HAEMATOLOGY IN THE REPUBLIC OF MACEDONIA: PRESENT SITUATION AND BRIEF HISTORY

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Abstract
The development of clinical haematology in Macedonia has taken place over the past nine decades. The greatest expansion of its development took place in the second half of the 20th century. The official start of clinical haematology dates from 1956, when the Department of Haematology was founded within the framework of the Internal Medicine Clinic in Skopje. In the beginning, haematology represented a form of virtual sub-speciality, but its expansion was so progressive and rapid that it reached the highest peaks of Yugoslav haematology in those times. The period from 1968 to 1979 was a period of integral development of haematology and blood-transfusion science in Macedonia. Nowadays, the autonomous Public Health Institution, the University Hematology Clinic, is a unique healthcare, educational and scientific establishment in the Republic of Macedonia in its field of work. The diagnostics algorithm comprises cyto-morphologic and cyto-chemical analysis, through immunologic characterization with the assistance of a flow cytometer, to sophisticated molecular analysis for detecting genetic abnormalities. The therapeutic approach is based upon modern poly-haemotherapeutic protocols, application of monoclonal antibodies, immuno-modulatory agents, molecular target therapy and the use of alogeneic and autologous transplantation of fresh bone-marrow and frozen haemopoietic stem-cells. The current motto of the Haematology Clinic is: always help those who seek help, provide precise and early diagnostics, and apply all up-to-date therapeutic strategies, scientific research, continual education and day-to-day implementation of the latest achievements in the field of haematology in daily practice.

Key words: haematology, history, chemotherapy, flow-cytometry, molecular analysis, stem cell transplant, target therapy, immuno-modulatory agents.

The medical history recollects only minimal data about the events and people that played a crucial role in the growth and expansion of medical work and service in Macedonia at the beginning of the 20th century. Particularly, knowledge about the advancement of haematology during this period is quite modest.

The development of clinical haematology in Macedonia has taken place over the past nine decades. In general, its growth is continually increasing, although some oscillations have occurred during this period. The greatest expansion of its development took place in the second half of the 20th century. During that period, this expansion was so progressive it even reached the highest peaks of Yugoslav haematology, and therefore took the leading place in implementing certain organizational and diagnostic procedures. Numerous achievements by Macedonian haematology scientists also contributed to the expansion of world advancement in haematology. Nowadays, the professional team of the Haematology Clinic is striving to achieve the modern world standards and norms in the diagnosis and treatment of malignant and benign haematological diseases.

In short, the first records of the growth of haematology work on the territory of the Republic of Macedonia during the 1920s are extremely modest. Throughout this period the country was facing deep social, revolutionary and torrid times. After World War I, the newly constituted state of the Serbians, Croatians and Slovenians took the first steps in providing basic healthcare for the massively imperilled population, whose health
status, in those days, was at an extremely low level. The greatest problem was the endemic type of malaria that was widespread in the agricultural regions of the country. Between the two wars, the annual average number of diagnosed (microscopically inspected) patients infected with malaria was 140,000.

After WWI, the strategy for improving the health status of Macedonia’s population was primarily set on the battle against malaria and TBC infections. The period from 1921 to 1923 records a massive institutional action against malaria. One of the fundamental hoops for a successful execution of the health service work was haematological microscopic diagnostics. Those were the first official steps in the field of haematology on the territory of today’s Macedonia.

However, the first record of existing microscopic laboratory diagnostics in Macedonia was evidenced in 1919 in Skopje. Later on, in the late 1920s, some minor laboratories were established within the healthcare and anti-malaria stations. Their primary activity was the examination and investigation of blood for malaria parasites. In 1930, Dr. Aleksy Duma, within the capacity of his private ambulance in Bitola, established a practical laboratory for blood cell examination. In Veles, in the private practice of Dr. Panče Vaskov, a lab technician was employed for blood and urine testing. In Eastern Macedonia, in the 1930s, Dr. Kostadin Trenčev performed examinations on peripheral smear and blood sedimentation.

