The history of the Laboratory of Pathology of the Cluj-Napoca Oncological Institute

G. SIMU, R. BUIGA

Laboratory of Pathology, "Professor Ion Chiricuţă" Oncological Institute, Cluj-Napoca

Abstract

The Laboratory of Pathology of the actual "Professor Ion Chiricuță" Oncological Institute of Cluj-Napoca, former "Iuliu Maniu" Institute for Cancer Study and Prophylaxis, had the privilege that in its framework carry on an important part of their activity professors Titu Vasiliu and Rubin Popa, who are forming, beside Victor Babeş, the golden trinity of the Romanian pathology. The Cancer Institute of Cluj, one of the first in the World, was founded in 1929, especially by the clear-sightedness and the efforts of Professor Iuliu Moldovan, the master of the modern Romanian school of hygiene. The clinic division was assisted by a Laboratory of Pathology, whose chief was appointed the young pathologist of high competence, Rubin Popa, associate Professor of this department of the Cluj School of Medicine. In 1942' he became director of the Institute, function accomplished until his premature disappearance in 1958. Titu Vasiliu worked in the Oncological Institute from 1949, a year after his forced retreat from the chair of pathology, up to 1958. Fortunately, his premature disappearance did not interrupt the activity of the laboratory, because the management of the Oncological Institute was committed to Ion Chiricuță, an experimented and modern surgeon of Bucharest. From 1960, the Laboratory of Pathology has been led by Professor Augustin Mureşan, an experimented, rigorous and prudent pathologist, who has imprinted these indispensable qualities to his disciples learning under his leadership. The activity of the laboratory has been very favorably influenced by the presence of Professor Gheorghe Badenski from the Department of Microbiology. The collaboration with Professor Eugen Pora from Babeş-Bolyai Department of Animal Physiology and his disciples, Virgil Toma, Draga Nestor, Sena Roşculeț, Carmen Stugren and Georgette Buga has carried on the performance of interesting works concerning the thymus involution in tumor-bearing hosts and its signification for the depressed immunity in the advanced stages of cancer. In the same direction, the behavior of mast cells has been studied in collaboration with Professor George Csaba from the Budapest medical university department of biology. The observations brought about were remarked by the Canadian scientist Hans Selye. Most of these works have been included in the book "Immunity and cancer", distinguished with "Victor Babeş" Prize of the Romanian Academy. The arrival in the Institute of Professor Ion Macavei, disciple of Iuliu Haţieganu and founder of the Clinical Hematology in Cluj, expert in blood and bone marrow cytology, has given a strong impulse to the studies of malignant hemopoietic diseases. The current use of cytologic and histopathologic examinations in this field of pathology and, especially, the introduction by him, for the first time in Romania, of the osteomedullary biopsy has permitted the elaboration of an appreciated work about the cytologic and histologic diagnosis of lymphadenopathies. In the histochemical–histoenzymatic period of the microscopic diagnosis, between the years 1960–1990, the laboratory has enjoyed by the advices and the material help of Professor Raymond Wegmann from the Paris University Institute of Histochemistry, the founder-editor of the International Review of Histochemistry, from 1976, of Cellular and Molecular Biology, who visited our laboratory in 1992. From 1965, in an adjacent Laboratory of Cytogenetics, Corneliu D. Olinici has performed the first karyotypes in Cluj and has teached the method to several other specialists. Despite the technical difficulties, the works performed in the Laboratory of Pathology have succeeded sometimes to reach the quality required by Professor Chiricuță to a valuable scientific work in cancerology. This performance has been obtained by a study concerning Crabtree effect variations in tumoral metastases or about lactic-dehydrogenase behavior in breast carcinomas.

***Keywords*:** Laboratory of Pathology, "Professor Ion Chiricuță" Oncological Institute Cluj-Napoca, history.

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The clinic division, where surgical and radiological treatments were applied, was assisted by a Laboratory of Pathology, whose chief was appointed the young pathologist of high competence, Rubin Popa, associate Professor of this department of the Cluj School of Medicine.

In 1942' he became director of the Institute, function accomplished until his premature disappearance in 1958. Titu Vasiliu worked in the Oncological Institute from 1949, a year after his forced retreat from the chair of pathology, up to 1958.

Titu Vasiliu and Rubin Popa represent one of the most exceptional master-disciple couple of the history of Romanian medicine, by the similitude of their scientific preoccupations and the contrast between their mind and temperament.

