UDK 61(091)(497.5):616-022.08/.9:611.77
Review
Received: 14 December 2007
Accepted: 20 February 2008

BEGINNINGS AND DEVELOPMENT OF ALLERGOLOGY IN CROATIA FROM 1870 TO 1970

Stella Fatović-Ferenčić

Department for the History and Philosophy of Sciences, Division for the History of Medicine, Croatian Academy of Arts and Sciences, Zagreb

Summary

Development of allergy as an immunologic and experimental phenomenon in Croatia went similar as in surrounding neighboring countries. In the present article, I describe the most important events and discoveries that led to the understanding the origin of allergy in the 1870-1970 period. The crucial moments in the development of allergology in Croatia were first linked to the production of vaccines and foundation of the Institute of Immunology and its forerunners in the first half of the 20th century. Establishment of these institutions represented a strong institutional vertical that has played a key role in the development of allergology and immunology in Croatia. The analysis of articles published in *Liječnički vjesnik* in the 1877-1977 period showed the extent to which allergology was represented and the roles of the most important figures in the field of allergology, such as internist Ivan Hugo Botteri (1876-1963), pediatrician Ernest Mayerhofer (1877-1957), and dermatovenereologist Franjo Kogoj (1894-1983), who paved the way to the scientific research and roused the interest of physicians in this medical area. However, *Liječnički vjesnik* is not representative source for the development of allergolgy for the whole analyzed time period due to the fact that since 1960-ies large part of Croatian immunologists and allergologists started to publish the best part of their results within various international publications. Gathering of different medical specialists who were interested in allergology resulted in the establishment of Allergology Section of the Croatian Medical Association in 1952. The Section played an important role in the education of a wider academic community through symposia, congresses, and seminars. The analyzed records have shown that the institutional and physicians' activities in the first half of the 20th century laid a firm foundation to modern research, subspecialties, and allergologic centers and units within different medical institutions across Croatia.

Keywords: *history of medicine – Croatia; development of allergology – Croatia; Liječnički vjesnik – allergy; 19th century; 20th century.*

Correspondence to: Stella Fatović-Ferenčić, Department for the History and Philosophy of Sciences, Division for the History of Medicine, Croatian Academy of Arts and Sciences, Zagreb, Gundulićeva 24/III, E-mail: stella@hazu.hr

The mechanism and appearance of allergic reactions have not changed over time. The biological constancy of this phenomenon is evident from many medical texts of ancient writers. There are records of asthmatic attacks and cases of hypersensitivity from Medieval times as well as later centuries. However, the key events in the development of allergology as a modern medical discipline include a series of discoveries in the 19th and 20th centuries. If we go back to the early 1800's, we find Bostock's description of hay fever from 1819 and Magendie's observations on the occasional sudden death of rabbits injected with egg albumin from 1839. Once it was shown that animals could be immunized by immune serum to the toxins produced by the diphtheria and tetanus bacilli, the attention shifted to humoral immunity. Opposing the view that resistence to the bacteria resides in the serum, a Russian pathologist Ilya Ilych Metchnikoff offered a counter theory of phagocytes, and the dispute became the scientific expression of Franco-German and Russo-Japanese rivalry [1]. At the beginning of the 20th century, the significance of early discoveries was brought into greater focus. To describe increased sensitivity to and the absence of protection against the effects of toxin in immunized animals, Richet and Portier introduced the term *anaphylaxis*. Their investigations were later continued and extended by numerous other investigators across Europe, such as Maurice Arthus, who demonstrated the possibility of inducing local anaphylaxis in rabbits, and Bela Schick and Clemens von Pirquet, two pediatricians from Vienna who recognized that the clinical features of serum sickness differed from those of infectious diseases and suggested close links between human reactions to foreign sera and experimental anaphylaxis in animals, thus paving the way to the idea of immunological basis of anaphylaxis. Various immunological research findings were given greater clarity by von Pirquet, who, in 1906, offered a semantic framework for classification and better understanding of different phenomena within the domain of immunology [2].

The key events and discoveries in the field of immunology and allergology soon resounded in Croatia. In this article, the analysis of allergology development in our geographical area in the 1870-1970 period is focused on the beginnings and development of institutionalized vaccination against infectious diseases and the earliest work of Croatian physicians published in *Liječnički vjesnik* (Table 1). Special attention is paid to the role of the most important figures in the first half of the 20th century responsible for raising the interest of medical community in immunology and allergology and paving the way for scientific research in this area.

FROM SERUM THERAPY TO SERUM SICKNESS

In Croatia as well as in Europe, the beginnings of allergology were closely linked with public health actions related to the vaccination of population. The 19th century was a period when mass vaccination and systematic antitoxin treatment brought bacterial

disease surveillance, diagnosis, treatment, and prevention closer to the center of interest. In the 1870's in Croatia, there were intensified endeavors to vaccinate population with animal vaccines and produce adequate vaccines, which culminated in the establishment of the Institute for Production of Small Pox Vaccine upon the initiative by Izidor Schlick, a county physician and city coroner, in Bjelovar in 1890. The following year, the Law on Pox Vaccination was passed in the Kingdom of Croatia and Slavonia; the first article of the Law specified that small-pox vaccination was to be performed *only with animal vaccine.* In 1893, the Royal Institute for Production of Animal Small-pox Vaccine was founded in Zagreb, joining fifteen other similar institutes that had already been established across Austro-Hungarian Empire [3,4].

