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## ZVONIMIR MARETIĆ (1921–1989): THE HISTORY OF DISCOVERY OF THE FIRST EUROPEAN ANTILATRODECTIC SERUM AND ITS PREPARATOR ON THE OCCASION OF THE 30<sup>th</sup> ANNIVERSARY OF HIS DEATH

### ZVONIMIR MARETIĆ (1921. – 1989.): POVIJEST OTKRIĆA PRVOGA EUROPSKOG ANTILATRODEKTIČKOG SERUMA I NJEGOVA PRIREĐIVAČA U POVODU 30. GODIŠNJICE NJEGOVE SMRTI

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#### SUMMARY

*Zvonimir Maretić was the pioneer of the study of venomous animals and plants, toxicology, and tourism medicine. His achievements have been recognized, but insufficiently researched. His work covers a broad range of biomedical sciences: from public health, ecology, and environmental protection, to epidemiology and infectology. Maretić was one of the founding members of the International Society on Toxinology and the Toxicon journal's first Editorial Board. He was the first in Europe to prepare the antilatrodectic serum and to successfully apply the weever and scorpionfish antiserum on humans. This brief note tries to*

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*commemorate the achievements of Maretić, up to now poorly recognized and insufficiently researched.*

**Keywords:** *Zvonimir Maretić, history of medicine, toxicology, antivenom, latrodectism*

## HIGHLIGHTS OF BIOGRAPHY AS THE INTRODUCTION

Zvonimir Maretić (Zagreb, May 5, 1921 – Pula, April 23, 1989) initiated the venomous animal research and pioneered tourism medicine in Croatia. With a formal education in internal medicine and infectology, he was one of the most important but insufficiently studied Croatian and European toxicologists. The grandson of a well-known Croatian lexicographer and philologist, Tomislav Maretić (1854–1938), Zvonimir Maretić studied at the Zagreb University Faculty of Medicine from 1940 until 1947.<sup>1,2</sup> In the same year of his graduation, following a decree by the Ministry of Health, he moved to Pula on the Istrian peninsula, where he completed his internship and encountered latrodectism for the first time.<sup>3</sup> After a short period in 1949 that he spent in Glina and Banija (the border between Croatia and Bosnia) as the leader of a medical team fighting syphilis, Maretić returned to Pula, where he remained for the rest of his life. The field of his interests was broad, including neurology, psychiatry, epidemiology, public health, and environmental protection, and resulted in the studies of salmonellosis, Q-fever, intestinal infections, hepatitis, venereal diseases, drug addiction, smallpox, toxoplasmosis, tick-borne encephalitis, food allergy, water supply in Istria, and other. Nevertheless, Maretić will certainly be most remembered for his research in toxicology, particularly venomous animals' and plants' toxins.<sup>4</sup> Already as a young boy, Maretić was demonstrating passion for nature and biology, hunting butterflies and registering and describing insects, eventually becoming true connoisseur of them: Maretić's major achievement, accomplished at the age of 30, in 1951 – the preparation of the first antilatrodectic serum in Europe – was certainly a result of that passion.<sup>5</sup> Besides the specialisation in internal medicine and infectology, Maretić was also awarded a diploma in tropical medicine from the Swiss Tropical and the Public Health Institute in Basel. He

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<sup>1</sup> Dekaris, Dragan (1990). Zvonimir Maretić (1921–1989), in: Požar, Hrvoje ed., *Ljetopis Jugoslavenske akademije znanosti i umjetnosti*. Zagreb: JAZU, 402–403.

<sup>2</sup> Dekaris, Dragan (1991). *Spomenica preminulim akademikima: Zvonimir Maretić: 1921.–1989*. Zagreb: JAZU, 11.

<sup>3</sup> Maretić, Zvonimir (1966). *Latrodektizam*, in: Perović Drago ed., *RAD Jugoslavenske akademije znanosti i umjetnosti, odjel za medicinske nauke*. Zagreb: JAZU, 133–157.