Titu Vasiliu has been the main disciple of Victor Babeş practicing pathology his whole life, unlike

other illustrious disciples who have required international reputation in clinical domains, as Gheorghe Marinescu and Constantin Parhon.

He was a Moldavian born in Hârlău in 1885, educated in the famous Lazăr College of Bucharest and graduated of the school of medicine of the same city. Disciple of Victor Babeş as well as of the great clinician Nanu-Muscel he was and erudite and ingenious pathologist, full of fantasy, redoubled by an experimented practitioner.

Following the recommendation of Victor Babeş, during 1913–1914, he studied in the famous institute of pathology of Ludwig Aschoff, in Freiburg, Germany, appreciated in that time, as the top institute of pathology, by the ingenuity of the experimental works performed there, and the recent discovery of the reticulo-histiocytary system. He was in good relation with another visiting pathologist, the Russian N. N. Anitschkow, who first demonstrated experimentally the role of the cholesterol in atheromatosis.

He took actively part, as laboratory physician, to the Ist World War. In 1919, he came together with Victor Babeş, to Cluj, to organize in the new Romanian school of medicine the teaching of pathology. In 1920 he was appointed Professor of pathology and was active in this function until 1948.

All this time, he directed the activity of the department, the work of his numerous disciples, endowing the laboratories both to teaching and research. By his extensive and profound learning, he acquired in short time the respect and the affection of his Transylvanian colleagues and became the indispensable coworker of the reputed medical school of Cluj founded by Iuliu Haţieganu and Ion Goia.

His mind was very keen and movable, some times surpassing his power of verbal expression: in such occasions small gaps were appearing in his peroration and his students, even his younger coworkers did not understand the exact meaning of his sentences. It was then the mission of his close coworker, Rubin Popa, to explain in few and very clear words the original conclusions of the master.

Titu Vasiliu was the first to be amused by his inclination to lose his way in the jungle of his erudition. Attending one day a lecture delivered by Rubin Popa about the reticulo-histiocytary system, he, who learned about this phenomenon directly from Aschoff, its discoverer, and has written several books in the matter, exclaimed: "At last I have understood what is this reticulo-histiocytary system !" One is thinking to the Goethe's confession that he understood better his own Faust in French translation of Gerard de Nerval.

The influence of Aschoff has, indeed, determined the major scientific preoccupation of Titu Vasiliu: the pathology of blood and hematopoietic organs. In 1924, he published the first Romanian treaty of hematology, "Blood and hematopoietic organs. Hematology" [1].

In 1927, he published, together with Ion Goia, an ample study about lymphogranulomatosis in the French review of pathology [2]; their original suggestion above a possible role of a filterable form of tuberculosis virus in the etiology of this disease was retained by Gustave Roussy in his famous textbook of pathology [3].

In 1929, published together with Rubin Popa, a study above intestinal lymphogranulomatosis [4].

Subsequently a great treaty of "Clinical Pathology", for students and physicians, appeared in three editions [5].

During his activity in the oncological institute, he has written a lot of works about the malignant tumors, as the tumors of the reticulo-histiocytary tissue" [6] or the substantial monograph about "the cancerous disease" [7], in change of whose Pierre Masson sent him his prestigious treaty about human tumors. In this last book, he was the first Romanian scientist to dwell upon antitumoral immunity.

He has written that "the ideas about host resistance and fight against pathogens according the model of infectious diseases were applied also to cancer disease. Since the cancer cell is innocuous for the host, one must check whether the host does not act against it as against an antigenic foreign body, by antibodies or antitoxins, which bind and neutralize these antigens, inactivating them and producing the cure.

Characterizing with modesty his activity in a short autobiographic sketch [8], he was writing: "I fulfilled and still fulfill one of the imperious needs of a teacher, the training of disciples, as stated by the youth friend and colleague from Aschoff's institute, N. N. Anitschkow, when he visited us in Cluj. I think that I succeeded in forming a scientific school of pathology and hematology by a close collaboration with the clinics".

Commenting the scientific work of Professor Titu Vasiliu, Iuliu Haţieganu emphasized his remarkable contribution to the knowledge of the blood diseases and especially of leukemias and reticulosis. He may be considered the promoter of the study of diseases and syndromes of reticulo-histiocytary system in Romanian medicine.

