SHORT HISTORICAL REVIEW

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Morphological and immuno-clinical researches during the first half of the 20th century in Cluj, Romania. Overview of the experiments done by Iuliu Moldovan

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Abstract

During the second half of the 19th century and the whole 20th century, numerous studies concerning the immune system were carried out using different methods of approach. In time, many methods were forgotten, because they were overwhelmed by more modern techniques. The aim of our paper is to present the researches done by the Romanian physician Professor Iuliu Moldovan (1882–1966) regarding one of the defense mechanisms of the human body, having the old name of reticuloendothelial system. Our paper is focused on his experiments done with Reticulin-M. He obtained this substance in 1923, by blocking the reticuloendothelial system of different animals with China ink. Moldovan considered Reticulin-M as a hormone produced by the reticuloendothelial cells. In our paper are also mentioned some important therapeutic effects of this substance on human patients having various diseases.

Keywords: reticuloendothelial system, morphological and immuno-clinical experiments, Iuliu Moldovan, Reticulin-M.

Introduction

Along the second half of the 19th century and the whole 20th century, many studies were done regarding the immune system, from the viewpoint of histology, physiology, pathology, etc. Unfortunately, although this scientific emulation produced many achievements, only some of them have become known over time, many of them being forgotten. Among the latest are the results obtained by the Romanian hygienist Professor Iuliu Moldovan (1882–1966) in the cellular immunity.

From the outset, we present the context of the immunological knowledge at the beginning of the 20th century in order to put into evidence the role of Moldovan in this medical field.

Few data relating to the most significant cellular and humoral immunologic discoveries done until the beginning of the 20th century

At the end of prewar period, when Moldovan started his immunological researches, this domain was complex and in a very dynamic evolution.

Many medico-historians considered that in cell-mediated immunity the most important discovery since the late 19th century was phagocytosis. This phenomenon was described in 1884 by Elie Metchnikoff (Ilya Ilych Mechnikov, 1845–1916). His cellular theory of immunity gained prominence within the French scientific community. However, because at that time it was a significant rivalry between France and Germany, in Germany Metchnikoff's cellular theory was regarded with skepticism. One of the promoters of this skeptic view was Robert Koch (1843–1910) [1].

Regarding the evolution of the humoral immunity, there were many important discoveries done only in a few years at the end of the 19th century and at the beginning of the 20th century. Thus, Emil Adolf von Behring (1854–1917) and Shibasaburo Kitasato (1852–1931) obtained in 1890 the antitoxin against diphtheria. In 1891, Paul Ehrlich (1854–1915) created the term "antikörper" and formulated the antibody theory [2]. Hans Ernst August Buchner (1850–1902) discovered in 1889 the alexins (soluble components of the serum). These components were redefined in 1892 by Paul Ehrlich as complement. In 1896, Jules Jean Baptiste Bordet (1870–1961) detailed the properties of alexins. Together with Octave Gengou (1875–1957), he discovered the complement fixation test. In 1897, Rudolf Kraus (1868–1932) discovered the precipitins. In 1894, Richard Friedrich Johannes Pfeiffer (1858–1945) conceived the concept of endotoxin. The agglutinins (special types of antibodies) were discovered in 1896, by Herbert Edward Durham (1866–1945) and Max von Gruber (1853–1927). Three years later, Bordet described the immune hemolysis arising from the immunization of animals with foreign red blood cells [3]. At the beginning of the 20th century, in 1903, Almroth Edward Wright (1861–1947) discovered the opsonins. As soon as Ladislaus Deutsch (also known as László Detre, 1874–1939) introduced the term antigen (in 1903), the antigen–antibody reaction has proved to be easier to decipher [4]. In 1893, Behring observed the phenomenon of hypersensitivity. Charles Robert Richet (1850–1935) together with Paul

Jules Portier (1866–1962) put into evidence the general aphylaxis and in 1902, Richet modified the term in anaphylaxis. In 1903, Maurice Arthus (1862–1945) discovered the local phenomenon of anaphylaxis, called later as Arthus reaction [5]. In 1906, Clemens Peter Freiherr von Pirquet (1874–1929) and Béla Schick (1877–1967) introduced the term allergy in order to describe the hypersensitivity reaction, which occurred after the second injection of horse serum. In his treatise entitled *Allergy*, published in 1910, Pirquet claimed the idea that there were two categories of responding to antigens, a classic mechanism of protection against infectious diseases and an allergic reaction or an altered reactivity, to which the immune response itself causes a clinical disease. In the category of allergies, Pirquet included some diseases, such as serum sickness, anaphylaxis reactions, Arthus reaction and bronchial asthma [6].

