

# Scientific importance of Serbian Pasteur Institutes

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## SUMMARY

Only 12 years after Paris, the first Pasteur Institute in Serbia and the Balkans was founded in Niš, in 1900. Its contribution to preventive medicine of Serbia was enormous, primarily in production of vaccine against variola and rabies. After the liberation in 1919, the Pasteur Institute was re-established and it continued its scientific work under the management of Gerasim Alivizatos, a Greek who had come to help Serbian people. He is the author of the so-called mixed method in rabies prophylaxis, in which he combined dilution of live vaccine with concentrated ether treated vaccine. He published his work on this method in the journal *Deutschen Medicinische Wochenschrift* in 1922. After 1928, the only active Pasteur Institute in the whole Kingdom of Serbs, Croats and Slovenes was the Pasteur Institute in Novi Sad, which has remained the central anti-rabies institution to the present day. Its first director, Dr. Adolf Hempt, born in Novi Sad in 1874, was the author of the world famous vaccine against rabies, which was named after him and was in use from 1925 to 1989. He was the first in the world to have made a completely inactive, i.e. dead vaccine, which was much safer for use, so many European countries such as Austria, Czechoslovakia, Germany, Hungary gradually accepted it under the name of Hempt, and from the Novi Sad Institute it was exported to some African countries as well. Dr Hempt published his first work on the new vaccine in the magazine *Annales de l'Institut Pasteur* in 1925 in French, and he also published a monograph in German by Bering Institute in 1938, nowadays ranked as a monograph of international importance.

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## INTRODUCTION

Apart from the enormous importance for public health, Pasteur Institutes are also famous for scientific work. The same as a hundred years ago, a scientific significance of a work can be assessed according to published scientific works and according to their acceptance by other researchers, nowadays called indexes of scientific competence and citation. Even 100 years ago, it was important to publish a work in an international, widely accepted medical journal, therefore, on the basis of published works, we can nowadays easily evaluate scientific importance of past time researchers. The immense scientific and practical importance of Pasteur's discoveries promptly led to founding of Pasteur Institutes worldwide. One of Pasteur's first and most important discoveries was refuting the theory of spontaneous generation of microorganisms. Pasteur's law *Omne vivo ex vivo* brought to recognition that diseases of animals and people are caused by microorganisms against which it is possible to fight and even prepare vaccines. Pasteur's law that alive becomes only from alive is used today by creationists as the only scientific explanation of the creation of life given so far.

### Pasteur Institute in Niš

The first Pasteur Institute in the Balkans was founded in 1900 in Niš, twelve years after the one in Paris or ten years after the one in Budapest. The Institute was under military management and it was located on the outskirts of Niš, near Skull Tower (1). Dr. Milan Jovanović-Batut, Pasteur's student, wrote at that time „... in Serbia, over half (58%) of children dies before the age of 14 ...” (Preface for „The Book on Health”, 1896). Dr. Dragutin Petković (1873–1947) was the first manager of Pasteur Institute in Niš and for the production of anti-rabies vaccine, he used Hegyes method from Budapest. This method represented a significant improvement of Pasteur's method, but with all the methods of that period, a small percentage of patients died in spite of vaccination. As the functioning of Pasteur Institute in

Niš was tragically stopped during the World War I, there were no significant scientific discoveries. Nevertheless, Dr. Petković published a work on bacteriology in a German journal *Centralblatt für die Bakteriologie*, which can be nowadays evaluated as a leading international journal (2).

After the World War I, Dr. Gerasimos Alivizatos became a director of Pasteur Institute in Niš in the period from 1918 to 1926. In the rabies prophylaxis, he left a significant work on introducing ether in the technology of preparation of anti-rabies vaccine. He published that work in 1922 in the journal *Deutsche Medicinische Wochenschrift*, and he sent an offprint of the work with inscription to Dr. Adolf Hempt to Pasteur Institute in Novi Sad.

### Pasteur Institute in Novi Sad

Dr. Hempt was born in Novi Sad in 1874, grew up in Sarajevo, studied medicine in Munich and Graz, worked as a military doctor in Grosssenzersdorf near Vienna till 1905 and then as a county doctor in Lukavac near Tuzla. During the World War I, he was the commander of military hospital in Trieste. In 1918, he went back to Lukavac and in 1922 he was appointed as director of Pasteur Institute in Novi Sad, where he died in 1943. His name and the name of Pasteur Institute in Novi Sad became famous worldwide. Of all doctors of Novi Sad to the present day, only Dr. Hempt presents a familiar name in the world history of medicine (3).

Dr. Hempt wrote a paper on the new procedure of preparation of vaccine against rabies and reduced protocol of vaccination to only 6 days. It was published in French, in one of the most influential journals, *Pasteur Institute Annals*, in Paris in 1925. At that time, he pursued specialization in Pasteur Institute as a Rockefeller's scholarship holder.

In 1927 (April 25 to 30), Dr. Hempt participated in the First International Conference on rabies held in Pasteur Institute in Paris. After five years of practical work in Pasteur Institute in Novi Sad, he gained great experience in rabies prophylaxis, which made him not only an equal but also one of

the most influential participants of the conference. He was a representative of modified vaccine, i.e. completely avirulent vaccine, and reduced time of vaccination protocol to only six days.

Dr. Hempt submitted an especially detailed account in 1938 in the monograph of Bering Institute in Marburg am Lana (Figure 1), where he went to introduce his technology in Germany (4).