It is important to mention the young Macedonian physician Dr. Boris Spirov, who in 1928 at the Faculty of Medicine in Leipzig (Germany) wrote his graduation thesis in the field of haematology. His work was entitled: "About the Problem of Pernicious Anaemia", and elaborated a particularly real medical problem of that period. Some 20 years later, when the Faculty of Medicine was founded in Skopje, Dr. Boris Spirov was selected as Associate Professor of Internal Medicine.

In the middle of the 1930s, the young surgeon Dr. Panče Karagjozov performed the first direct blood transfusion in Macedonia.

After the Bulgarian occupation of Macedonia, most of their numerous medical personnel remained in the country. The Bulgarian medical workers were performing their routine medical activities, but also organized haematological and laboratory activities in Skopje and other larger towns. It is also notable that in the post-war period a large number of charity sisters came to work in the hospitals in Skopje and Bitola. Some of these had solid laboratory experience and knowledge.

In 1945, with the end of WWII, a 6-month training course for laboratory technicians and microscope examiners was organized in Skopje, following the foundation of the first Medical High School in 1946. The first class of educated lab technicians graduated from this school in 1950.

Immediately after the war, the Army Hospital was established in Skopje, having an organized haematology laboratory within its work system. The second half of the 20th century brought a positive turning point in Macedonian healthcare and service. The most significant event happened in 1947, when the Faculty of Medicine and the Clinics were founded.

The newly appointed professors, most of them educated and previously working at prominent world medical centres, in addition to their teaching curriculum, initiated the establishment of laboratorial departments as essential units for the function of the institutes and the clinics. Dr. Isak Tadzer was working at the Haematology Department of the laboratory of the Internal Medicine Clinic. Next to the blood sedimentation tests, blood tests, peripher- al blood smear tests, some other tests were implemented such as the examination of bone marrow puncturing, lymph nodes and other cytological examinations. The haematological part of this laboratory was significantly improved when Prof. Dr. Aleksandar Ignjatovski was appointed Chief of the Internal Medicine Clinic.

The second clinic that focused on haematological laboratory diagnostics was the Pediatric Clinic and in that period it was managed by the experienced paediatrician Dr. Haralampije Mančev. He paid special attention to the diagnostics of parasitic blood diseases. Later on, after his academic stay with the Swiss haematologist Professor Fanconi, he advanced and deepened his interest and comprehension in the field of haematology. He personally analysed the smears of peripheral blood and bone marrow, while with the assistance of Dr. Panče Karagjozov and Dr. Melkolijan he introduced and implemented the diagnostic methods of aspiration puncturing of the spleen and the liver.

In 1943, Dr. H. Mančev diagnosed the first case of Kala-azar in Macedonia, which number increased to 170 cases in 1948, and in the 1950s it reached even 240 reported cases. In 1952 he diagnosed the first case of Cooley’s anaemia in Macedonia. His great historical and scientific significance is presented in his comprehensive study "Kala-azar in Macedonia". His work was printed on 46 pages and is the first work published in the newly established journal "Macedonian Medical Review". Dr. Mančev himself was the first editor of this journal in 1946.
During the same period, as previously mentioned, one of the few doctors who focused on haematological laboratory problems was Academic Prof. Dr. Isaac Tajer. At first, he acquired his experience in haematological laboratory diagnostics at Professor Čilov’s Clinic in Sofia (Bulgaria). Later, in the early 1950s, he stayed for six months at the most prominent haematology centre in France, the Haematology Clinic, managed by the famous Professor Chevalier. There, he encountered and worked on haemostasis investigations. Upon his return to Skopje, he founded the first coagulation laboratory in Macedonia, within the newly-founded Pathophysiology Institute.

The beginnings of clinical haematology officially date from 1956 when the Haematology Department was founded within the framework of the Internal Medicine Clinic in Skopje.