Rubin Popa, the successor of Titu Vasiliu, born in 1901 in a Transylvanian village as son of a farmer, was a very sober and reserved man, endowed with a clear, synthetic mind, expressing in the most intelligible form the most difficult problems of the pathology. He studied in the College of Blaj, the famous little town which was, for two centuries, the cultural centre of Transylvania. He obtained his M.D. in Cluj, working during his studies near Professor Vasiliu.

After graduation, he improved his instruction near the pathology personalities of the time, Gustave Roussy, Rhoda Erdmann or Robert Mayer, in France or Germany. In Haţieganu's Clinic he became a valuable specialist in internal medicine.

His lectures and reports were producing indelible impression in the memory of his numerous colleagues, disciples, coworkers and students. "He was distinguished", said Alexandru Şerban, one of his main disciples, "by a clear and well-ordered thought, a beautiful, fluent, natural language, a faculty to express simply the most complex problems, qualities attracting the admiration, even the veneration of his disciples and his auditory."

Peoples having the happiness of living and working around him never will forget his locutions synthesizing with Latin lapidary concision the essential problems of the pathology, beginning with his famous aphorism "every thing is possible in pathology". He was insisting not only about a geographic, but also about a historic determination of the pathology: each time had its characteristic diseases. As doctor Ilie Neamțu has said, he was a prince of the thought.

He had an exceptional career: associate Professor at 25 years, head of the Cancer Institute Laboratory at 28, Professor of general pathology and director of the Cancer Institute at 41. His best friend, the distinguished radiologist Valeriu Secarea, was saying, by joke, that this rapid *cursus honorum* was the follow of the help furnished by the "Greek-Catholic mafia" existing this time in the Cluj School of Medicine. Indeed, this school was founded especially by Iuliu Hațieganu and Iuliu Moldovan, both Greek-Catholic priest sons, with the help of Iuliu Maniu, chief of the Transylvanian government but also the lawyer of the Greek-Catholic archbishop of Blaj. Rubin Popa was the son of a Greek-Catholic psalm-reader and the brother of Augustin Popa, well-known Professor at the Theological Academy of Blaj and a protagonist of Christian-democracy in our country. In fact, this brilliant career was the follow of his intellectual qualities and solid professional preparation.

Under his master influence, his main preoccupation was the study of the malignant, especially hematopoietic tumors. At beginning of his activity, he introduced new, in that time, laboratory techniques, as intraoperatory microscopic examination and cytologic examinations.

After 1945, impressed by the anatomo-clinical changes induced in the evolution of certain diseases by the large use of antibiotics, especially in staphylococcal infections, he called attention above the increased incidence and the gravity of complications produced by such strains of organisms become resistant to antibiotics following an insufficient or inadequate treatment. Unusual forms of prolonged septic states were frequently observed, as well as numerous mycotic infections. By these ideas he was a promoter of medical ecology.

Observations that in patients with prolonged septic states the characteristic suppurative lesions were progressively replaced by an expressed lympho-histiocytary hyperplasia in lymph nodes, spleen or liver, remembering microscopic changes seen in leukemias or lymphomas, guided Rubin Popa to the hypothesis that prolonged or repeated inflammatory responses may escalade, in certain conditions, into neoplastic lymphoid processes.

This concept was clearly and firmly expressed with occasion of the sessions of the anatomo-clinic circle of hematology, between 1950–l958, and especially to a session of the internal medicine section of the medical sciences society, in spring 1957. It is exposed also in a paper above antibiotics-resistant staphylococcal *post-abortum* infections [9].

To his proposal, such changes were experimentally reproduced by Maria Bedivan [10] in rabbits inoculated intravenously with staphylococci and subjected to a prolonged but insufficient treatment with antibiotics.

In the same sense, Ion Macavei and Victor V. Papilian [11] have published their observations above patients in whose lymph nodes, on repeated biopsies during several months or years, inflammatory changes transformed into lymphomatous ones.

By these works, Rubin Popa appears as a protagonist of the theory above the transformation of the inflammatory or immune responses into lymphomas and leukemias, confirmed the next years by numerous clinical and experimental observations. Twenty five years later, especially Robert Lukes [12] affirmed that many, if not all malignant lymphomas are immune responses blocked in a certain more or less differentiated phase of their development. It is a necessity for the pathologist to recognize this phase for an exact immunological characterization of the lymphomas, moment with great prognostic and therapeutic signification. This goal has been accomplished by the last microscopic classifications of these diseases, especially by the recent REAL–OMS one.

