The Influence of Academician Franjo Kogoj on Global Dermatology

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ABSTRACT

Academician Franjo Kogoj graduated medicine in 1920 in Prague, where he then pursued training in dermatovenereology. During later years, he also visited other dermatology clinics in Europe, where he collaborated with renowned dermatologists of the time, such as in Breslau (present day Wroclaw in Poland) with Josef Jadassohn and in Strasbourg with Lucien-Marie Pautrier. He was also active in the famous Saint-Louis hospital in Paris. Academician Kogoj’s scientific interests were especially focused on allergies, exanthemas, skin tuberculosis, and keratoderma. Kogoj was very active in defining a precise and useful terminology for various dermatological conditions, where the terminology was in many ways confusing and often overlapping, such as in cases of eczema and dermatitis. Kogoj performed experimental studies of allergic reactions in eczema and atop dermatitis and introduced the term pruridermatitis (Pruridermatitis allergica chronica) into dermatological terminology instead of the name neurodermitis and other synonyms essentially describing atop dermatitis (endogenous eczema, prurigo-asthma, prurigo Besnier). Academician Kogoj managed to define Mal de Meleda as a separate form of hereditary keratoderma and was engaged in the clinical symptomatology, serology, and therapy of syphilis, whereby he emphasized the so-called “critical moment” in the treatment of syphilis. Academician Kogoj’s most famous scientific achievement was his histological definition of the spongiform pustule in the pathomorphology of psoriasis, which became a groundbreaking histological novelty in the classification of psoriasis, thus bearing Kogoj’s name in the medical literature to this date. Academician Kogoj published many scientific and professional articles, books, monographs and contributions to manuals and textbooks. He was honored nationally as well as internationally as a leading expert in the field of medicine and dermatology, receiving many eminent awards and recognitions throughout his scientific career.

KEY WORDS: Franjo Kogoj, allergology, Mal de Meleda, the spongiform pustule of Kogoj, endemic syphilis

FRANJO KOGOJ’S PROFESSIONAL CAREER

Franjo Kogoj was born on October 13, 1894 in Kranjska Gora, in the Austro-Hungarian Empire (modern day Slovenia). The son of a practicing physician, he studied medicine in Graz and Prague, where he graduated in 1920. Doctor Kogoj then pursued training in dermatovenereology in Prague and Brno, where he habilitated in 1925 as a private lecturer on the topics of scleroderma and scrofuloderma (1). He also received advanced training at various renowned dermatology clinics such as in Breslau (present day Wroclaw in Poland), where he worked with Josef Jadassohn, in Strasbourg with Lucien-Marie Pautrier,
as well as in Saint-Louis hospital in Paris. In 1928, the dermatovenerology Clinic in Zagreb was newly opened and located on Šalata, where, under the auspices of then already professor Kogoj, it was soon to become one of the most developed dermatological institutions in Europe. Franjo Kogoj headed the Clinic until 1965 with a break period during the Second World War from 1941 to 1945. He was a full professor at the Zagreb School of Medicine and served as its acting dean during the academic years of 1933/1934, 1946/47, 1948/49, and 1951/52 (1,2).

KOGOJ’S INFLUENCE ON MEDICAL TERMINOLOGY

During his academic and research work, Kogoj was very interested in defining a precise and useful terminology for various dermatological conditions, since their terminology was in many ways confusing and often overlapping at the time. On the topics of eczema and atopic dermatitis (also termed “neurodermitis” during Kogoj’s active research years) academician Kogoj was especially scientifically prolific and active in discussing and discerning multiple approaches to these conditions in theory and practice. In 1948, Kogoj published an article titled “Eczema and neurodermitis” in which he presented a broad discussion on the term “eczema” and its relation to the term “dermatitis”. In 1948, a number of conditions were related to or termed eczema, such as: eczema acutum, eczema chronicum, neurodermitis, dermatitis simplex, eczema pediculosum, eczema seborrhoicum, lichen Vidal, eczema mycoticum, eczema retroauriculare, eczema infantile, and many others (3). A common approach in differentiating eczema from dermatitis was to regard dermatitis as a skin lesion which is formed at exactly the same, well-bordered location that the causative factors are affecting. Eczema, on the contrary, was regarded as a skin lesion that persists on hypersensitive skin, outside of the area affected by a particular agent and even after the offending agent has been eliminated. Kogoj, however, realized that these alleged differences between eczema and dermatitis had not really been substantiated when examining the histologic and clinical picture of both eczema and dermatitis. Instead, he saw the causative agent as the main factor in determining whether the two conditions (i.e. eczema and dermatitis) should be classified as two distinct entities. If the same agent is causing both conditions and is, in addition, harmless to most of the population, then, according to Kogoj, this agent identifies a certain subgroup of people in which it causes skin lesions and therefore unifies both eczema and dermatitis into one nosological entity.

