Đorđe Joannović – First Serbian oncologist-scientist (On the occasion of the 75 anniversary of his tragic death)

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Ancestors of Đorđe Joannović came from Metohija (Southern Serbian Province Kosovo and Metohija) to the Village Beodra (today called Novo Miloševo) in Banat (Northern Serbian Province Vojvodina). His parents Hariton and Marija moved then to Vienna, where Đorđe was born in 1871. Đorđe and his older brother Simeon-Sina were brought up in patriarchal spirit of the old Serbian tradition.

Đordje completed elementary and secondary school in Vienna and graduated from the prestigious Medical School in Vienna. As native of Vienna, he started to work in the Institute of Pathology of the Vienna Medical School with the famous pathologist Prof. Richard Paltauf (1858-1924), who was Pasteur's and Koch's student.

Soon enough he became lecturer 1896, assistant professor 1904, associate professor 1910, and full professor 1919. Before the First World War Vienna was one of the centers of the medical world. Rector of the University of Vienna was the famous pathologist, academician, and president of Academy Carl von Rokitansky (1804-1878) and the Paltauf's Institute of Pathology was his successor.

Rivals of the Vienna Medical School could be in the world only Berlin, Paris, London, and to certain point St. Petersburg.

Joannović was at that time a Serb with the greatest university medical position in the world, especially interested in experimental oncology and pathology as well oncologic pathology and pathological morphology (1).

Such a man comes from Vienna to Belgrade for pure and noble patriotism in 1920, to found and organize, in triumvirate with Prof. of hygiene and public health Milan Jovanović-Batut (1847-1940) and Prof. of surgery Vojislav J. Subbotić (1859-1923), the Belgrade Medical School and lay foundation of the Serbian oncology and pathology. He had to cope with tremendous organizational and other difficulties and unfortunately he had experienced unjustified obstacles by some people.

He was associate Dean and Dean for several terms of office. He built the Institute of Pathology in 1926 (2,3) and was its first director. His associates were: Ksenofon Šahović (1898-1956), Dimitrije Tihomirov, Marija Višnjić, Živojin Ignjačev, and others.

In September 27, 1927 he founded the Yugoslav Society for the Study and Treatment of Cancer and was its first Chairman (Secretary General was K. Šahović, Serbian academician). At that time the Society was the forth in the world, i.e. after Vienna 1910, Washington 1917, and Paris 1920. He was the one to support construction of the central Oncology Institute in Belgrade.

Joannović was the Chairman of the Serbian Medical Society and great friend of medical students; he was elected for lifelong Honorary President of the Yugoslav Medical Students Associations.

He represented Serbia and Yugoslavia at numerous medical congresses in Europe and United States (4-9).

He never married nor had children believing that science wants a whole person. However, he visited frequently his brother Simeon-Sina in Village Beodra.

Đorđe Joannović (Thanks to the kindnees of Prof.dr Nada Kovačev- -Šljapić, Prof. of Pathology of the Medical School, Novi Sad, relative of Đ.J.)

Scientific work of Joannović has an impressive world-wide reputation. Naturally, basis of his work had been set already in Vienna. He wrote 58 significant scientific papers. In 1926 he becomes a corresponding member of the Serbian Royal Academy of Sciences.

WORK ON EXPERIMENTAL ONCOLOGY AND ONCOLOGIC PATHOLOGY

Joannović was the first Serbian oncologist-scientist (10,11); he began his work in oncology in 1920 (10). At his time, thanks to the Berliner pathologist and Prof. Rudolf Virchow (1821-1902), "father of pathologic anatomy" and the writer of the revolutionary book *Cellular Pathology* (1858) (12,13), the initial basic data on oncologic pathology has been already recognized. Namely, Virchow made great discoveries and contributions in this field: discovery of leukemia: splenic (myeloid) and lymphoid and its differential diagnosis from leukocytosis and pyemia; local origin of cancer and occurrence of metastases by cellular spread (analogy between embolism and metastasis); hematogenous spread of sarcoma (existence of lung metastases without involvement of local lymph nodes); Virchow's lymph node (supraclavicular, left) – site of metastatic stomach or ovarian carcinomas; Virchow's tumor – psammoma; description and classification of some tumors; new names for certain tumors: myxoma, myoma, myosarcoma, angioma, lymphangioma, neuroglioma, teratoma, etc.

Joannović investigated pathologic morphology of some tumors, i.e., branchiogenic carcinoma (carcinoma originating from the remnants of branchial arches) and cystic tumors of the neck (14); calcification and ossification of atheroma; development of tumors by irritation (15); multicentric origin of tumor in some organ (10); etc.

He investigated tumor growth *in vivo* (16) and *in vitro* on tumor tissue cultures (18). He noticed that castration and splenectomy promoted tumor growth (17); rise but not oats also promoted tumor growth while toxic substances (e.g. toluilendiamin intoxication) and small doses of morphine and cocaine and quinine slow down tumor growth.

Joannović believed that disposition, local changes, and general metabolic disturbance are important for cancer development (19).

Immunological aspects of cancer therapy using fermentative extracts of tumor tissue of the same patients were presented in papers 20 and 21. Lymphectasia, accumulation of plasmocytes and proliferation of connective tissue with sequestration of carcinoma cells indicated cure from cancer in experimental animals. Taking into account that erysipelas infection can destroy the skin carcinoma, Joannović, *per analogiam*, used the bee venom in therapy of carcinoma.

Extensive reviews of experimental investigations of cancer and effects of radiothorium were given in papers 22 and 23.

Joannović's general review on the etiopathogenesis of cancer (24) gave us the relevant and authentic data about the state of art of this problem in his time. Therefore, if we compare the present status of oncologic pathology with the status at the beginning of XXI century (25) we must be amazed by the fantastic progress of world of medicine.