<sup>4</sup> Dekaris, D. (1991), 13.

<sup>5</sup> Maretić, Zvonimir (1988). *Crna udovica ipak nije bauk*. Zagreb: Stvarnost.

was among the first eighteen candidates receiving the Ph.D. degree from the University of Zagreb, with a dissertation entitled “Araneism – With Special Reference to Istria: an Epidemiological, Clinical, and Experimental Study”. A large part of his life, Maretić spent travelling, sometimes because of his work, and sometimes privately. As a WHO epidemiologist, he spent one year (1959–1960) in Sri Lanka, working on the Ceylon-38 project. He lectured at the Harvard University in 1960 and 1966. Among many societies, he also was a member of the *International Federation on Infectious and Parasitic Diseases*, *British Arachnological Society* and *Centre International de Documentation Arachnologique*.<sup>6</sup> In 1962, Maretić’s close friend and colleague, the internist and toxicologist Findlay Ewing Russell,<sup>7</sup> invited Maretić to join the founders of the International Society on Toxinology and the *Toxicon* journal Editorial Board, which Maretić gladly accepted.<sup>8</sup> A year later, Maretić started researching the Adriatic Scorpaenidae and Trachinidae and, in 1965, prepared the first weaver and scorpionfish antiserum, which was successfully applied to humans.<sup>9</sup> At the age of 43, Maretić was appointed head doctor and honorary docent at the Zagreb University Faculty of Medicine, habilitating with a lecture on *Steatoda paykulliana*, a newly discovered venomous species of spider.<sup>10</sup> Maretić also successfully balanced between the various disciplines of zoology and botany, and at the same time was an enthusiastic hunter and angler.<sup>11,12,13</sup> Art was not extraneous to him either: namely, he used to immortalise his inclination to humour in the form of caricature (figure 1). He was not only once in trouble when the political officials saw themselves pictured in his cartoons. He also painted on canvas and participated in exhibitions (“Doctors-artists”).<sup>14</sup> In 1981, Maretić became a Full Professor at the Faculty

<sup>6</sup> Dekaris, D. (1991), 17.

<sup>7</sup> Russell, Findlay E. (1989). In memoriam: Professor Zvonimir Maretić M.D., Ph. D. 1921-1989, *Toxicon*, 27(11), 1169-1170.

<sup>8</sup> Russell, Findlay E. (1987). History of the International Society on Toxinology, *Toxicon*, 25(1), 3–21.

<sup>9</sup> Matić–Piantanida D, Vidaković–Bival V, Radman V, et al. (1980) Antisera against weaver and scorpion fish venoms, in: Eaker D, Wadstrom T, eds., *Natural Toxins: Proceedings of the 6th International Symposium on Animal, Plant and Microbial Toxins*. Uppsala: Pergamon Press, 99–108.

<sup>10</sup> Požar, Hrvoje (1987). Zvonimir Maretić (biografije novih članova akademije), in: Požar Hrvoje, ed., *Ljetopis: Za godinu 1986*. Knj. 90. Zagreb: JAZU, 544–546.

<sup>11</sup> Maretić, Zvonimir (1967). Poisoning by the mushroom *Clitocybe olearia* Maire. *Toxicon* 1967, 4(4), 263–267.

<sup>12</sup> Maretić, Zvonimir (1975). *Životinje otrovnice i otrovne životinje Jadranskog mora*. Zagreb: JAZU.

<sup>13</sup> Maretić, Zvonimir (1986). *Naše otrovne životinje i biljke*. Zagreb: Stvarnost.