This classification includes among lymphomas several lympho-proliferative disorders appreciated formerly as reactive (angioimmunoblastic lymphadenopathy, lymphomatoid granulomatosis, lymphomatoid papulosis). The demonstration of essential role of *Helicobacter pylori* infection in gastric lymphomas genesis is especially a conclusive confirmation of Rubin Popa hypothesis.

Fortunately, his premature disappearance did not interrupt the activity of the laboratory, because the management of the Oncological Institute was committed to Ion Chiricuță, an experimented and modern surgeon of Bucharest.

His arrival to Cluj, was, in the words of Professor Ion Goia, as a running fresh air in the scientific atmosphere of this University City, dusted by mitchurinism and exaggerated pavlowism.

Ion Chiricuță has come with the mission to build a new and modern oncological institute. From beginning, he has realized that the success of this mission is depending of the quality of his coworkers. Endowed with skilful managerial sense, redoubled by a toreador energy and combativeness (he liked to meet opposition and to defeat it), he completed the experimented staff of the Institute, doctors Ilie Neamțu, Gherghina Muşatescu or Elisabeta David, with new persons of verified professional quality.

Because he resorted sometimes to the services of some professors or young assistants rejected from the university, to the malicious insinuations that the new institute has become a reactionaries' paradise, he responded that it is an institute of former and future professors: and he has had right.

From 1960, the Laboratory of Pathology has been led by Professor Augustin Mureşan, an experimented, rigorous and prudent pathologist, who has imprinted these indispensable qualities to his disciples learning under his leadership. In that time, when the pathology, before immuno-microscopy, was still in a subjective,

romantic phases, diagnosis being set on classic preparations, using some histochemical or histoenzymatic techniques, he was insisting for the choice of the most frequent alternative. He recommended special caution for a firm diagnosis of malignancy, but also to exclude completely this diagnosis in uncertain cases. He was emphasizing also the importance of a good collaboration between the pathologist and the clinician, insisting above only a gently contradiction of clinician's diagnosis.

Concomitantly, an efficient service of cytologic diagnosis was developed. It was initiated by Elisabeta David, especially in the field of genital and breast pathology. It was developed by Natalia Galatar, appreciated by Victor V. Papilian as his most talented disciple, who by her current activity, but especially by periodical organization of lectures of practical cytologic diagnosis for physicians and biologists, had an essential contribution to the achievement of one of the main Professor Chiricuță target: a national network of laboratories for early cervical cancer detection. Her textbook in the problem is a quite reference book [13].

The activity of the laboratory has been very favorably influenced by the presence of Professor Gheorghe Badenski from the department of microbiology.

At his suggestion and with the enthusiastic impulse of Professor Chiricuță, the first researches above tumoral immunology were performed in our country. In 1963, Professor Mureşan reported to the International Congress of Histochemistry, at Frankfurth am Main, a work about the brain lympho-histiocytary cells behavior in Walker tumor-bearing rats [14].

Other interesting works, proving the intervention of immune factors in cancer genesis and evolution has been performed in collaboration with laboratory of immunology led by the erudite Titus Mureşianu and his coworkers, Doina Ionescu and Monica Crişan (the latter has become a true "egeria" of Professor Chiricuță, in his last years of life).

The collaboration with Professor Eugen Pora from Babeş-Bolyai department of animal physiology and his disciples, Virgil Toma, Draga Nestor, Sena Roşculeț, Carmen Stugren and Georgette Buga has carried on the performance of interesting works concerning the thymus involution in tumor-bearing hosts and its signification for the depressed immunity in the advanced stages of cancer.

In the same direction, the behavior of mast cells has been studied in collaboration with Professor George Csaba from the Budapest medical university department of biology.

The observations brought about were remarked by the Canadian scientist Hans Selye. Most of these works have been included in the book "Immunity and cancer", distinguished with "Victor Babeş" Prize of the Romanian Academy [15].

Also, remarkable observations of comparative cancerology and the identification for the first time in Romania of certain animal tumors have been performed in collaboration with Ion Ivaşcu from the Veterinary Medicine School of Cluj [16].

In the same time, researches performed in the experimental cancer laboratory by Cornelia Papilian and Rodica Risca, as well as ones performed in the laboratory of cancer biochemistry by Iancu Mustea and Dan Postescu have soon conferred to the oncological institute of Cluj the quality of center of experimental studies about cancer, beside "Victor Babeş" Institute and Oncological Institute of Bucharest.

The arrival in Institute of Ion Macavei, disciple of Iuliu Hațieganu and founder of the clinical hematology in Cluj, expert in blood and bone marrow cytology, has given a strong impulse to the studies of malignant hemopoietic diseases. The current use of cytologic and histopathologic examinations in this field of pathology and, especially, the introduction by him, for the first time in Romania, of the osteomedullary biopsy has permitted the elaboration of an appreciated work about the cytologic and histologic diagnosis of lymphadenopathies [17].

In his clinical division the first cases of Burkitt lymphoma in our country has been diagnosed. Observations about lympho-proliferative syndromes able to transform into malignant lymphomas has drawn Robert Lukes' attention [18].

In that histochemical–histoenzymatic period of the microscopic diagnosis, between the years 1960–1990, the laboratory has enjoyed by the advices and the material help of Professor Raymond Wegmann from the Paris University Institute of Histochemistry, the founder-editor of the international review of histochemistry, from 1976, of cellular and molecular biology, who visited our laboratory in 1992.

At the Ist International Congress of Cellular and Molecular Biology, at Paris, in 199l, a member of our laboratory has moderated the panel about the transformation of the immune response into malignant lymphoma [19].

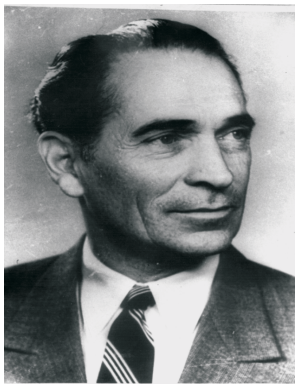
From 1965, in an adjacent Laboratory of Cytogenetics, Corneliu D. Olinici has performed the first kariotypes in Cluj and has teached the method to several other specialists. His work, "Chromosomes in Cancer" [20] includes the results of the activity of this laboratory about tumoral cytogenetics.

Despite the material, technical difficulties, the works performed in the laboratory of pathology have succeeded sometimes to reach the quality required by Professor Chiricuță to a valuable scientific work in cancerology, i.e. to be published in the review Cancer of Philadelphia or, better, to be quoted in a paper appeared in this review. This performance has been obtained by a study concerning Crabtree effect variations in tumoral metastases [21] or about lactic-dehydrogenase behavior in breast carcinomas [22, 23].

The technical assistants of the laboratory, especially the skilful, unforgettable Emilia Pinca, whose frozen sections had the accuracy of the paraffin ones, but also her numerous disciples, especially Magdalena and Laczi Lorinczi, Aghi Craioveanu, Elisabeta Furcovici and many others have contributed to this success.

The necropsy master Gavrilă Pop, who was able to collect thymus and even hypophysis of any animal species, must be included in this glorious team.

Titu Vasiliu
(1885–1961)



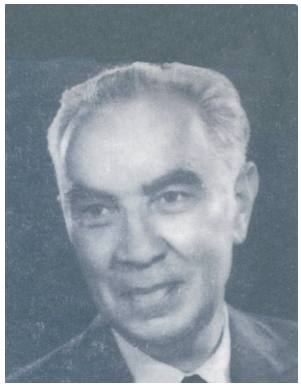
Rubin Popa
(1901–1958)

Ion Chiricuță
(1918–1988)

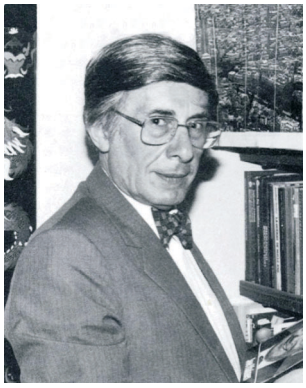
Gheorghe Badenski
(1901–1978)

Augustin Mureşan
(1908–1983)

Ion Macavei
(b. 1911)



Eugen Pora
(1909–1981)



Raymond Wegmann
(b. 1923)

Laboratory of Pathology, 1960. From left to right: George Simu, Cornelia Papilian, Augustin Mureşan, Elisabeta David, Emilia Pinca

Laboratory of Pathology, 2005. From left to right: Marina Bârsu, Natalia Galatîr, George Simu, Liliana Resiga, Corneliu D. Olinici, Mihaela Galatîr, Rareş Buiga, Daniela Todea

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Mailing address
George Simu, Professor, MD, PhD, Laboratory of Pathology, "Professor Ion Chiricuță" Oncological Institute Cluj-Napoca, 34–36 Republicii Street, 400 015 Cluj-Napoca, Romania; Phone/Fax +40264–598 361, E-mail: raresbuiga@yahoo.fr

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