At the beginning of the 20th century, the term *allergy* did not exist and neither did the knowledge about the mechanisms of that disease, today classified under the disorders of allergic or immunologic origin. Even when Clemens von Pirquet coined the word *allergy* in 1906, this nosologic concept attracted only a limited number of researchers and only to the extent related to the pathogenesis and therapy of serum sickness. Since health care priorities at that time were high child mortality, especially from infectious diseases, it is understandable that hay fever seemed a comparatively peripheral problem. In Croatia, increasing efforts were being made with respect to mass vaccination and administration of antitoxin and serum against variola and rabies, and later on against dysentery, typhus, and cholera. These activities resulted in the foundation of the first Institute for Human Microbiology and Chemistry in Zagreb in 1907, primarily due to the persistency of Ljudevit Gutschy [3,4]. However, it soon turned out that serum could have not only unwanted, but also fatal consequences for human health, as Pirquet and Schick [5] explained in length in their article on serum sickness in 1905. Croatian physicians published their experience with serum administration as well. The first one who described the consequences of antidiphtheric serum administration was Oto Müller [6]. Here is what he wrote in his article from 1912:

> *A death due to anaphylaxis after the third injection of antidiphtheritic serum*
> I had the following case. A 3-year-old child took ill with diphtheric croup in late December of 1910. It was the third attack of the disease; the first one occurred in December 1908, and the second one in March 1910. The first attack, according to the parents, was over 24 hours after the injection without any further consequences: the signs of the so-called serum sickness, *Serumkrankheit*, did not appear. How much antitoxin the child received, and how much serum, I could not learn. On the occasion of the second attack, I injected 3000 A. U. in 12 ccm of serum; in 30 hours, the serum was successful again and the child was free of disease, but 8 days later after the serum injection exanthema appeared again. The third time the disease occured at the end of the previous year, as early as 9 months after the

second attack; the peril of anaphylaxis was that much greater as the child was be injected with horse serum for the third time within the interval of only 2 years. Still hoping that the child only had pseudocroup – diphtheritic layers in the pharynx could not be observed – I tried to alleviate the stenosis with inhalations, and hot baths. But all in vain: the stenosis advanced in only three hours so much that I decided with heavy heart, warning the parents about the peril, to try with the third injection. I gave the child 2000 A. U. in 4.5 ccm of serum. The next morning, the child's breathing improved, the stenosis was smaller, the voice stronger, the pulse and sensorium relatively favorable. But around noon, there was a sudden collapse without any clearer pre-symptoms. The child managed to come to life with help of camphor, caffeine, alcohol, and heart massage, but remained soporous until the death. The pulse was between 150-160, of poor quality, breathing indeed was not stenotic anymore, but the child was nevertheless dyspnoic (40-50 breaths per minute); at 3 o'clock in the morning, 30 hours after the injection, the child passed away. We are to assume that death was caused by anaphylaxis, which developed due to reinjection of horse serum. If, namely, an animal parenterally, i.e. „outside of intestines", receives albuminate of another species, e.g., serum, than after a particular length of time, the animal develops anaphylactic disposition. If the same serum is injected at that stage, even in a negligible amount which, like the first injection, could do absolutely no harm, then the animal, after the injection of the same serum, becomes very sick, and is often killed. According to the interpretation of Ehrlich's *Seitenkettentheorie*, after the first injection of any heterologic serum, specific so-called "antikörper" are created in the organism in a significantly greater amount than what would be needed for neutralization of the antigens to the first injection. These "antikörper" circulate in blood, sometimes for many years. With the injection of the same serum, the newly formed "antikörper" couple with the antigen significantly faster and in greater extent than after the first injection. This biological process is always coupled with the decomposition of protein, a process considered to be similar to the decomposition to which the protein is subjected during digestion in the intestines, only that the decomposed protein, if it circulates in the blood, affects the organism like poison, and is therefore to be considered the cause of anaphylactic phenomenon. In our case, the alternative was as follows: either to observe calmly while the child suffocates from diphtheritic croup or to counteract diphtheria with antitoxic serum, ensuring for the amount of serum to be as small as possible to avoid the peril of anaphylaxis. As long as we do not have at our disposal a serum which originates from an animal other than horse, we cannot do anything differently in cases such as this one [6].

In those times, diphtheria was one of the greatest public health problems. The disease had a severe clinical picture, croup – mostly tonsillary – frequently occurred, and descending tracheal diphtheria was often accompanied by severe pseudodiphtheritic paralysis. The above case report written by the hand of a private practitioner, railway physician, and pediatrician in Zagreb, Oton Müller, indicates how grave a situation was for patients as well as physicians who just met with the fatal phenomenon of hypersensitivity. Serum sickness and other manifestations of allergies raised numerous questions and doubts, which became even more acute after Pirquet's attempt to provide a common semantic frame for these phenomena, so that they could be classified and investigated.

For Pirquet, the crucial question was the relationship between the immunity and hypersensitivity. He suggested the term *allergy* to designate a condition of changed organism reaction. He considered immunity and hypersensitivity mutually opposite, but closely related, manifestations of allergy and tried to prove that allergy was the result of the reaction of organism rather than the result of toxic effect of allergens. Thus he set the foundations to allergology [7].

Physicians in Croatia shared similar thoughts. Institutionalization of vaccine production and practical experience with vaccine administration in Croatia were fertile soil for the development of immunology, at the time a discipline in its formative stage, as illustrated in the article published by Ljudevit Gutschy in *Liječnički vjesnik* in 1908, intended to inform a wider readership on the role of immunology in the development of medicine [8]. On the other hand, the rapid evolution of biochemistry made studies in chemical properties of antibodies and nature of the antigen-antibody bond a rewarding research subject. Studies into specificity of immunological reactions brought immunology closer to the more advanced disciplines, such as chemistry. A series of articles by Fran Bubanović, published in 1913, are a good illustration of this statement. In these articles, the author describes the multiplicity of attitudes toward the area and role of immunochemistry, summing them up as follows [9]: *From this discussion it may be learned that studies in an interesting and important field of serotherapy and science of immunity have yielded several theories, in addition to abundant material, related to close observation of experimental data, the theories that are conveniently called* ***immunochemistry.*** *Quantitative examination of experimental material, first introduced by Paul Ehrich, is the basis of immunochemistry. The diversity of the aforementioned theories, as well as contradictive experimental data, have its roots in the lack of knowledge about chemism and lability of substances, which are activated during immunochemical reactions. But in the end, we must admit that despite all the difficulties and complicated circumstances, we somewhat managed to take a glance at the quantitative situation in the field, so there is no doubt that, with advancement in all branches of life sciences coming into contact in this important field, the first steps will continue further and*

even deeper into area of serotherapy and science of immunity. Equally justified is the hope that the scientific work in this field will be crowned with practical results that can be successfully used in the field of therapy [9].