<sup>14</sup> Sepčić, Juraj (2015). Franjo Jelašić: Čovjek i neurolog bolji od svog vremena, Rijeka; Medicinski fakultet Sveučilišta u Rijeci, 28.

of Medicine in Zagreb and in 1985, also in Rijeka. He was a chief editor of the Istrian Health Services proceedings. Zvonimir Maretić died in Pula on April 23, 1989.<sup>15</sup>

### THE (HI)STORY OF THE SERUM

After the end of World War II, Italian medical doctors emigrated from Istria to Italy. The shortage of physicians in Pula encouraged Maretić to leave Zagreb. It was in Pula in 1948 where Maretić started the research of the then poorly understood poisoning caused by the sting of black widow spider – latrodectism<sup>16</sup> that spread all over Istria. As Maretić states,

*Latrodectus* comes from the Greek “lathrodektes” meaning “secret biter”, while *tredecimguttatus* comes from Latin and means “13 drops”, which is associated with red spots on the black widow’s abdomen.<sup>17</sup> The word latrodectism is a compound of an uncertain etymology: the first part of the compound may be from Latin (*latro, latronis*), meaning a robber or thief, or from Greek (*latra*) standing for secretly and stealthy. The extension of the second part of the Greek verb (*daknein*) explains the nature of biting. Maretić characterised latrodectism as an occupational disease in Croatia, particularly in rural areas where the population is engaged in agricultural activities, especially harvesting. The black widow’s natural habitat is precisely the dry area, the rocks and the underwood, so the spider usually hides in corn and dry bundles of twigs and crops (figure 2). Most of Maretić’s patients were stung in the areas of the thighs and forearms.<sup>18</sup> Maretić’s initial research was



Figure 1. Zvonimir Maretić’s caricature of himself as a scientist and adventurer (family archive)

<sup>15</sup> Dekaris, D. (1991), 11.

<sup>16</sup> Maretić, Zvonimir; Lebez, Drago (1985). *Otrovni pauci: Araneizam s posebnim osvrtom na Istru*. Pula: Zbor liječnika Hrvatske.

<sup>17</sup> Maretić, Z. (1966), 133.

<sup>18</sup> Maretić, Z. (1966), 133-157.

unsuccessful: initially, he exposed experimental animals to the bites of a tarantula, believing that it was a tarantula that caused neurotoxin poisoning that affected the entire organism. Eventually, he discovered that the cause of the poisoning was a much smaller spider. Maretić noticed in his experiments that the sting of the *Latrodectus* male is entirely non-venomous, while the female's bite is venomous. The spider, in general, is not aggressive at all, but bites in self-defence. Maretić performed experiments on more than 300 animals (rats, guinea-pigs, cats, mice, rabbits, dogs, etc.): in 1951, he finally successfully prepared and applied the first antilatrodectic serum in Europe.<sup>19</sup>

Centuries before, Celsus, Galen, and Ibn Sina used to prescribe hot baths, opiates, and wine in their works, which made sense due to the vasodilation effect. All kinds of rituals were applied to try to find the cure: in Croatia, recorded was the belief that persons stung by a black widow spider will be cured if they are dangled on the ropes by their nine namesakes for nine days. The dance was also used for "healing". Actually, any physical effort may have alleviated the pain. Maretić recalls examples of patients who came to the hospital by bicycle without feeling pain, but, after hospitalisation, the clinical picture worsened. Maretić subdued ten experimental rabbits to the sting of a black widow: he immunised them until they could survive 120 bites at a time. The Zagreb Immunological Institute took over the production of Maretić's serum.<sup>20</sup> A year later, Stanić prepared the antilatrodectic serum in the Zagreb Central Institute of Hygiene.<sup>21</sup>

Maretić's wife Vlasta remembers the period when they both were (then still single) employees of the Pula General Hospital. Maretić used to have a small room at the Infectology Department, where he secretly performed experiments. He had support from his colleagues, even if they had to chase mice that once escaped into the hospital corridors.

In addition to terrestrial venomous animals, Maretić also paid close attention to the marine venomous animals. He focused on the fish from the Scorpaenidae and Trachinidae families, the most venomous fish of the Adriatic, and compared their venomous apparatus to one of the spiders. In 1963, Maretić started producing and applying the serum against those fish species. It was challenging work because fish toxin has a temperature-unstable, complex chemical compound. Maretić immunised rabbits by exposing them to the venomous fish stinging. The polyvalent antiserum protected

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<sup>19</sup> Maretić, Zvonimir (1988). *Crna udovica ipak nije bauk*. Zagreb: Stvarnost.

