her understanding and time she offered me to write this paper while taking care of our small children.

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Ključne riječi: Bolnički odjeli – povijest – Hrvatska; Laboratoriji, bolnički – povijest – Hrvatska; Hematologija – povijest – Hrvatska; Koagulacija krvi, poremećaji