Considering all said above, we would expect to find an increasing number of case reports on hypersensitivity. However, there were only two from early decades of the previous century, published in *Liječnički vjesnik*. In addition to the aforementioned article by Oton Müller from 1923, written by Dr. Aleksandar Stangl, physician in Vukovar county entitled ***An interesting case, serum anaphylaxis*** [10].

FROM REVIEW ARTICLES TO SCIENTIFIC RESEARCH

Pirquet's neologism was not well received by his peers. In 1912, Charles Richet, who received the Nobel Prize in 1913 "in recognition of his work on anaphylaxis," suggested that the term was redundant. But, dismissals of von Pirquet's formulation proved premature. Certain reservations toward the use of the term *allergy* were evident in writings of Croatian medical writers. If we look at the chronological sequence of articles on allergies published on the pages of *Liječnički vjesnik* (Table 1), we can see that the first two review articles carry the title *Anaphylaxis* [11,12]. By listing individual case reports on hypersensitivity from the literature, Bogomil Kohout writes: *This complex of symptoms, which sometimes appeared after repeated injections of different sera, was called after Richet – anaphylaxis*. He further states that the absolute immunity for revaccination can never be obtained and that the reaction always appears. In the same article, he introduces the readership to the results of experiments on guinea pigs, which were performed by Arthus (Arthus' phenomenon), Rosenau, Anderson, Smith (Smith's phenomenon) and others, and writes about passive and active anaphylaxis, emphasizing that passive is shorter and lasts 13-15 days. Anaphylaxis can be inherited by offspring and is as Kohout writes, *a blood sister to immunity and they sprout together. When an organism has become immune to a disease, it has also acquired hypersensitivity against a protein (serum)* [11]. Both articles seem to be reviews leaning exclusively on the results of experimental and clinical research of foreign authors. It is understandable, especially if we take into account the fact that before 1920's, there was no original research performed in our country. The beginnings of such research may be traced back to 1920's, to research pioneers and founders of different clinical disciplines, such as internist Ivan Hugo Botteri (1876-1963), pediatrician Ernst Mayerhofer (1877-1957) and dermatovenereologist Franjo Kogoj (1894-1983). Botteri was one of the first to introduce skin test to diagnose echinococcus. Ernst Mayerhofer, Pirquet's student, worked on allergy in children, and Franjo Kogoj was interested in manifestations of hypersensitivity in skin and venereal diseases. The first extensive work on allergy signed by the two contemporaries, Botteri and Mayerhofer, appeared on the pages of *Liječnički vjesnik* already in the twenties and thirties of the 20th

PAPERS ON ALLERGY PUBLISHED IN LIJEČNIČKI VJESNIK 1877-1977

No	Year	Author	Article title
1	1912	Muller O.	A death due to anaphylaxis after the third injection of antidiphteric serum
2	1916.	Kohout B.	Anaphylaxis
3	1917.	Bujwid O.	Anaphylaxis
4	1922.	Botteri I. H.	On anaphylaxis by echinococcus
5	1923.	Botteri I. H	Anaphylaxis in Internal Medicine
6	1923.	Botteri I. H.	On anaphylaxis by echinococcus
7	1923.	Stangl A.	Interesting case of anaphylaxis
8	1925.	Botteri I. H.	On anaphylaxis by echinococcus
9	1927.	Berlot J.	Mechanism of anaphylaxis in blocked animal
10	1928.	Mayerhofer E. Lypolt-Krajanović M	Erithema toxicum neonatorum-Leiner as a main symptom of allergy of newborn
11	1929.	Mayerhofer E.	Infectious diseases in children and their realtion to Pirquet's term of allergy
12	1930.	Mayerhofer E.	News about allergy and the allergic syndrome of newborn
13	1931	Vuletić V.	Diagnosis and therapy of allergies with particular emphasis to hay fever and asthma
14	1932.	Franković V.	Drug hypersensitivity
15	1935.	Winter-Grossmann Š.	Idiosincrasis against cow milk
16	1940	Kogoj F.	Treatment of drug eritrodermias
17	1940.	Stein B.	Allergic syndrom of intestinal tract and its healing with efedrin and fenilizopropilamin
18	1941.	Banić M.	About allergy
19	1942.	Čajkovac Š.	About so far unknown alergoderma with broncial asthma
20	1946.	Stern P.	About new antihistaminic and their mechanisms
21	1948.	Skrivaneli N.	Syndrom allergicum neonatorum (Mayerhofer)
22	1948.	Grobelnik I., Pansini K.	Penicilin as cause of allergy
23	1949.	Forenbacher G.	Dermatitis caused by streptomycin sensibilization
24	1952.	Marchionini A.	The problem of allergy in Dermatology
26	1953	Milojević B.	Therapy of allergic rhinitis with cortisone
27	1959.	Lopašić R.	Alergie in Neurology
28	1960.	Čupar I.	The importance of alergic manifestations in mouth
29	1962.	Radonić M.,Čepelja Z.	Granulocitopeny caused by gralipirin and penicilin anafilaxis
30	1962.	Puretić Š.	The first Congress of allergologists in FNRJ
31	1963.	Mimica M, Babić D., Kohler-Kubelka N., Volarić-Mršić I.	Pollinosis
32	1963.	Horvat Z., Marinšek-Broz V., Čičin-Šain Š.	Gastrointestinal Food Allergy under the Clinical Picture of Malignant Tumour
33	1963.	Kalačić I.	The fifth alergological congress
34	1963.	Vurdelja B.	Pollinosis Calendar
35	1964.	Šakić D.	Allergie Recurrent Palpebral Oedema in Children
36	1965.	Čvoriščec B.	Skin tests in allergic patients
37	1966.	Rumbolt Z, Juretić M.	Basophil Degranulation Test in Penicilin Sensitivity
38	1967.	Krstulović S.	Allergie Recurrent Palpebral Oedema in Children with Eosinophilie Meningitis
39	1968.	Periš Z.	Dermatitis Contacta Allergica Medicamentosa
40	1970.	Krmpotić-Nemanjić J, Keros P.	Allergic Rhinitis
41	1972.	Knežević M .	Therapy of allergic manifestationsof respiratory system with gamma globulin
42	1974.	Kolbas V .	Present day child allergology in Croatia
43	1975.	Kolbas V.	The fifth meeting of allergoslogists of Yugoslavia
44	1975	Kolbas V., Pansini K.	Clinical testing of Indulian in hay fever in children
45	1976.	Kolbas V.	The fifth Congress of allergosogists
46	1976.	Šrenger Ž	A combined treatment of allergic conjunctivitis
47	1977.	Paleček I.	Clinical evaluation of penicilin hypersenitivity by PPL test