Knowing mostly of these discoveries, Iuliu Moldovan wanted to investigate the reticuloendothelial system (RES) for obtaining a substance able to reduce the reactions occurring in the anaphylactic shock.

A brief overview of the reticuloendothelial system (RES)

The RES is an old-fashioned histological term, very rarely used at the beginning of the 21st century. Another name of RES – not very often present in today's medical terminology – is the macrophage system. In present, the current name of this entity is the mononuclear phagocyte system. This is a part of the immune system and consists of mononuclear cells with pronounced phagocytic ability. Among the phagocytic cells are included: tissue histiocytes and macrophages, Kupffer cells of liver, dendritic cells of lymph nodes, Langerhans cells of skin, alveolar macrophages of pulmonary alveolus, osteoclasts and microglia [7].

The term of RES was elaborated in 1922, by Karl Albert Ludwig Aschoff (1866–1942) [8]. From the medico-historical point of view, this concept about RES was prefigured by Kenji Kiyono (1855–1955), who had elaborated the term of histiocyte in 1913, together with Aschoff (as mentioned Jean-Marc Cavaillon). In Aschoff's opinion, this system was composed by mesenchymal cells distributed throughout the human body, with different morphologic characteristics and names and having various degrees to incorporate and store vital dyes into cytoplasm.

Aschoff included in RES the following groups of cells: (1) endothelial cells, (2) fibrocytes, (3) reticular cells of spleen and lymph nodes, (4) reticuloendothelial cells of lymph and blood sinuses, inclusive Kupffer cells, (5) histiocytes and (6) splenocytes and monocytes. Further, admitting that endothelial cells and fibrocytes were weakly phagocytic cells, he proposed to remote the groups 1 and 2. Also, he considered usefully to combine the group 3 with 4 and to name them in a strict sense RES (as mentioned Jean-Marc Cavaillon) [9].

In 1927, Aschoff's RES concept was criticized by Alexander A. Maximow (1874–1928) and other researchers. In the same year, M. Volterra elaborated an equivalent term – the reticulohistiocyte system. In 1934, Roger Denio Beker (1902–1994) mentioned that the RES term was improper, but being so frequently used, it would be impossible to be replaced. Only 15 years later (in 1949) with all difficulties, J. A. Thomas managed to reintroduce the term of reticulohistiocyte system, proposed by Volterra. Ralph van Furth *et al.* proposed in 1969 a new classification of phagocytic cells, giving the general term of mononuclear phagocyte system [10].

However, the RES term was used even in the 1970s by some scientists. Victor V. Papilian (1920–1982) and Gheorghe Roşca considered that RES system represented a notion more functional that morphological [11].

Regarding the term used by Iuliu Moldovan in his experiments, which lasted until 1948 and in all his papers, he preferred the name RES.

Iuliu Moldovan's researches concerning the blockage of RES

Starting from 1908, Moldovan elaborated a series of research on the antigen–antibody reaction. He began these studies in Vienna Laboratory of Bacteriology of the Army, where he had just been appointed as assistant. During that period, the director of the Laboratory was Robert Doerr (1871–1952), who had focused his attention on the anaphylaxis reaction. At that time, it was known that an antigen (a protein) injected at an animal determined the production of a specific antibody (sensibilisine). It was also known that the reinjection of the same antigen led to a shock, determined by the encounter between the antibody and the antigen. The animal, which had survived from a sublethal shock, became immune to a new administration of the same antigen. Moldovan and Doerr published several papers in which they demonstrated that the anaphylactic shock was the consequence of a violent antigen–antibody reaction [12]. They observed that the extremely intense reaction occurred predominantly on sensitive cells, especially on the cells of the capillary endothelium [13, 14].

After the First World War, Moldovan – this time being professor of hygiene and social hygiene at the Cluj Faculty of Medicine – continued his research for combating the anaphylactic shock. Together with his coworkers, among them being Mihai Zolog (1894–1943) and Titus Slavoaca, Moldovan has done many experiments on animals. Moldovan and his team administered red blood cells from horse (antigen) during the first subcutaneous or intravenous injection on guinea pigs, rabbits and sheep [15, 16]. In this way, they obtained animals sensitized at horse red blood cells. Before the re-injection of the same antigen (which would have produced a lethal anaphylactic shock), Moldovan had a very ingenious idea to block the animal's RES with relatively high doses of China ink, administered intravenously [17]. Indeed, the animals having the RES blocked, have never suffered a lethal shock. Moldovan observed that the administration of China ink had reduced the hypersensitivity of sensitized animals only if the blockade was done at a time from one hour up to 10 days before their re-inoculation of the same antigen [18]. He concluded that there was a desensitizing phenomenon, as a protective effect against the anaphylactic shock. As consequence, the capillary endothelial resistance was increased. Moldovan described the same desensitizing effect after intraperitoneal injection with various vital dyes, as Trypan blue or saccharated iron oxide [19]. The tissular distribution and

elimination of China ink particles were different in comparison with those of Trypan blue. While the particle of China ink disappeared from the blood circulation a few minutes after their intravenous injection, in animals injected with Trypan blue they remained up to 14 day in blood, coloring the serum.

The rigorous scientific logic of Moldovan allowed him to conclude that the intravenous injection of China ink was followed by the appearance in the blood of a substance with protective role against anaphylactic effects [20]. He named this substance Reticulin-M. He chose the name Reticulin because this substance was obtained after RES blocking, followed by RES cells hyperplasia. In order to avoid the confusion with reticulin fiber of the connective tissue, he added the letter M. Thus, he paid an homage in the memory of Metchnikoff.

It is interesting to know some data regarding Iuliu Moldovan's conception about the origin of this protective substance. He appreciated that this active substance – obtained after the blocking of RES – was secreted by the whole RES, even by the epiploon after intraperitoneal injection with China ink. He thought that Reticulin-M was a hormone of RES – the first well-defined product of RES's hyperplasia secretion [21]. He elaborated this conclusion, because he compared RES with a complex organ of the human body. Therefore, seems to be justified the conclusion of Iuliu Lenghel and Antipa Ivanov (1926–1991), who considered that "Moldovan has priority in knowing the secretory function of RES – in what nowadays is called monokine of the mononuclear phagocyte system" [22].

Iuliu Moldovan's opinion was completed by one of his colleagues of the same Faculty from Cluj – the histologist Cornel Crişan (1895–1958) – lecturer at the Chair of Histology. From the experimental point of view, he observed on guinea pigs injected with China ink that the charcoal particles were phagocyted by the elements of reticuloendothelial tissues, distributed in various organs and having role in immunity [23]. After the first minute until the 20th day post-injection, these particles were found in variable amount in liver, spleen and lymph nodes. He considered that all these three organs could produce the protective substance, but mostly the liver. Thus, Crişan gave arguments for Aschoff's conception regarding the fact that RES was spread in different organs.

Few data about Moldovan's technique for preparing Reticulin-M

Most frequently, Moldovan and his team used horses in order to produce Reticulin-M. Other animals used in Moldovan's experiments were guinea pigs, rabbits and sheep. For blocking their RES, the team employed most often China ink, but also other electronegative colloidal solutions administered intravenously or intraperitoneally. Moldovan injected various quantities of China ink through repeated attempts, in order to obtain hyperplasia of RES and the maximum function of its cells. He collected blood from horses in the moment when the Reticulin was in its highest concentration. Then, the plasma was ultrafiltrated. After its vacuum evaporation, the substance obtained was put into 2 cm^3 ampoules and sterilized at 60^0C, three times in three consecutive days.

After many chemical determinations, Virgil Galea (1904–1989) and Titu Turcu (1894–1976) demonstrated that the substance resisted at a temperature of 80^0C only five minutes and was destroyed at 100^0C. They observed that Reticulin resisted in acidic medium at the action of pepsin, but was destroyed by trypsin. Also, they found that it was soluble in water and in chloroform, but insoluble in alcohol absolute, in acetone, in ether and benzene. For that reason, Moldovan's team precipitated the active substance using alcohol or acetone and, through successive purifications of residues, they obtained a homogeneous microcrystalline product, which contained the active principle in state of almost complete purity. Retained in the desiccator and adding calcium chloride, Reticulin-M kept its effectiveness more than five years. Moldovan calculated the "guinea pig unit" of active principle per cm^3. This substance was capable for preventing the anaphylactic shock at guinea pig in dilutions up to 1:1 thousand million. Moldovan's experiments proved that guinea pigs tolerated intravenous injection of 12 000 protective units of Reticulin-M, without any negative reactions. He found that in human patients, the intravenous injection of Reticulin-M has produced no change in hematological blood tests, pulse, blood pressure, other biochemical constants (in use during the interwar period) and different neurological reflexes.

Reticulin-M had the following characteristics: had no toxicity, produced the slowing down of antigen–antibody reaction and had a protective effect against anaphylactic shock, which lasted up to 48 hours. Other characteristics of the same substance were: it acted on endothelium of blood capillaries, maintaining or restoring the normal capillary permeability and it stopped the muscular contraction of smooth muscle. Moldovan observed that the protective action of Reticulin-M was canceled by high doses of pituitary hormone and that caffeine acted synergistically with Reticulin-M. He mentioned that adrenaline had no influence on the actions of Reticulin-M. The substance had no protective effect against injections of histamine, peptones or fresh serum of ox [24].

Professor Iuliu Moldovan published his results regarding Reticulin-M not only in Romania, but also abroad, *e.g.*, in the "Comptes-rendus de la Société de Biologie" from Paris (a very prestigious publication in the interwar period).

A short presentation of Reticulin-M effects on human patients

Reticulin-M was the product of ultrafiltration of horse serum blocked with China ink. For the treatment of different human patient illnesses, the optimal dose for having an effect anti-anaphylactic was calculated by doing experimentally titration of Reticulin on sensitized guinea pigs.

Iuliu Moldovan and his team prepared two types of Reticulin-M, depending on the substance's concentration. Their names were: simple Reticulin-M and forte Reticulin-M. The latter contained a concentration of 5 to 10 times higher than the simple Reticulin.

He demonstrated that in human patients, the subcutaneous injection of 2 cm^3 simple Reticulin-M (at least five minutes before the antigen-antibody reaction) was a

sufficient quantity to prevent an anaphylactic shock. For having a doubtless therapeutic effect, he recommended the repetition of simple Reticulin-M injections during 1–2 weeks. A common anti-allergy treatment for moderate allergies included six subcutaneous injections. In emergencies that required an action more intense and in a shorter time, the subcutaneous injections of simple Reticulin-M could be repeated either during the same day or in a doubled dosage.

All these results were encouraging, but it was noticed that under certain circumstances the administration of large doses (50–200 protective doses) have not prevented the anaphylactic shock, but even increased it.

This Reticulin-M, which was received very positively by the majority of the physician from Cluj, was prescribed in the treatment of various diseases with different medical profiles: internal medicine, dermatology, pediatrics, neurology, surgery, gynecology and otorhinolaryngology [25].

A very obvious therapeutic success of the treatment with Reticulin-M was obtained in allergic manifestations, ranging from urticaria to bronchial asthma [26]. A favorable effect was obviously observed in some pathological conditions, which were accompanied by neurovegetative unbalance, as migraine [27]. In the treatment of some skin diseases as eczemas, post-Salvarsan dermatitis, pox ulcers, bullous dermatoses and burns have been recorded good results [28]. In few skin illnesses, Reticulin-M manifested also a trophic effect. Positive results were noted in only few cases of arterial hypertension [29] and in some local and general reactions on therapeutic administration of serum [30]. Regarding the treatment of obstetrical diseases as eclampsies, dermatitis in pregnancy and hyperemesis gravidarium, Reticulin-M had a moderate therapeutic effect [31].

Professor Iuliu Haţieganu (1885–1959) – the founder of the Romanian internal medicine school from Cluj – mentioned in 1940 that "Reticulin-M was discovered very ingeniously by Iuliu Moldovan" [32]. Haţieganu added that this drug was very well documented and experienced on animals. Indeed, Moldovan has done an impressive number of experiences with the Reticulin-M on animals, carried out over a period of almost 30 years. All these studies regarding the therapeutic effects of Reticulin-M were stopped in 1948. A few months later, Moldovan was kicked out of the Faculty of Medicine and sent to prison on political reasons.

Conclusions

The numerous international researches made in the first half of the 20th century, regarding the role of RES in immunity (although old-fashioned in comparison with the scientific level of the actual immunology), represented a solid groundwork for the modern subsequent discoveries in cell mediated immunity. At that time, there were many studies concerning the RES' blockage. However, Professor Iuliu Moldovan had the priority in discovering the secretory function of RES – which is nowadays known under the terms of monokine of the mononuclear phagocyte system. Reticulin-M – the drug discovered and prepared by Iuliu Moldovan – had, at that time, a beneficial effect for the treatment of human patients with allergic disease, some moderate vascular alterations (restoring the normal capillary permeability), but especially to prevent different forms of anaphylactic shock.

Conflict of interests

The author declares that he has no conflict of interests.

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