Many renowned dermatologists, such as F.J. Darier, H. Gougerot, or J. Jadassohn, have taken a similar standpoint on the subject (3). Still, academician Kogoj found the difference between obligatory and non-obligatory noxiousness of the offending agent to be the marker that helps us differentiate between dermatitis and eczema. He further proposed that skin lesions obligatorily caused by an offending agent, regardless of its concentration, should be termed “dermatitis artefacta”. One example of such a dermatitis would be toxic dermatitis caused by substances that are primarily toxic and cause visible lesions to any human skin. True eczema, on the other hand, is non-obligatory and appears only in some predisposed individuals. Another important characteristic of true eczema, according to Kogoj, is its polymorphic appearance of skin lesions, whereas dermatitis tends to be rather monomorphic. A third entity, clinically similar to eczema, but of entirely different origin, was termed by Kogoj as “dermatitis detritiva” and essentially corresponded to what the German dermatologist Friedrich Bering called “attrition dermatosis” (Abnutzungsdermatose in German). This dermatitis develops because of chronic or repetitive exposure to harmful substances that change the surface of skin, making it prone to their damaging effects, thus creating eczematous skin lesions. During this process, the skin becomes hypersensitive to external influences, without being allergically sensitized. At a later stage, however, the skin may also become sensitized to the same substances that caused the aforementioned dermatitis (3). But the question how to define eczema still remained. This problem especially preoccupied academician Kogoj, since it was very much related to sensibilization and allergy which were, as mentioned before, one of Kogoj’s favorite fields of interest. He then noted that not only was eczema a chronic condition, but it was also related to a chronic eczematous state that a patient was in, and that it was usually a lifelong condition in such individuals. The question now was whether or not eczema could be regarded as an allergic entity. Although hypersensitivity was an essential part of eczema, this itself did not necessarily indicate an allergic etiology. Furthermore, one important, commonly assumed prerequisite for true allergic reactions was the ability of a passive transfer of specific antigens from an allergic to a non-allergic individual, such as in the well-known Prausnitz-Küstner reaction. This procedure could generally not be applied to cases of eczema. Despite this incomplete concept of allergy in eczema, Kogoj still considered it to be an allergic phenomenon. The reason for this was his observation that sensibilization itself is of allergic origin and that one could provoke an eczema-
tous reaction in every individual by artificially sensiti-
izing him or her. Kogoj therefore proposed the term
Eczema vulgare to describe an allergic, inflammatory
skin reaction which is non-parasitic, histologically
characteristic, but clinically non-specific (4). Eczema
vulgare is thereby, according to Kogoj, always a skin
reaction to substances that are harmless to non-sen-
sitized individuals (5). Three major criteria for defin-
ing this condition are its characteristic morphology,
allergic pathogenesis, and a non-living organic or an-
organic agent. Two additional terms defined by Kogoj
and related to eczematous reactions were Dermatitis
nummularis eczematoides and Dermatitis papulove-
siculosa eczematoides (6). Special attention and
research were given to the complex eczematous con-
dition previously called neurodermitis (today atopic
dermatitis) which Kogoj famously termed Prurider-
matitis allergica chronic (3). He divided this condi-
tion into two main variants: a localized and a gener-
alized variant. The localized variant was termed Pru-
idermatitis allergica chronica circumscripta, which
corresponded to Lichen simplex chronicus Vidal. This
variant was further subdivided into a unilocular and a
multilocular type, which Kogoj also termed dissemi-
nata in placibus. All of these variants of neurodermitis
were further divided into a lichenoid and an eczema-
tous type. Kogoj also made an important observation
on the difference between eczema in early childhood
and eczema in older children and adults in terms of
its localization and overall symptomatology. Therein,
he stressed the importance of a well-known fact that
nurslings and infants who have eczema often react
to egg whites with an urticarial allergic reaction. This
reaction, however, subsides gradually as the child
grows older. This childhood eczema was then termed
eczema infantum, and Kogoj adopted the hypothe-
sis that the eczema was actually a manifestation of
food allergy. At the time, it was generally accepted
that food allergy and eczema in infants were the re-
sult of “endogenous”, i.e. hematogenous sensibiliza-
tion, whereas eczema in adults was usually the result
of sensibilization by external contact with the aller-
gen. Kogoj, however, was of the strong opinion that
eczema, regardless of its exogenous or endogenous
origin, was to be considered as an allergic phenom-
eron, leading to the conclusion that eczema in both
children and adults was in fact identical and should
be viewed from the same perspective (3).