century, whereas the work of their younger colleague, Franjo Kogoj, was published in the same journal in the 1940's and in greater extent in other journals or group publications.

BOTTERI, MAYERHOFER AND KOGOJ – BEGINNINGS OF RESEARCH IN ALLERGOLOGY IN CROATIA

Having finished medical school in Vienna in 1901, Ivan Hugo Botteri spends a year in Vienna clinic of internal medicine and then moves back to Croatia, where he starts working as a physician at the Regional hospital in Zadar in 1902. In 1910, he becomes a *primarius* at the Regional hospital in Šibenik, then Head of the Department of Tuberculosis, and then the hospital director in 1915. In 1922, he arrives to Zagreb, where he assumes the position of Head of Department of Tuberculosis at Sisters of Mercy Hospital. After he was habilitated in 1923, he became a honorary professor of internal propaedeutics at Zagreb University School of Medicine. From 1934 to 1936, he run the Department of Internal Medicine in Foundation Hospital in Zagreb; in 1936, he was elected a full-time professor at Zagreb University School of Medicine and Head of Department of Medicine. Botteri was one of the fathers of internal medicine in Croatia. He published many works in the field of pneumophtysiology, hematology, cardiovascular pathology, gastroenterology, and diagnosis and therapy of Mediterranean subtropical diseases [13].

While he was working in Šibenik hospital, he conducted and published research related to echinococcosis [14,15]. He published his work on sensitization of a man to echinococcal antigen, transfer of the allergy onto another person, and desensitization by intravenous administration of the same antigen in local and international journals [16-19]. As early as 1923, Botteri prepared echinococcal antigen – a preserved hydatid liquid from an echinococcal cyst, which can be used in testing allergies to echinococcus. He was also the first to perform experimental investigation and describe anaphylactic shock caused by echinococcal antigen, otherwise known as *Casoni-Botteri reaction*. He discovered latent eosinophilia as a sign of the existing allergy to echinococcal antigen and tried to use it in therapy. He investigated the mechanism of penetration of echinococcus into bronchi and designed a diagnostic skin test to distomiasis [20].

Botteri's interesting understanding of the notion of allergy and anaphylaxis was published under the title *Anaphylaxis in Internal Medicine* [17]. Here is an excerpt from the article:

> So, step by step, we have arrived to the notion of anaphylaxis as we understand it today, which allows us to articulate quite a firm definition despite some exsisting differences in opinion among researchers. Here is the definition: *In capite*, there is the word ***allergy,*** which quite conveniently does not say anything more than the reactivity of an organism has changed,

> without prejudicating anything further. This allergy may be related to antigen and non-antigen substances: the main representatives of allergy, in the latter case, are idiosyncrasies to medications, as forms of hypersensitivity. There is also another form – reduced sensitivity. What interests us here the most is the former form of allergy, the one directed at antigens. In this form of allergy, we have two fundamentally different forms of antigens: toxins, which are primarily toxic, and protein antigens, which are not primarily toxic. In the organism toxins elicit production of antitoxins, which act without a complement; protein antigens, on the other hand, elicit the production of anti-substances, which are active only in combination with complement binding. As a result of antigen-anti-substance reaction, reduced sensitivity (antitoxic immunity) develops typically in the former case, whereas in the latter case, hypersensitivity develops. It is the hypersensitivity to protein antigens that is, *sensu stricto,* called– anaphylaxis. Both forms can be passively transferred. There are atypical forms of this reaction, which cannot be passively transferred, for example, the hypersensitivity to toxin in the former case, and anaphylaxis in the latter case. We are going to deal with atypical anaphylaxis in the strict sense of the word, i.e. with hypersensitivity to protein antigens (anaphylactogens) [17].