Throughout this period, the Clinic for Internal Medicine was managed by Dr. A. Ignjatovski and was in the process of organizing and coordinating its primary activities, providing better health-care and carrying out the teaching curriculum in internal medicine. After his retirement in 1953, the chief position was filled by Prof. Dr. Dimitar Arsov, who was the only professor at this Clinic until 1957, and his young and enthusiastic medical team specialized in internal medicine. In those days the Clinic operated as part of an integrated Internal Medicine Centre. As they settled into the new clinical building in 1956, the first floor of the eastern wing was committed to the formally determined Departments of Haematology, Nephrology and Rheumatology. Prof. Dr. Jonče Nedelkoski was appointed to the Haematology Department. He was then a young resident doctor and in 1959 was elected as Assistant Professor of Internal Medicine. The deputy chief of this department was Ass. Dr. Sunčica Apostolova. Later, the team was joined by Prof. Dr. Todor Stojčevski and Prof. Dr. Nenad Markovic. (Fig. 1 presents some of the difficulties facing the establishment of health care on the territory of today’s Macedonia).

In the late 1960s, the Haematology Department of the IMC (Internal Medicine Clinic) represented a form of virtual sub-specialty. In that period a special cabinet was founded for microscopic diagnostics of haematological preparations. The equipment for haematology diagnostics was one Reihert microscope and an accompanying photo-camera. The blood cells were counted manually. The haemoglobin was determined by Sahli’s method. Prof. Dr. Stojčevski introduced specialized therapeutic laboratory methods with radioactive elements.

During those years, the application of radioisotopes was considered to be a huge contribution to the great advancement in the medical science, diagnostics and the treatment of many diseases. In a word, it represented an attractive medical and optimistic "fashion" in medical development. Many new methods were introduced, such as: investiga-

Figure 1 – In 1963, after the earthquake the Internal Clinic was working under irregular and difficult conditions. From right to left Prof. Dr. T. Stojčevski and Prof. D. Arsov
ting the ferric metabolism with F-59, determination of the life duration of Er in various haematological diseases, determining the iron in blood serum, and the use of R.A. phosphorus R-32 in therapeutic purposes. The complex investigations and tests that were performed on 36 sick patients were published in the Macedonian Medical Review, vol. 16, pp. 317–328 in 1961, entitled: "Our First Experiences in the Application of Fe-59 in Diagnostics" by Jonče Nedelkoski, Todor Stojčevski and Dimitar Arsov.

During the same period, Prof. Dr. Jonče Nedelkoski, in collaboration with the doyen of Yugoslav internal medicine and haematology Prof. Dr. Stanoje Stefanovic, introduced the methods of bone marrow, spleen and liver biopsy into routine diagnostics and internal medical practice (Fig. 2).

A huge step forward in the development of the haematology in Macedonia and in the world, as well, was the study of qualitative and quantitative changes in haemoglobin synthesis, by Prof. Dr. Gjorgi Efremov. Even today, these studies play a great role in the diagnostics of congenital anaemia, especially thalassemia and abnormal haemoglobin. We may mention the first of the numerous published works on this topic: Duma H, Efremov G, Sadikario A, Teodosiev D, Mladenovski B, Vlaski R, Andreeva M. A Study of Nine Families with Haemoglobin Lepore. Br. J Hematology 15; 161–172, 1968.

In the mid 70s of the last century, on the territory of the former Yugoslavia, the developing pathways of haematology and transfusion science intersected. The period from 1968 to 1979 is a period of integral development of haematology and blood-transfusion science in Macedonia. During this period the Director of the Blood Transfusion Department was Prof. Dr. Nedelkoski, and Prof. Dr. Stojčevski managed the clinical department of the same institution. This is considered as a turning-point in paving the direction and perspective of a more integrated haematology and blood-transfusion link. In 1968, Clinical Haematology was the first autonomous and separate internist subspecialty at the Medical Faculty.