**KOJO AND ALLERGOLOGY**

In 1952, a discussion from Kogoj was published,
where he laid out his observations and conclusions
about the contemporary concepts related to aller-
gies (7). He was particularly interested in the relation-
ship between allergy and idiosyncratic skin reactions.
Throughout the first half of the 20th century, the con-
cept of allergic reactions was largely influenced by
the famous allergist Arthur F. Coca. In his works, Coca
defined idiosyncrasy as a distinct entity, fundamen-
tally different from genuine allergic reactions (8). The
reason for this was that idiosyncrasy was perceived as
a hypersensitivity reaction which occurred imme-
diately after the first contact with an antigen, without
prior sensibilization. Kogoj, however, was entirely of a
different opinion on the matter. The first objection to
Coca’s hypothesis was that it was virtually impossible
to determine when and how the first contact with the
antigen occurred. That is to say, the so-called idiosyn-
cratic reaction may well have been an allergic reac-
tion after sensibilization already occurred, while the
first contact with the antigen went unnoticed.

In 1952, Kogoj and the Croatian dermatovenerolo-
gist Albin Brnobić founded the Allergology Section
of the Association of Doctors in Croatia in order to
unify the work of medical professions whose practice
and research dealt with allergic diseases.

In 1964, the renowned German dermatologi-
cal journal Hautarzt published an article from Kogoj
titled Ueber allergische ekzematoid (On Allergic Ec-
zematoids) in which he laid out several conclusions
based on the literature and his own research work.
Kogoj performed microbial swab tests of eczematous
herds and hemoculture findings in 12 children diag-
nosed with nummular allergic dermatitis (the precise
diagnosis was “Dermatitis nummularis eczematoides
allergica”) (6).

The results showed local findings of various micro-
organisms, with Staphylococcus pyogenes being the
most common (isolated in all 12 patients, of whom it
was the only isolated microorganism in 9 patients).
The most interesting finding in this research, how-
ever, were the hemocultures, which were positive in
a total of 5 patients. Hemocultures were performed
several times, usually on consecutive days, and the
total percentage of positive hemocultures was 41.66%.
This percentage was, thus far, the highest observed in
contemporary literature. The isolated microorganism
was always Staphylococcus pyogenes (aureus).