<sup>20</sup> Ibid.

<sup>21</sup> Maretić, Z. (1966), 133-157.

guinea-pigs: in the same way, the monovalent serum against the Trachinidae venom was produced in 1965. It was the first antiserum successfully applied to eight patients.<sup>22</sup>

As a WHO epidemiologist, Maretić was sent to Ceylon (Sri Lanka). He used to recall that local doctors (even if they had studied at prestigious faculties all over the world) practiced various rituals and remained inclined to black magic. On one occasion, a person collapsed due to an epileptic seizure. Most of the present doctors ran away, suspecting the spells. Maretić was the only one to remain, along with one local doctor. Maretić first believed that the doctor stayed because he recognized the disease. However, Maretić was wrong: the doctor stayed because he had a chain with a shark's tooth as a protection against the spells.<sup>23</sup>

It was usual for wild dogs to wander around the hospital courtyard. One time, an accident occurred when a child was attacked and killed by those wild dogs. Maretić raised his voice against tolerating the dogs around the hospital, but the domestic colleagues told him it was just the "child's karma". Maretić later secretly poisoned the dogs, one after the other. When the colleagues became anxious about the situation, Maretić told them it was the "dogs' karma".<sup>24</sup>

Some 300 published papers (preserved by his family, bound and chronologically arranged from 1949 until 1984), books, and book chapters legitimise Zvonimir Maretić as a scientist of a broad range of research and knowledge. He wrote in native, English, Italian, German, and French language. His works are cited 30 years after his death, and the most cited are those published in the *Toxicon*. Within the field of epidemiology and infectology, he has published about 100 articles; on araneism, about 50, with 23 focused on latrodectism. More than 40 papers have been published on fish and the sea world, and more than 20 on other venomous animals and plants. He also studied mushrooms and published 12 papers on them. About 30 of his articles are devoted to tourism medicine he pioneered, as well as medico-historical topics, public health, hunting, etc.

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<sup>22</sup> Matić–Piantanida D. et al. (1980), 99-108.

<sup>23</sup> Anecdote of family members' memory.

<sup>24</sup> Ibid.

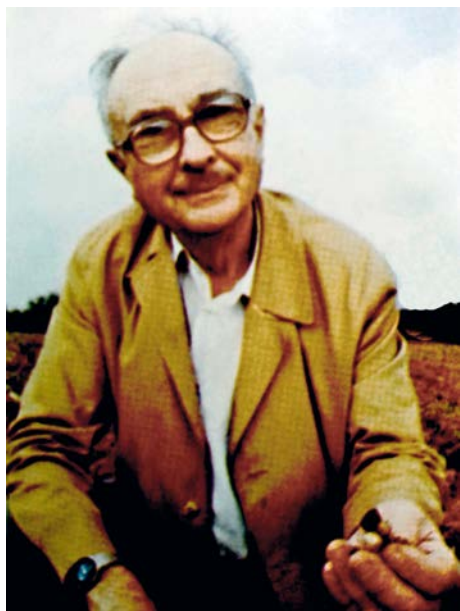


Figure 2. Zvonimir Maretić with the black widow spider<sup>25</sup>

### INTERNATIONAL SOCIETY ON TOXINOLOGY AND THE TOXICON JOURNAL

Following the basic idea of Eleanor E. Buckley, F. E. Russell continued to realise the vision of founding a society focused on animal poisons and venoms. In 1960, he sent a letter to some 20 experts all over the world, suggesting the foundation of the society and a journal. Out of 18 answers, 17 welcomed the idea (one