In 1970, the Blood Transfusion Department was declared as an educational basis of the Medical Faculty in Skopje. The same year, a special section for haematology and transfusion science was formed within the Macedonian Doctors’ Society. The same association divided into two separate groups, the Haematology Association of Macedonia and the Blood Transfusion Association of Macedonia. In 1971, the Blood Transfusion Department was transformed into the Institute of Blood Transfusion and Haematology. The period from 1968 to 1979 was marked by the introduction and implementation of modern diagnostics, therapeutic and research methods in haematology and transfusion in Macedonia. The following methods were implemented: cytostatic and cytotoxic therapy in malignant haemapathies and for the first time fibrinolitic therapy was applied. Many transfusion stations were formed in all major centres in the country and blood-donation was significantly improved. In that period the production and practical use of blood components was initiated.

In the same period, Macedonian haematology played a significant role on the Yugoslavian and global scientific scene. Prof. Dr. J. Nedelkoski was the President of the 2nd Congress of Haematologists and Transfusionists of Yugoslavia held in Ohrid (29.V.–01.VI.1974), and its General Secretary was Prof. Dr. T. Stojčevski. From 1974 to 1978, Prof. Dr. Nedelkoski was the President of the Haematology and Blood Transfusion Association of Yugoslavia, and in 1962/63 he was the President of the Board of Management of the Macedonian Doctors’ Society. Prof. Dr. Stojčevski again held the position President of the Haematology and Blood Transfusion Association of Yugoslavia from 1982 to 1984.

In 1977, Prof. Nedelkoski and Doc. Stojčevski started the preparation of a textbook on Internal Medicine, the section on Haematology. The textbook was issued in the beginning of 1979, with an imprint of 2000 copies.

In 1980, with its separation from the Blood Transfusion Institute, the new Haematology Clinic was founded, known in those days as "the youngest" working unit of the Medical Faculty in Skopje.

The development policy of this clinic moved in 3 main directions: creating a highly specialized haematology laboratory, forming a bone marrow transplantation centre and implementing up-to-date information technology for processing hospital material and data.
Nowadays, the autonomous Public Health Institution the University Clinic of Haematology is a unique healthcare, educational and scientific establishment in the Republic of Macedonia in its field of work.

Since the year 2,000 until today, the Haematology Clinic has noted an increasing trend in the incidence of malignant haemopathies, with an average of 300 cases per year. The Clinic includes 20 hospital rooms, a sterile unit with 4 boxes, 41 hospital beds and 3 ambulances.

The Clinic’s average patient quotient per year is > 3500 clinical (1,200 stationary and 2,500 day hospital) and 10,000 polyclinic patients, and over 50,000 laboratory analyses are carried out. The healthcare service of the Haematology Clinic is organized in 6 divisions, each of them organized into relevant subdivisions. The main support for the Clinic’s function is the highly organized system of specific laboratories, diagnostics and therapeutic cabinets as part of the Main Laboratory for specific haematological diagnostics. The educational, scientific and healthcare activities are carried out by 98 employees and at the moment it is managed by Prof. Dr. Lidija Čevreska (Fig. 3).

Today, the Haematology Clinic in Skopje performs numerous highly sophisticated therapeutic and diagnostic procedures. The diagnostics algorithm comprises cyto-morphologic and cyto-chemical analysis, through immunological characterization with the assistance of a flow cytometer, to sophisticated molecular analysis for detecting genetic abnormalities. The therapeutic treatment is based upon modern polyhaemotherapeutic protocols, the application of monoclonal antibodies, immuno-modulatory agents, molecular target therapy and the use of allogeneic and autologous transplantation of fresh bone-marrow and frozen haemopoietic stem-cells. The results achieved in the treatment of patients with aggressive and indolent NHL who are treated at the Haematology Clinic are identical with the results of global multicentre studies (graph number 2). Since 2,000, the Haematology Clinic has introduced the transplantation of haemopoietic stem-cells in the treatment of malignant haemopathies. To date, 149 transplantations have been performed, in which 44 underwent allogeneic transplantations and 105 autologous (Graph 1). In 2005, several various research groups independently came to a revolutionary discovery about the role of JAK2V617F mutation in the pathogenesis of Chronic myeloproliferative disorders in Macedonia [1]. In 2008, the World Health Organization (WHO) installed this mutation as a diagnostic criterion for this disease group.