From his research, Kogoj concluded that allergic
eczematoids were skin lesions formed either at the
very site of disease (in loco morbi) or at distant sites
through lymphogenous or hematogenous dissemi-
nation. The second main conclusion from his obser-
vations was that the allergen responsible for eczema-
tous lesions may not be only of microbial origin, but
could also have a dermogenic component. Therefore,
the term microbial eczema would not be completely
justified (6).
In April 1959, Kogoj’s review paper on therapy for urticaria was published, in which he laid out a detailed synthesis of the previous 3 decades of various therapeutic options for the treatment of acute and chronic urticaria (9). In this article, he discussed the possibility of therapeutic desensitization through histamine which had been, at that time, a possible therapeutic option for chronic, histamine-related urticaria. Kogoj dismissed this possibility as he rightly realized that histamine in urticaria was not part of an antigen-antibody reaction and that the deliberation of histamine was only one component in urticarial reaction. Another very interesting work published by Kogoj was an article addressing allergies and fungal infections, which was published as early as 1927 (10). In this article, Kogoj observed, based on his own research with animal models, that different portions of the skin react somewhat differently to the same infectious agent (e.g. Trichophyton). His conclusion from this research was that there was a locally-dependent allergic reaction which depended on the distance between the primary and secondary skin lesions and served as yet another argument for the cellular origin of allergic skin lesions. Only two years later, in 1929, another valuable article from Kogoj was published on the differences in grades of allergic reactions in experimental mycoses (11).

For this purpose, twenty guinea pigs were infected with a fungus then known as Achorion quinckeanaum (today Trichophyton quinckeanaum), and the reaction on the skin was observed. The conclusion of this experimental research was that the grade of allergic reaction could not be determined by the intensity of skin changes alone, since the fungal allergens could be widely distributed throughout the skin, showing only minimal or no significant skin changes. Otherwise, if the allergens were densely located on a smaller portion of the skin, visible skin changes, i.e. mycotic skin lesions, occurred.

Kogoj showed special interest in histamine and its role in allergic reactions. An example of this was his research conducted on guinea pigs to assess the possible role of histamine in eczematous reactions (12). The research animals were sensitized with 2,4-dinitrochlorobenzene (DNCB) in order to provoke an eczematous reaction on the skin and subsequently treated with a histamine liberator and an antihistamine. After this treatment, the guinea pigs were again treated with the same sensitizing agent, and the reactivity of the skin before and after treatment with antihistamine and histamine liberator was compared. This comparison was the basis of assessing the influence of histamine on the development of skin eczema. Ultimately, there was no significant difference in eczematous reactions before and after the application of a histamine liberator, as well as before and after the application of antihistamine. This meant that histamine in itself did not affect the intensity or nature of eczematous reactions. Kogoj’s results differed from some other similar and well-known contemporary research (e.g. research performed by Stern and Raab). Thus, Kogoj’s conclusion was that other concomitant factors, such as genetics and nutrition of the animals, may have played a significant role in the final outcome (13).

MAL DE MELEDA

Mal de Meleda or Meleda disease is a hereditary, autosomal recessive disorder within the group of palmoplantar keratoderma. The name derives itself from the Croatian island of Mljet (Italian: Meleda, Latin: Melita) where it was firstly recognized and described. The main clinical feature of the disease is a thickened corneal layer (hyperkeratosis) of the skin on palms and soles. Other associated features that are often present are hyperkeratosis on the knees and elbows and changes of the nails and teeth. The disease usually starts to be visible already in the first weeks to months after birth. The first signs are erythema on the palms and soles, along with excessive sweating (hyperhidrosis). Other associated early signs considered to be obligatory for diagnosis are nail dystrophy, short fingers and toes (brachydactyly), as well as finger contractures. Non-obligatory signs and symptoms of the disease are periorificial keratosis, fissured tongue, high arched palate (gothic palate), syndactyly of the toes, solitary fibrotic nodules on the elbows, knees, and backs of the hands, and osteolytic lesions of the hands and feet. Over time, the initial lesions tend to gradually become more widespread, finally involving much of the area of the dorsal aspects of the hands and feet, the extensor surfaces of the knees and elbows, as well as the skin over the Achilles’ tendon. The affected skin is usually hyperhidrotic, with more or less pronounced pruritus. There is a reduced sensitivity to heat and pain in parts of hyperkeratotic skin, but the overall sensitivity is preserved (13-16).