During the 20th century, not only did the steady growth of immunologically-mediated diseases attract increasing attention from scientists and clinicians, but the term *allergy* also became widely accepted. In our geographical area, Ernest Mayerhofer, student of the coiner of this word, was a typical representative. His research laid the foundation to scientific research into allergies in pediatrics. He observed that the process of biological allergization of a newborn occurs by constant passage of protein substances by placental blood from the mother to the fetus, especially during the last months of pregnancy. According to Mayerhofer, all biological allergic reactions may be classified into four groups: skin, gastrointestinal, genital, and other benign reactions. The first group comprises *erythema toxicum neonatorum*, (*Leiner –Moussous-Mayerhofer*). He set the age limit for biological allergization of a newborn to the 42nd day of life, because biological changes in the body of a newborn may appear until that time. All these achievements are included in a chapter titled *Allergic syndrome in newborn – Mayerhofer* in the famous Mayerhofer's pediatric textbook [21]. In that chapter, Mayerhofer explains how his observation of Leiner's rash in newborns, as well as his opinion that the rash is of allergic nature, prompted him to look for one single cause to all similar and, at the time, known phenomena, which partly carried the name "pregnancy reaction". As early as 1925, he announced that many of these phenomena could be present in one and the same newborn simultaneously, appearing gradually one symptom after the other, and

how he *often had the chance to establish simultaneous existence of toxic exantema, vaginal bleeding, and swollen breasts* [21-23]. Mayerhofer clearly understood that allergic syndrome in newborns included not only *erythema toxicum* as the main symptom of general allergy, but also many other symptoms, such as peripheral swelling of lymph glands, hypereosinophilia, and initial leukopenia with leukopenic tumor of the spleen *(Mayerhofer-Lemež)*. His list of symptoms also included the reactions of smooth muscles, transitory diarrhea, traces of blood in the stool or even melena, bleeding from the uterus, famous "pseudowasserman's reactions," and some particular characteristics of vaccine reaction in newborns [21-24]. What seemed different was the same, and Mayerhofer managed to raise interest in research in the field of allergies and gather a group of young investigators. He himself stated that further improvement of allergic symptomatology in newborn occurred due to research performed by his student, L. Lemež, who found absolute eosinophilia in the blood of newborns and allergic leukopenia analogous to leukopenia in serum disease, which was first found by Bianka Bienenfeld [23]. The list of researchers later included the names of Niko Skrivaneli, Mayerhofer's successor, internist Vinko Vuletić, and pediatrician Branko Dragišić [24].

The third stronghold in the development of allergology in our geographical area doubtlessly belongs to Franjo Kogoj (1894-1983), Head of the Clinic for Skin and Venereal Diseases in Zagreb (1927-1965). It was due to his efforts that the laboratory for allergies, an outpatient office for professional diseases, and a laboratory for medical biochemisty were established in 1948 at the Clinic. Albin Brnobić whose later interest was especially dedicated to allergies became their first Head [25,26]. Kogoj introduced a *critical moment* as an objective criterion for evaluation of the time needed to cure syphilis and superimposed epidermal reaction as a diagnostic method. He gave a final definition of Mljet disease and introduced a histological novelty in the world dermatovenereologic literature – *spongiform pustule* [27-29]. More about his role within the development of allergology in Croatia can be found elsewhere.*

ALLERGOLOGY RESEARCH: OPENING COMMUNICATION AMONG DIFFERENT MEDICAL FIELDS

In addition to serum sickness, anaphylaxis was rapidly implicated in the pathogenesis of hay fever (1906), urticaria (1907), food idiosyncrasies and eczema (1908), asthma (1910), hypersensitivity to aspirin (1912), reactions to bee stings (1914), and a variety of non-specific clinical manifestations. The impact of this was to stimulate the recognition and aggregation of a constellation of previously disparate conditions increasingly referred to as *allergic disorders*, in which the clinical and pathological manifestations were generated by the patient's immunological (allergic) idiosyncrasies rather than by the allergen itself [2].

Accordingly, if we follow the course of the development of allergology on the basis of the titles of articles published in *Liječnički vjesnik,* we can see that, in the early 1930's, authors wrote on diagnosis and therapy of asthma and pollenosis, hypersensitivity to medications, and sensitivity to food. As the administration of specific therapy, especially antibiotics, became a regular practice in 1940's, the number of reports of hypersensitivity to medication, especially to penicillin, started to increase (Table 1). A line of thinking linked to the public health mouvement of the period aimed to incorporate questions of employment and life stile thus profesional diseases were on their way to establish a place for themselves. Profesional alergic dermatosis attracted interest of variety of physicians such as Dušan Jakac who pioneered in founding dermatovenerology as an academic discipline in Rijeka [30,31]. Having in mind current problems and hazards of industrialization Andrija Štampar then president of Yugoslavian Academy of Sciences and Arts (YASA) proposed the foundation of Institute for Industrial Hygiene in 1947 later called Institute for Medical Research and Occupational Health in Zagreb, whose activities have been directed towards study of effects of chemical and physical agents upon human health. In the beginning its work was mostly concentrated on the effects of occupational exposure on worker's health but later, it gradually expanded to studies of environmental exposure of the general population [32]. Among the earliest publications considering occupational hypersensitivity which appeared in Liječnički vjesnik was one written by Tihomil Beritić describing the relationship between hypersensitivity to flour and chronic bronchitis in bakers [33].

In 1950's, the interest in allergy spread across many other fields of medicine and there was almost no clinical or other area where, at the time, allergology research was not performed or at least a case report published. It was in those times that he need arouse for synthesizing knowledge and opening communication among different medical fields. In result and upon Kogoj's initiative, the Yugoslav Academy of Science and Arts organized a symposium on allergy in 1951. The symposium lectures were published in the works of YASA the following year [34], when the Allergology Section of Croatian Medical Association was founded as well, with Franjo Kogoj elected the president and Štefanija Puretić the secretary [35].

The fact important for the development of allergology in Croatia was that Drago Ikić had run the newly-opened Department for Control and Testing of Sera and Vaccines. Actually when the Institute for Control and Testing of Immunologic Preparations and Serovaccination Institute were separated from the Central Hygiene Institute, Ikić became the director of the former (by the Decision of the Council of the Public Health dated May 16th 1956) and director of the latter (by the Decision of the Council of the Public Health dated Jun 25th 1956) [36]. Serovaccination Institute changed the name into Institute of Immunology in 1961 and merged with the Institute for Control and Testing of

Immunobiological Preparations in 1969. Drago Ikić was directing the Institute of Immunology for 21 years, from 1961-1982 [37]. In these institutions, a special attention was paid to the production of allergens for testing and desensitization, a procedure first performed by Neda Keler-Kubelka, who earned her PhD degree in 1964 by defending the thesis titled, *Testing of pollen allergens by different immunologic methods and analysis of the value of these methods for standardization of allergens*, and published a series of works in this field [37]. In the same year another PhD thesis was completed in this field by Dragan Dekaris entitled *The Effect of antiserum antibody injection in rats.* Further on Dragan Dekaris has successfully applied the results of basic into clinical immunology and allergology [38], has established the Croatian Referral Center for Clinical Cellular Immunodiagnostic [39], and published the first book on basic allergology [40]. During different periods he obtained the role of Head of Section (1971-1982), Head of Department (1982-1992), Scientific Director (1992-1994), Vice-Director (1994-1997), Head of Department for Research and Development of the Institute of Immunology. Generally, the Institute of Immunology offered a strong support to the technological and research development in the field of allergology. At the same time, it provided education and stimulation to a long range of experts specially interested in allergology, as it does so today.

The spread of interest in allergology influenced its penetration into different medical fields during the second half of the 20th century, and specialized units for allergology were being opened within Croatian hospitals as well as research and medical centers. In 1958 in Dubrovnik (Lapad) the Climatic Centre for recovery and curing of the respiratory diseases was opened. In the beginning only one physician Željko Radić was in charge of making intra-cutane tests on inhalation and nutritive allergens, but this early beginnings of allergology in Dubrovnik were followed up by work of Nikša Sindik and Ivo Kalačić in the later periods. In the 1962 the special hospital for allergic diseases was established in Dubrovnik regularly supervised by reputable experts of the field Milorad Mimica and Tihomil Beritić. In its laboratories tests on group and specific antigens as well as provocation tests were performed. Very noticeable is the foundation of the Pulmology and Allergology Unit of Dr. Josip Kajfež Hospital Internal Clinic, established by internist and one of the prominent pioneers of allerollogy Milorad Mimica in 1963. Its first Head was Branimir Čvorišćec succeeded later by Ivan Paleček and Zdenko Tuđman. The Unit was the leading institution in Croatia oriented in development of clinical allergology as well as *in vitro* and *in vivo* diagnostics and therapy. In its immunological laboratory established by Neva Sket-Janković the first IgE antibody test was completed in this part of Europe as well as the first biological standardization of allergens and RAST inhibition [41,42]. In the Institute for Protection of Mother and Child, Head of Allergology Department was a pediatrician, Vladimir Kolbas, whose interest lay in syndrome of agammaglobulinemia, respiratory allergies in childhood,

immunoallergic aspects of idiopathic pulmonary hemosiderosis, dynamics of neurovegetative response in atopic diathesis in children. We also have to mention the work of the founder of the Department of Immunology and Head of Pediatric Pulmonary Department at Zagreb University Hospital Center, Drago Buneta.

Allergies gradually attracted interest even of physicians in surgical specialties, like Ear, Nose and Throat specialists Željko Poljak and Zvonimir Krajina at the ENT Clinic of Zagreb University School of Medicine. Željko Poljak's earned his PhD degree in the field of allergology, his PhD thesis titled *Rhinitis Allergica and Infection of Nasal Mucosa* in 1969, and the topic of his habilitation lecture that he held at Zagreb University School of Medicine in 1971 was *Problems of Aerosol Therapy in Rhinology*. He was the Secretary of the Association of Allergologists of Yugoslavia and the Secretary of the Allergology Section of the Croatian Medical Association. There was almost no medical discipline where the names of researchers in the field of allergology could not be found. Their work certainly deserves much deeper attention, but it would go much beyond the scope of the present article.

In 1961, the congress of allergologists of Yugoslavia took place in Zagreb; in 1962, a professional meeting of allergologists of Yugoslavia was held in Dubrovnik; and in 1964, followed an International Symposium in Allergology in Zagreb, Split, and Hvar. In the fall of 1964, at the 3rd Congress of Croatian Physicians held at "Dr Josip Kajfeš" hospital and Clinic of Dermatovenereology in Zagreb, the first seminar in allergology was held under the title "Basics of clinical allergology". The seminar was attended by 25 participants. In 1966, Zagreb branch and Allergology Section of the Croatian Medical Association held a panel discussion on *Allergy for Practitioners*. In 1967, Allergology Section of Croatian Medical Association also organized counseling of allergologists in Croatia at the republic level, and in May of the same year, a symposium on allergic diseases of respiratory system on the island of Hvar, and since 1973, a journal *Glasilo alergološkog centra JAZU* (The Journal of Allergology Center of YASA) has been published in Hvar . We also have to mention the establishment of health care institutions for treatment of allergic diseases at the Adriatic coast, in Dubrovnik, Veli Lošinj, Hvar, and Baška Voda [35].

Liječnički vjesnik used as a main source for interpretation of allergoloy development in Croatia is not, however, representative source of the allergology development for the whole analyzed time period particularly for the reason that since 1960-ies large part of Croatian immunologists and allergologists started to publish the best part of their results within various international publications. The second half of the 20th century witnessed a strong takeoff in the field of allergology, a medical field that had clearly defined its scope and goals in the previous decades and established a fruitful cooperation between basic and clinical research. In Croatia those developments have gained a considerable

scientific importance since second half of the 20th century particularly when the work of Nikša Alegretti, Borislav Nakić and Vlatko Silobrčić have gained a considerable scientific importance and become internationally well-recognized (44-47). In 1970's, the phenomenon of immunity took the central place in biomedicine and became a meeting point of cell biologists, immunochemists, genetics, and molecular biologists, announcing a new stage in research and development of allergology.

References

[1] *Porter R. Porter R.* The greatest benefit to mankind. New York, London: W.W. Norton&Company; 1999.

[2] *Jacksom M.* Allergy and History. Stud. Hist. Phil.&Biomed.Sci. 2003; 34: 383-98.

[3] *Berlot J.* Razvitak mikrobiologije i imunologije u Hrvatskoj do 1923.god. U: Topolnik E. (ur) I simpozij o historiji mikrobiologije i imunologije u Hrvatskoj do 1923.godine. Zagreb: JAZU 1973.

[4] *Belicza B.* Od proizvodnje animalnog cjepiva za zaštitu od velikih boginja do proizvodnje prvih humanih virusnih cjepiva, antibakterijskih preparata i antitoksičnih seruma, te osnivanje prvog odjela za proizvodnju lijekova biološkog podrijetla u zagrebu. U: Vranešić B. (ur) Od «Kraljevskog zemaljskog zavoda za proizvadjanje cjepiva proti boginjam» do Imunološkog zavoda Zagreb 1893-1993. Zagreb: Imunološki zavod; 1993.

[5] *Pirquet C., Schick B. Serumkrankheit*. Leipzig: Deuticke 1905.

[6] *Miller O.* Slučaj smrti uslijed anafilakse iza trećega uštrcavanja antidiftericnoga surutka. Liječ Vjesn 1912;34:55.

[7] *Silverstein AM.* Clemns Freiherr von Pirquet : a pediatrician explains immune complex disease in 1906.

[8] *Gutschy Lj.* Pregled novijih radnja i teorija u nauci o imunitetu. Liječ Vjesn 1908; 30:335-38.

[9] *Bubanović F.* Savremeno stanje imunokemije Liječ Vjesn 1913;35:214.

[10] *Stangl A.* Zanimiv slučaj serum anafilaksije Liječ Vjesn 1923;45:369.

[11] *Kohout B.* Anafilaksija Liječ Vjesn 1916;38:4-12.

[12] *Bujwid O.* Anafilaksija Liječ Vjesn 1917;39: 347

[13] *Dugački V. Botteri Ivan Hugo.* Zagreb: Jugoslavenski leksikografski zavod «Miroslav Krleža» 1989. sv. 2 str. 215-16.

[14] *Botteri I. H.* O mehanizmu prodora plućnih ehinokokovih cista u bronhe. Liječ Vjesn 1938;60:1-3.

* The paper on Franjo Kogoj will be given by professor Jasna Lipozenčić, pp 53-66

[15] *Botteri I. H .* O nekim problemima endemične ehinokokoze kod nas. Liječ Vjesn 1953;75:99-101.

[16] *Botteri I. H.* Referat prethodnog izvješća o ehinokokovoj anafilaksiji. LiječVjesn 1922;44:64-67.

[17] *Botteri I. H.* Anafilaksija u internoj medicini Liječ Vjesn 1923;45:230 -31.

[18] *Botteri I. H.* O ehinokokovoj anafilaksiji Liječ Vjesn 1925;47:185-196.

[19] *Botteri I. H.* Serologija ehinokokove bolesti 1930;52:591-610.

[20] *Botteri I. H.* Distomatoza. Liječ Vjesn 1935;57:196-99.

[21] *Mayerhofer E, Dragišić B.* Pedijatrija (II izd.). Zagreb: Nakladni zavod Hrvatske 1948; p. 321.

[22] *Mayerhofer E.* Općenitosti o infekcioznim bolestima djeteta i njihov naročiti odošaj prema Pirqetovom pojmu alergije. Liječ Vjesn 1929;51:410-433.

[23] *Mayerhofer E.* Nove radnje o alergiji i moj alergični sindrom novorodjenčadi. Liječ Vjesn 1930 52:345-49.

[24] *Skrivanelli N.* Syndrom allergicum neonatorum (Mayerhofer). Liječ Vjesn 1948;70: 3-9.

[25] *Lipozenčić J, Čikeš N, Marinović B.* (ur.) Katedra za dermatovenerologiju Medicinskog fakulteta Sveučilišta u Zagrebu. Medicinski fakultet Sveučilišta u Zagrebu: Zagreb; 2006.

[26] *Fatović-Ferenčić S.* The Chair of Dermatovenerology at Zagreb School of Medicine. On the occasion of the 80th anniversary of its foundation (1921-2001). Acta Dermatovenerologica Croatica 2001;9:267-273.

[27] *Holubar K.* Franjo Kogoj and the spongiform pustule. Am J Dermatopathol 1985; 7:191-195.

[28] *Dobrić I, Miljević A* et al. Psoriasis Pustulosa:Classification and Light Microscopy. Seventy Years of Kogoj's Spongiform Pustule: 1927-1997. Psoriasis 1997; 39: 6-9.

[29] *Fatović-Ferenčić S, Holubar K.* Mal de Meleda: From legend to Reality. Dermatology 2001;203:7-13.

[30] *Fatović-Ferenčić S.* Dušan Jakac. Hrvatski biografski leksikon Zagreb: Leksikografski zavod «Miroslav Krleža» 2005. sv. 6 p. 240-41.

[31] *Fatović-Ferenčić S, Lipozenčić J.* Dušan Jakac: The Life in Dermatovenerology. Acta Dermatovenrologica Croatica, 2003;11:35-38.

[32] *Reiner E, Banić N.* Institute for Medical Research and Occupational Health Zagreb 1948-1993. Zagreb: IMI; 1994.

[33] *Beritić T, Valić F.* O odnosu preosjetljivosti na brašno i kroničnog bronhitisa u pekara. Liječ Vjesn 1971;93:991-96.

[34] *Kogoj F.* (ur) Simposion o alergiji. Zagreb: JAZU; 1952.

[35] *Mimica M.* Alergološka sekcija. U: Keros P. (ur) Zbornik Liječnika Hrvatske; Zagreb: ZLH 1974.

[36] Archive of the Institute for the History of Medicine of the Croatian Academy of Sciences and Arts – original document donated by Drago Ikić.

[37] *Pende B.* Prilog novijoj povijesti Imunološkog zavoda. U: Vranešić B. (ur) Od „Kraljevskog zemaljskog zavoda za proizvadjanje cjepiva proti boinjam „ do Imunološkog zavoda Zagreb 1893-1993. Zagreb: Imunološki zavod 1993; p 73.

[38] *Fauve R. M., Dekaris D.* Macrophage spreading: Inhibition in delayed hypersensitivity. Science 1968;160:795-96.

[39] *Dekaris D.* Founding and activity of the Croatian Referral Center for Clinical Cellular Immunodiganostic. Rad Hrvatske akademije znanosti i umjetnosti 1994; 466:51-64.

[40] *Dekaris D.* Temeljna alergologija. Zagreb: Školska knjiga 1983.

[41] *Paleček I, Čvoriščec B, Lipozenčić J.* Povijest internističkih struka u Hrvatskoj. Zagreb: AMZH 1998;95-105.

[42] *Bušić M.* Opća bolnica Sveti Duh. Zagreb : Opća bolnica " Sveti duh"; 2006.

[43] *Poljak Ž.* Doprinos otorinolaringologa alergologiji i kliničkoj imunologiji. U: Krajina Z, Poljak Ž. (ur) Otorinolaringologija u Hrvatskoj. U povodu 80. obljetnice osnutka prve ORL klinike u Hrvatskoj. Zagreb: Klinika za otorinolaringologiju KBC-a u Zagrebu; 2001, pp. 107-8.

[44] *Silobrčić V.* Forty years of Transplantation immunology in Croatia. Period biol 97:167-170.

[45] *Silobrčić V.* Boris Nakić začetnik transplantacijske imunologije u Hrvatskoj: Liječ vjesn 1982;104:140-142.

[46] *Dekaris D.* Nikša Alegretti (1920-1982) U: Ikić D. (ur) Spomenica preminulim akademicima vol. 21, Zagreb: JAZU 1984, p.39.

[47] *Dekaris D, Čulo F.* (ur) Klinička imunologija u nas. Zagreb :JAZU&Naprijed 1990 pp. XXVI and 590.

[48] *Rabatić S.* Croatian Immunological Society – 30 years of organized activities. Immunology Letters 2000;73:23-7.

Sažetak

Početak i razvoj alergologije u Hrvatskoj u razdoblju od 1870. do 1970. godine

Razumijevanje podrijetla alergije kao imunološkog i eksperimentalnog fenomena, odvijalo se na području Hrvatske slično kao i u bliskim europskim zemljama. Najvažniji događaji i otkrića prikazani su u ovom radu za razdoblje 1870-1970.godine.

Pokazalo se da su ključni momenti razvoja alergologije u nas, isprva bili vezani uz proizvodnju cjepiva te nastanak Imunološkog zavoda i njegovih preteča, tijekom prve polovice 20. stoljeća. Utemeljenje ovih ustanova predstavljalo je čvrstu institucijsku vertikalu presudnu za razvoj alergologije i imunologije u Hrvatskoj sve do danas. Raščlambom radova objavljenih na stranicama Liječničkog vjesnika za razdoblje 1877-1977. prezentirana je zastupljenost alergoloških tema te uloga pojedinih najznačajnijih ličnosti. Ovi radovi, međutim, ne daju potpunu sliku alergologije u Hrvatskoj osobito od 60. godina 20. stoljeća nadalje, kada naši autori veći dio svojih istraživanja objavljuju u međunarodnim časopisima. Istaknuta je uloga interniste Ivana Huga Botterija (1876-1963), pedijatra Ernesta Mayerhofera (1977-1957) i dermatovenerologa Franje Kogoja (1894-1983), koji su svojim radom utrli put znanstvenoistraživačkom radu te uspješno poticali interes za ovo područje.

Objedinjavanje interesa za alergologiju stručnjaka različitih medicinskih specijalnosti rezultiralo je osnutkom Alergološke sekcije Zbora liječnika Hrvatske 1952.godine. Ova je udruga odigrala daljnju važnu ulogu osobito u edukaciji šire akademske zajednice organizacijom simpozija, kongresa i seminara.

Pokazalo se da je rad institucija i liječnika tijekom prve polovice 20. stoljeća, dao čvrst temelj suvremenim istraživanjima, oblikovanju subspecijalnosti te nastanku alergoloških centara i jedinica unutar različitih medicinskih institucija diljem Hrvatske.

Ključne riječi: Povijest medicine– Hrvatska; razvoj alergologije –Hrvatska; Liječnički vjesnik – alergija; 19. stoljeće; 20. stoljeće

** Acknowledgement: I appreciate help of Professors Drago Ikić, Dragan Dekaris, Branimir Čvoriščec, Željko Poljak and Nikša Sindik

*** This research was part of the project Croatian medical identity and its European context supported by the Ministry of Science and Technology of Republic of Croatia.