The educational and scientific research activities of the Haematology Clinic are achieved by participating in numerous bilateral and multi-disciplinary projects, doctorates, magisterial works and abundant publications.

The first scientific projects date from 1980. By today, numerous projects have been approved and financed by the Ministry of Science of the Republic of Macedonia. In the period from 1993 to 1996 the Lymphoproliferative Disorders: Novel Diagnostic, Prognostic and Therapeutic Strategies Project, led by Prof. Dr. Siljanovski was running at the Clinic. Then in the period 1999–2002 we performed the Molecular Analyses of Immunoglobuline Genes in Chronic B-cell Lymphoproliferative Disorders Project, led by Doc. Dr. Dimitar Efremov.

The Clinic also takes an active part in numerous international clinical studies and scientific research projects. In the period from 1998 to 2001 the Clinic participated in two studies led by Doc. Dr. Dimitar Efremov. The first was in collaboration with ICGEB, Trieste, Italy and was named "Anti-
Receptors on Malignant B-lymphocytes: Role in pathogenesis of B-cell lymphoproliferative disorders and targets for active tumour-specific immunotherapy. The other, named "Molecular Detection of Genetic Abnormalities in Haematological Malignancies", was funded by the Open Society, Macedonia.

To date, the following EORTC and SAKK studies have been completed at our Clinic: CLL-1 EORTC 06991 (1999): Fludarabine versus high-dose chlorambucil in advanced B-cell chronic lymphocytic leukaemia; EORTC 06941 (2001): A feasibility study for the therapy of chronic myeloid leukaemia (CML) with recombinant interferon alpha (rIFN-alpha) plus all-trans retinoic acid (ATRA); CLL-3 EORTC 06992 (2002) Low dose chlorambucil maintenance vs. no treatment following high-dose chlorambucil induction in patients with advanced B-cell chronic lymphocytic leukaemia. A randomized phase III study of the EORTC LG, EORTC 06951 (2003) "ALL-4A randomized phase III trial comparing dexamethasone with prednisone in indu-

Figure 3 – The professional team of the Haematology Clinic: top row, from right to left: Dr. Terzieva, Dr. Sotirova, Dr. Trajkova, Dr. Panovska-Stavridis, biologist Sitnovska, Dr. Lozance, Dr. Stojanovski, Dr. Ivanovski, Dr. Genadieva-Stavric, Dr. Krstevska-Balkanov; bottom row, from left to right: Dr. Georgievski, Dr. Arsova, Dr. Stojanovic, Dr. Karanfilski, Dr. Cevreska, Dr. Stanimirovic, Dr. Nade-Pecov
action treatment and peripheral blood progenitor cell (PBPC) transplantation in adolescent and adult acute lymphoblastic leukaemia and lymphoblastic lymphoma", clinical trial SAKK 35/03 (2004): Comparing two schedules of rituximab maintenance in rituximab-responding patients with untreated, chemotherapy resistant or relapsed follicular lymphoma: A randomized phase III trial. The last is NHL 13 study "Rituximab as maintenance treatment in B-Cell NHL", and dates from 2006. In EORTC and SAKK Study Groups our clinic is represented by Prof. Dr. Lidija Čevreska.

Also, under the leadership of Prof. Dr. Stojanov, we are included in the study: "International, multicentre, randomized, open-labeled, 2-arm Phase III Study comparing Imatinib (STI571) standard dose (400 mg/d) with Imatinib high dose induction (800 mg/d) followed by standard dose maintenance (400 mg/d) in pre-treated Ph+/BCR-ABL + CML patients in chronic phase".