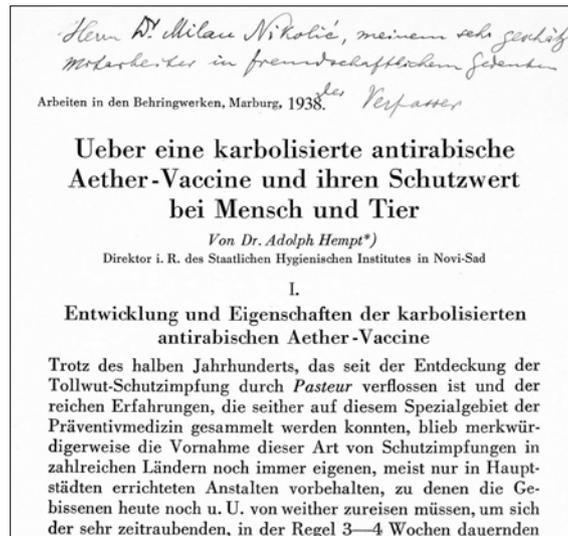


Figure 1. The beginning of Dr. Hempt's work published by Bering Institute in 1938, nowadays ranked as a monograph of international importance

Like other vaccines against rabies of nerve tissue origin, Hempt's vaccine also resulted in neurological complications in vaccinated patients. The most serious complication was allergic encephalitis that was manifested by rising Landry type paralyses. In the production procedure of vaccines from nerve tissue of grown up animals without ether application, as was the widely used Sir David Sample's vaccine, neurological complications appeared exceptionally frequently, in one report in as many as 1:200 of vaccinated patients (5). In the report on application of Hempt's vaccine in Germany, neurological complications were registered in 0.069%, approximately 10 times more sporadic than with Sample's vaccine (6).

Hungarian researchers gave in 1977 probably the best experimental explanation of advantages of Hempt's vaccine over Sample's or international referential vaccine over 30 years after Hempt's death; Hempt's vaccine was used in Hungary until 1989. It had been proved in that work that Hempt's vaccine was a great deal less harmful, as it contains as much as 3500 times fewer encephatogenic factors compared to control sheep nerve tissue (7).

In addition, Pasteur had tried to explain the nature of these complications as paralytic form of rabies in case of vaccine failure. The real nature of neurological complications of anti rabies vaccination, as allergic encephalitis was explained by Professor Đorđe Joannović (1871-1932), one of founders of Medical school in Belgrade.

Hempt's student since 1926 and his successor as director since 1946, chief of the staff, Dr. Milan Nikolić (1896-1974), published many works on rabies, some of which are quoted in modern textbooks, as well as a big monograph in Serbian 'Human and Animal Rabies' (1955, pp. 1-539) and a smaller one in German (Die Tollwut), which was published by one of the

most important publishers of the time in the world, *Gustav Fischer Verlag*, in Stuttgart, 1961. Of numerous works by Nikolić, here are presented only three, one from the beginning and two near the end of his rich career.

Nikolić published one of his more important works as a young doctor during his stay in Munich in 1932, also as a holder of Rockefeller's scholarship. This work was experimental and was carried out on dogs kept in Pasteur Institute in Novi Sad, who were infected with pseudorabies virus (Aujeszky's disease). Correspondence between Dr. Hempt and Dr. Nikolić has been preserved, from which it can be seen how Hempt had organised the experiment and sent the material to Munich for publishing.

Dr. Nikolić's work on rabies virus concentration and incubation duration from 1957, ten years after Hempt's death, shows the author as a mature and competent scientist (Figure 2). This work was quoted in one of the world's most influential contemporary infectology textbooks by *Mandell and associates* (8), eleven years after Nikolić's death.



Figure 2. Dr. Nikolić's work from 1957 was quoted in the contemporary world textbook on infectology by *Mandell*

The most quoted work of Nikolić and his associate, assistant professor, Dr. Zdravko Jelesić is the one from 1956 (Figure 3), in which they were the first in Europe to isolate bat rabies virus. This work was quoted in several international journals and monographs, which deal with rabies, several decades after its publication (9, 10).

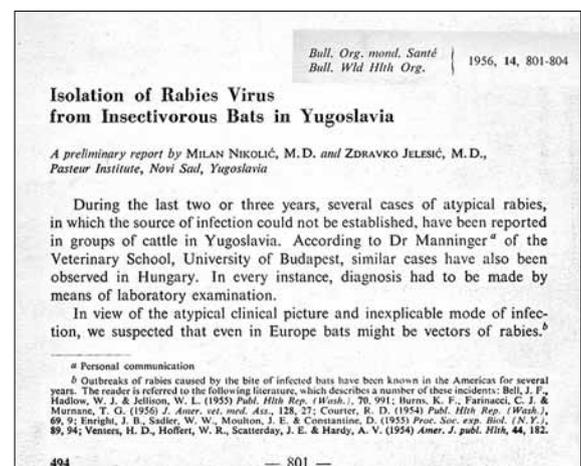


Figure 3. Work on the first isolation of bat rabies virus in Europe in the *Bulletin of the World Health Organization* 1956

## CONCLUSION

Pasteur Institute in Novi Sad between the two wars was one of the most respected in the world. Witness to that are not only scientific works of Dr. Hempt, but also the fact that his vaccine, under his name, had been accepted and produced over a number of years in Germany, Austria, Hungary, Czechoslovakia, and partially Romania and Bulgaria. In the 30s, many rabies researchers worldwide were coming to Pasteur Institute in Novi Sad to learn Hempt's technology of vaccine production. His worthy successor was Dr. Milan Nikolić, with numerous scientific works in international journals, quoted to the present day.

## Conflict of interest

We declare no conflicts of interest.

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