had not seen the sense of the proposal: eventually, he luckily changed his mind and even became one of the presidents of the Society). Among several ideas, the voted names of the society and the journal were “International Society on Toxinology” and “Toxicon”, respectively. The first president of IST became F. E. Russell and the secretary-treasurer, Paul R. Saunders. One of the founding members of the Society and a member of the first *Toxicon* Editorial Board was Zvonimir Maretić (figure 3).<sup>26</sup> With Russell, Maretić was more than just a collaborator and colleague (as well as with Erich Kaiser, the third Society’s secretary-treasurer). On the second plenary session of the 12<sup>th</sup> World Congress on Toxinology in Cuernavaca (1997, Mexico), Russell emphasised the crucial pioneering contribution of Maretić’s toxicology research, especially describing the clinical picture, prophylaxis, and the therapy of latrodectism.<sup>27</sup> Russell also used to come to Croatia many times to visit Maretić, with whom he sailed along the Adriatic and exchanged experiences on politics, fishing, and medicine.<sup>28</sup>

<sup>25</sup> Maretić, Zvonimir (1988). Crna udovica ipak nije bauk. Zagreb: Stvarnost.

<sup>26</sup> Russell, FE. (1987), 3-21.

<sup>27</sup> Sepčić, Kristina (1997). Zvonimir Maretić, suosnivač Međunarodnog društva za Toksinologiju, *Acta Fac med Flum*, 22(2), 73.

<sup>28</sup> Russell, F.E. (1989), 1169–1170.



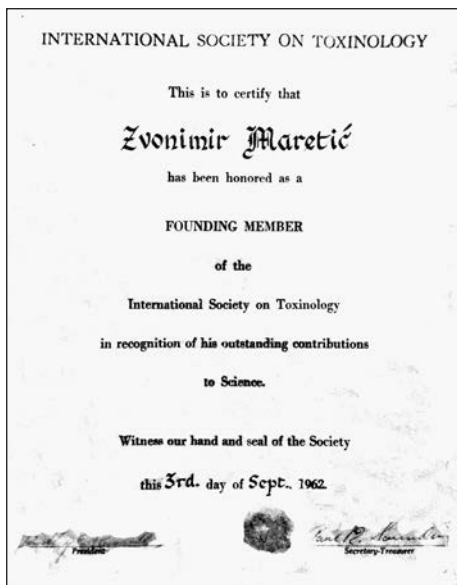


Figure 3. Founding member of IST certificate (family archive)

## CONCLUSION

Zvonimir Maretić has been rarely mentioned in the medical literature. Neglected in Croatian medical literature and European as well, he still remains to be one of the prominent figures in the history of medicine of the 20<sup>th</sup> century in Croatia and Europe. In 1951, he prepared the first anti-latrotoxic serum in Europe, and in 1962, following the invitation of F. E. Russell, Maretić joined the founders of the International Society on Toxinology and the *Toxicon* journal Editorial Board. Behind these groundbreaking professional activities, a curious

personality emerges: deeply in love with nature and all the living, Maretić was equally eager at collecting butterflies and fish species and securing antidotes to animal poisons. The major aim of the present paper is to unveil new data relating to the life and work of Zvonimir Maretić on the occasion of the 30<sup>th</sup> anniversary of his death.

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## DECLARATION OF CONFLICTING INTERESTS

The authors declare that there is no conflict of interest.

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## SAŽETAK

*Zvonimir Maretić pionir je proučavanja otrovnih životinja i biljaka, njihove toksikologije te turističke medicine. Njegovo djelo i rad principijelno je cijenjeno, ali slabo istraženo. Djelovao je u širokom području medicine i biomedicinskih znanosti: od javnog zdravstva, ekologije i očuvanja okoliša do zaštite ljudskog zdravlja u obliku epidemiologije i infektologije. Jedan je od članova i osnivača Internacionalnog društva za toksinologiju i član prvoga uredničkog odbora časopisa *Toxicon*. Prvi je u Europi priredio anilatrodektički serum i na ljudima primijenio serum protiv otrova morskog pauka. Ovaj rad nastoji komemorirati njegova dosad zanemarena i nedovoljno istražena postignuća.*

**Ključne riječi:** *Zvonimir Maretić; povijest medicine; toksikologija; protuotrov; latrodektizam*