Mal de Meleda was known to be an indigenous condition among the inhabitants of Mljet for more than 200 years. The disease was first described in 1826 by the physician Luko Stulli from Dubrovnik (17). In his famous article Di una varieta cutanea, Stulli described the newly observed disease in great detail, which he clearly defined as hereditary and non-infectious. Other dermatologists have later also showed interest in the disease and laid out various, sometimes contradictory, hypotheses on its etiology and relation to other similar dermatologic conditions (18-21). It was not until Franjo Kogoj’s research and published litera-
Influence of academician Kogoj on global dermatology

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Duvančić and Šitum

In the international scientific community (22), Kogoj’s work on the disease started around 1930 when he was conducting his first genealogical research of affected families on Mljet. One of the families was analyzed going back nine generations. The results showed that 20 out of 137 family members had typical features of the disease, which was equally present in both sexes (23,24). Upon this observation, Kogoj and his colleagues were able to conclude that the disease was inherited in an autosomal recessive fashion. This was confirmed almost 40 years later by Schnyder et al. (25). Academician Kogoj continued his research for decades, visiting Mljet again in 1946 and 1961. He summarized his observations in his famous booklet “Meleda disease”, pointing out the main characteristics of the disease: autosomal recessive inheritance, localization of lesions on all extremities, and gradual spreading of lesions over a longer period of time from the palms and soles proximally across the extremities. Based on these basic characteristics, Kogoj termed the disease Keratosis extremitatum hereditaria progrediens et transgrediens. Previous titles included Keratoma palmare et plantare hereditarium by Duhring and Unna and Keratosis palmoplantaris transgrediens by Siemens (18,20). The adjective “transgrediens” indicated that the lesions spread from their initial sites, the palms and soles, to other parts of the extremities. One important feature of the disease, however, was that the lesions evolved and spread over longer periods of time, changing the clinical picture in the same patient substantially over time. Since the term “transgrediens” referred only to a certain point in the clinical picture and did not take into account the evolvement of the disease course over time, it was academician Kogoj who proposed to add the adjective “progrediens” to the defining name of the disease. The term “progrediens” indicated the importance of observing the evolution of skin lesions over time, since it was only then the complete clinical picture of a patient could be appropriately assessed. Otherwise, if various individual patients were compared based on their current clinical condition, the impression would arise of more or less different clinical pictures of the same disease (26). Kogoj and colleagues thus presented a case of a 55 year old patient who had initially been evaluated for his skin lesions at the age of 25 when he already had keratotic lesions progressed to both of his knees, as well as isolated “flat nodules”. At the age of 55, however, his lesions had noticeably progressed, which clearly showed the importance of observing and documenting the clinical status of patients with Meleda disease as long as possible, preferably throughout their whole lifetime (24). Academician Kogoj especially emphasized the autosomal recessive mode of inheritance of the disease and specifically stated that none of the children of affected individuals showed any keratotic lesions on the palms or soles, not even in the most discrete form. It was this emphasis on the mode of inheritance that lead Kogoj to conclude that Meleda disease was a distinct entity that could be easily discerned from other forms of keratoderma, when also taking into account the overall clinical course of the disease, observed over a longer period of time (26). All of these observations and conclusions were presented by Kogoj in 1952 at the International Dermatology Congress in London at the invitation of its organizational committee. In 1962, at the International Dermatology Congress in Washington, Kogoj also presented a color motion picture film about Meleda disease (27,28). The definition of a special and distinct form of hereditary keratoderma, along with his introduction of the term “progrediens” into the medical term for Meleda disease, was a special achievement of academician Kogoj.