Namely, today (25) we know that cancer is a genes' disease of individual cell. Mutagenic factors make mutations of normal cellular genes: protooncogenes or tumor suppressor genes. The executive proteins, codified by mutated cancer genes, changes about 100 characteristics of normal cell. Cancer cell became immortal. The bases of cancer cell immortality are: (a) action of enzyme telomerase on the chromosomal telomeres, preventing their shortening after cell division, and (b) lack of apoptosis (programmed cell death –"cell suicide"). The initial cancer cells must break down the normal "immunological survey". Than occurs the favoritisms of one cancer cell clone with its uncontrollable proliferation, invasiveness, aggressiveness (i.e. infiltrative – destructive local growth) and manifestation of cells metastatic potential.

WORK ON EXPERIMENTAL PATHOLOGY AND PATHOLOGIC MORPHOLOGY

Joannovic also investigated staining of microorganisms in pathological tissues (27). His work on liver diseases (27-33) covered different aspects, and his work on pathogenesis of icterus was awarded by Belgium Royal Medical Academy) (28).

Joannovic's works in experimental pathology and pathologic morphology are related to different fields such as prophylaxis of tetanus and anaphylactic shock (34), transplantation problems (35), and pathology of nutrition (36).

DISCOVERY OF AUTOAGGRESSION

At the second part of XIX century and beginning of XX one in the medical circles dominated a dogma that "The human organism never creates substances against itself". The dogma was mostly inaugurated by the Nobel Prize Laureate (in 1908 with Elias Metchnikoff), immunologist Paul Ehrlich (1854 – 1915), inventor of Salvarsan and Neosalvarsan (drugs against syphilis) (37), who was a great friend of Joannović (who wrote obituaries for Ehrlich (38) and Metchnikoff as well for prominent Serbian physician Vladan Đorđević).

Today, in the XXI century, we know that this dogma is not true, for already at the cell level the organism sends a "death molecule" to its unnecessary or damaged cells, which then activates in the cell already built-in caspase enzyme system that cuts the DNA in pieces leading to "cell suicide" or apoptosis. Furthermore, we are aware today that there are many important autoimmune diseases.

However, Joannović noticed that the soldiers with healed firearm-related head and brain injuries sometimes had heavy headaches and died. Autopsy of such patients proved multiple areas of softened brain tissue, both in the vicinity and at a longer distance from the healed brain injury. He got the same results in his experiments on white rats which were subjected to mechanical head injuries.

From such human and animal observations, contrary to the prevailing dogma, he drew a brilliant conclusion: "The same brain elements, which have been as result of trauma source for multiplication of products of disintegration, later on are subject to action of their reaction products".

If we interpret this statement into today's language of autoaggression, it is obvious that disintegration brain products stimulate our immune system to make antibodies against them, but also against such substances (antigens) in the healthy brain cells, which causes multiple softening of the brain.

He tried to apply this original etiopathogenetic concept of some diseases in therapy of the superficial skin carcinoma and tuberculous granulomata of animals, injecting the disintegration carcinoma or granuloma tissue (or digested Koch bacilli) under the skin of the same humans or experimental animals. He also treated the dermatoses: *Trichophyton tonsurans* by its dissociated products as well the psoriasis by its sqammas.

Đorđe Joannović, therefore, was a pioneer in the discovery of the process of autoagression in medicine (10,39,1, 40-42) together with N. Fissinger and M. Masugi (43).

N. Fissinger opposed to Ehrlich's dogma, stating that the snake can have autoantibodies against its venom (receiving it by biting himself). Also, the animals and humans can produce autoantibodies against their spermatozoids. However, these two examples are dealing with products which are normally excreting from the organism. He stated, also, that liver cirrhosis is an autoaggressive disease.

According to M. Masugi (43), in the pathogenesis of glomerulonephritis and liver diseases, the autoaggression is implicated.

The discovery of autoaggression is the most important scientific achievement of Joannović – unfortunately a little known fact abroad as well as in Serbia. He communicated his discovery in 1920 before the Vienna Medical Association and published two papers in the same year: in the *Wiener klinische Wochenschrift* in Vienna the paper titled *The effect of the brain and bacterial products got by enzymatic destruction* (20) and *Serbian Archive* in Belgrade paper titled *New views on origin and therapy of certain diseases: Experimental studies* (21).

TRAGIC EPILOGUE

Unfortunately, the epilogue to the story on Joannović was tragic. In 1932, organizing the annual St. Sava Student's Ball, rebellious left winged medical students sent word that Serbian King Alexander the First was welcome

to come to the ball, but not his radical right-winged Prime Minister General Petar Živković.

General Petar Živković was furious of course, called Joannović to his office and allegedly told him: "You old fool can't you quiet down these rebellious students of yours", and what is even worse, slapped him.

Getting red with humiliation Joannović rushed out of the Office of Petar Živković and went to his Institute of Pathology, into his room, where he also lived. The lights in his room were on all night long. My late Prof. of Pathology Mrs. Marija Višnjić-Frajnd told me that a lot of ash was found in the fireplace in the morning, which meant that he had been burning his files, which proved suicide. Only in the morning on the January 28, 1932 he was found hung on the window knob and lying in his arm-chair. He was 61 years old and on the top of his creativity. Never before had Belgrade witnessed such mass and sad escort of coffin to Belgrade's railway station for burial in Beodra.

After the tragic death of Đorđe Joannović, the Serbian "wing wherewith we fly to heaven" (44,45) was gone.

On the occasion of the celebration of *Eighty years of fight against cancer in Serbia* on December 10, 2007, Joannović was posthumously awarded with Golden Medal of the Serbian Society for the fight against cancer (received by academician V. Kanjuh) (41).

Conflict of interest

We declare no conflicts of interest.

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