Prof. Georgievski participates in the study My star – the intracoronary application of bone-marrow derived autologous stem cells in AMI patients. The scientific collaborator Dr. Stankovic represents the Clinic in the international project: "Capacity Building of Haemophilia Health Care in Macedonia". The professional team of our Clinic has an active or associating group or individual membership in numerous domestic and international associations, and also treasures an abundant publishing tradition. In addition, we would mention with great pleasure, that Dr. Dimitar Efremov is the most widely-acknowledged Macedonian researcher in the field of medical sciences, with the highest number of published studies and number of quotes published in the most famous international medical journals such as the Journal of Clinical Investigation, the Journal of Clinical Oncology, the Journal of Experimental Medicine and the Proceedings of the National Academy of Sciences USA, Blood, Leukemia [2–5, 7–11].

In 1995 the textbook "Haematology" was written by a group of authors from the Haematology Clinic and edited by Prof. Dr. Stojčevski. A large number of original and clinical scientific research studies were published [2–11].

The professional team of the Haematology Clinic during its years-long activity has been awarded and honoured many times with numerous acknowledgements, recognitions, diplomas and decorations for special merit in the field of health care and service. The recipients of most the awards are the already retired personnel of the Clinic, our esteemed professors: Prof. Dr. Jonče Nedelkoski, Prof. Dr. Todor Stojčevski, Prof. Dr. Nikola Siljanovski and Prim. Dr. Risto Stojanovski, as well as Prof. Dr. Nenad Marković, Doc. Dr. Sašo Radovan, Dr. Sašo Todorovski, Doc. Dr. Dimitar Efremov and Dr. Aleksandra Crcareva-Rizo, who decided to pursue their careers abroad.

Hippocrates of Kos (480–375 BC), the most eminent doctor in world history, said that a doctor during his duty can rarely heal, in many cases he can improve the condition, but he is always obliged to help those who are seeking help. The current motto of the Haematology Clinic is: "always help those who seek help, provide precise and early diagnostics, and apply all up-to-date therapeutic strategies, scientific research, continual education, and day-to-day implementation of the latest achievements in the field of haematology in daily practice. Special acknowledgments to Prof. Dr. Jonce Nedelkovski and Prof. Dr. Todor Stojcevski for their contribution to this text by sharing their memories, photos and documents.

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Резиме

ХЕМАТОЛОГИЈАТО ВО РЕПУБЛИКА МАКЕДОНИЈА: АКТУЕЛНИ СОСТОЈБИ И КРАТОК ИСТОРИСКИ ОСВРТ

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Во Македонија хематологијата како наука се развива во текот на последните девет декади. Најголемата експанзија ја доживеа во втората половина на ХХ век. Официјалните почетоци датираат од 1956 год. кога е основан Оддел за хематологија во рамките на Клиниката за инфарцина медицина – Скопје. Во почетокот, хематологијата претставувала вирулентна субспекталност, но многу брзо прогредирала и го достигнала југословенското ниво од тоа време. Во период од 1968 до 1979 год. интегрално се развила со трансфузионална медицина во Македонија. Денес, автономната јавна здравствена институција, Универзитетската клиника за хематологија претставува единствен здравствен, едукативен и научен центар кој се занимава со оваа дејност во нашата земја. Дијагностичките алгоритми се состојат од цито-морфолошки и цито-хемиски анализи, преку имунолошка карактеризација која се изведува со проточен цитометар до софистицирани молекуларни анализи за детекција на генетски аномалии. Терапевскит пристап се базира на модерни полихемотераписки протоколи, приложена на моноклонални антитела, имуно-модулаторни агени, молекуларна таргет терапија и примена на аллогенна и автолозната трансплантација на свежа косена срцевина и срнзнати хематопоетски стем клетки. Девизата на Клиниката за хематологија е: секогаш помогни им на оните на кои им е потребна помош, направи рана и прецизна дијагностика и практикувай актуелни тераписки стратегии, континуирана едукација, научноистражувачка дејност и секојдневно имплементирај ги последните достигнувања во почето на хематологијата во секојдневната практика.

Ключни зборови: хематологија, историја, хемотерапија, проточна цитометрија, молекуларни анализи, стем клеточна трансплантација, таргет терапија, имуно-мулулаторни агени.