THE SPONGIFORM PUSTULE OF KOGOJ

In the 1920s, Franjo Kogoj visited, among other notable dermatology clinics of the time, the renowned dermatology department of professor Pautrier in Strasbourg, France. During his stay in Strasbourg, Kogoj had been systematically microscoping histological samples of pyodermas, when he came across an interesting case of acrodermatitis continua suppurativa of Hallopeau. The disease of Hallopeau is a chronic pustular dermatosis that affects the nail plates, nail beds, and distal portions of the fingers, ultimately leading to destruction of the nail plates. The lesions are usually localized, but can also occur in combination with generalized pustular psoriasis. By microscoping the histological sample of in this case, Kogoj noticed small cavities filled with pus, forming sponge-like structures. This type of morphological structure was a complete novelty at the time, never described before, which lead Kogoj to publish the case and to term the newly-discovered formation “pustula spungioformis” (29). In his original publication from 1927, Kogoj explained the pustule as being a result of neutrophils entering into epithelial cells and forming an initial unicellular pustule. It was not until 1970 and the ultrastructural studies of the spongiform pustule performed by Rupec that it was demonstrated that the neutrophils are located intercellularly, rather than intracellularly (30). Kogoj was also initially convinced that spongiform pustules and Munro’s microabscesses had to be regarded as intrinsically different entities, while ultrastructural studies showed they could be differentiated merely by...
degree of expression. As to the sponge-like appearance of the pustules, the same studies proved it to be the result of degenerated and flattened keratinocytes. Kogoj himself promptly adopted the findings from Rupec a year after they were published. To summarize, the spongiform pustule is defined as a sterile pustule located subcorneally in the epidermis, consisting of a collection of neutrophils that have migrated into the epidermis from dermal capillaries (31,32). It is a characteristic and crucial finding in pustular psoriasis and impetigo herpetiformis, as well as a valuable histopathological sign of skin lesions in Reiter’s syndrome. The major significance of the spongiform pustule, however, is its key role in the classification of psoriasis. The importance of this novel histopathological finding by Kogoj is reflected in its general acceptance by the global scientific literature, such as in the Dorland’s illustrated medical dictionary from 1974, where it is cited as “Spongiform pustule of Kogoj” (1).

ON THE SUBJECT OF ENDEMIC SYPHILIS

Academician Kogoj was very active in the research on syphilis and was especially engaged in research on endemic syphilis during the 1930s. In 1934 and 1935, Kogoj was part of an on-site research team conducting two surveys in Bosnia and Herzegovina on endemic syphilis. During the first study in 1934, a total of 4000 people were examined, while a total of 8000 people were examined during the second study in 1935 (33). The surveys showed that endemic syphilis was a disease which commonly started in childhood and would usually spread to other members of the same family (34). Besides the epidemiology of syphilis, Kogoj was especially interested in assessing the clinical symptoms of primary and tertiary syphilis. At that time, it was generally believed that endemic and sporadic syphilis were essentially two different pathogenetic entities. The results of the studies showed, however, that there was no major differences between the two, except that in endemic syphilis the primary chancre was almost always seated extragenitally, i.e. orally (1). Thus, Kogoj assumed endemic syphilis was acquired by either a direct (i.e. using the same dishes or other objects, circumcision, smoking, etc.), or indirect (i.e. kissing, sexual intercourse) mode of transmission of the infection. He also found that the most common mode of transmission was by using the same cutlery (i.e. eating with the same spoon and drinking from the same cup) (33,35,36). As to therapy for syphilis, both the sporadic and the endemic variant, Kogoj introduced a completely new approach based on the so called critical moment as an indicator for treatment duration, that was based on serologic improvement (1).

LATER PROFESSIONAL CAREER OF FRANJO KOGOJ AND CONCLUSION

In 1955, professor Kogoj became the expert leader and organizer of the scientific work of the Ljubljana Clinic for Skin and Sexual Diseases and remained in that position until 1964 (1). Kogoj was the organizer of the First Yugoslav Allergology Congress in 1961. In 1965, the Allergology Center in Hvar was established on Kogoj’s initiative. The Center was later on renovated and moved to modern facilities in 1973, where all the necessary expert work in the field of allergology and clinical immunology could take place. In 1967, Kogoj took up another important new post and became the director of the Institute for Clinical Medical Research at the Zagreb School of Medicine and the Clinical Hospital Center in Zagreb. He remained in that position until 1974. Professor Kogoj was also a Member of the Yugoslav Academy of Sciences and Arts since 1947. He was the first secretary of its Department of Medical Sciences and he served as its vice-chairman for several terms from 1958 to 1973 (1,2).

Academician Kogoj published a total of about 230 scientific and professional papers, five books, as well as many monographs and contributions to manuals and textbooks. Aside from his national recognition and honors, academician Kogoj won many international awards for his scientific, educational, and social achievements (1,28,37).

References: