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On the Role of Chemical and Molecular Biology in Inflammation Research

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Inflammation is an elaborate reflex response of the body to the action of harmful agents. This reaction manifests itself in the form of functional and structural changes of vascular tissues. The inflammatory response is the result of the human evolutionary process. It has three main stages, which are closely related to each other and evolve simultaneously: tissue dystrophy (alteration); impairment of blood circulation (transudation of fluid and migration of leukocytes) and multiplication of cellular elements (proliferation). These phenomena express both a disturbance of biological activity in body tissues and the defense mechanisms to restore the damaged areas. There are two interrelated processes which are often inseparable from each other in the inflammatory response. First, there is the pathological process itself, the tissue damage in form of dystrophy, necrobiosis or necrosis. Second, there is the physiological mechanism of defense, the process of recovery or the physiological response against the disease", manifested as exudation, phagocytosis and proliferation. Simultaneity of both processes is characteristic to inflammatory processes.

Keywords: inflammatory response, physicochemical theory, exsudative infiltrative processes, phagocytosis, proliferation

Inflammation is one of the most widespread pathological processes underlying many diseases that differ in their clinical presentation.

The inflammatory response was first described by Paracelsus and it included the following stages: swelling (*tumor*), fever (*calor*), change in color (*rubor*), pain (*dolor*) and functional impairment of the tissue (*functio laesa*). In normal conditions, the inflammatory response is tightly controlled by the body, but the excessive inflammatory response by itself can lead to diseases (eg. atherosclerosis and rheumatoid arthritis).

The causes of inflammation are extremely varied. The inflammation occurs mostly as a result of the action of various exogenous factors, such as infectious agents (bacteria and toxins), mechanical forces (impact or injury), thermal damage (burns or frostbite) or chemical agents (the effects of strong acids or bases).

Endogenous causes of inflammation are represented by tissue necrosis, thrombosis, infarction, extended hemorrhage, salt deposits and certain disturbances in the trophic function of the nervous system (symmetrical centrogenous inflammations) [1].

Dystrophy is a metabolism and nutrition disorder of tissue function and structure, which is more evident in the area where the tissue was exposed to the harmful agent.

The alteration of the physicochemical properties of the inflamed tissue leads to changes of tissue colloids and especially to changes in proteins. Their degree of dispersion and their ability to attract and retain water lead to an increase in coloidosmotic pressure or in the oncotic pressure of tissue colloids. To outskirts outbreak inflammatory oncotic pressure gradually decreases towards the periphery of the inflammatory site.

Therefore, phenomena related to increased metabolism and their subsequent physicochemical changes are found in the inflammatory area, such as accumulation of ions (increased concentration of hydrogen ions – hyper-ionic); increased osmotic pressure (hyper-tonic); increased oncotic pressure (hyper-oncotic). All these changes are the result of the trophic disorders of the tissues and they influence the magnitude of changes in the cells of the inflamed tissue.

Disorders of blood circulation are seen right from the beginning, as a reflex response, due to the effect of inflammatory agents on the receptors from the damaged area. A brief spasm occurs. The vascular spasm and subsequently the pallor of the damaged tissue area are the result of the excitation of vasoconstrictor nerves. This stage is followed by vessel dilation (arterioles and capillaries) and increased capillary bed volume, leading to an increased inflow of blood into the inflamed tissue area.

Vessel dilation is influenced by various factors. Vessel dilation is initially caused by a reflex following the action of a harmful agent. The increase in the concentration of hydrogen ions is also very important. Products of metabolism and products of tissue injury exert the most intense vasodilation. Changes in blood vessels of the inflamed tissue area occur immediately after the blood flow slows and stasis develops.

Inflammatory vascular processes are accompanied by exsudation, which is the escape of liquid and solid components of blood through the vessel wall into tissues. Changes in the permeability of vascular walls are among the most important factors that influence exudation of liquid and solid components of blood.

Increased blood pressure in the vessels of the inflammatory area leads to fluid extravasation. Increased osmotic pressure in the tissues of the inflammatory site plays an essential role in the formation of exudate, as high osmotic pressure produces a liquid stream directed from

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the vascular bed towards tissues. Fluid extravasation is promoted by the fact that water is fixed by colloids in the inflamed tissue and the oncotic pressure increases in tissue colloids underlying this phenomenon.

The so-called *proliferative or productive processes* are slightly manifested phenomena of multiplication of cell elements. They occur almost simultaneously with the alteration processes found in the periphery of the inflammation area.

These phenomena are highly active in the later stages of the inflammation. The inflammatory agent and the products generated by disintegration and disturbed metabolism, which accumulate in tissues, play an important role in developing proliferation.

Various processes prevail, depending on body's response and on the properties of the stimulant causing inflammation. There are several different processes: altering inflammatory processes, exsudative infiltrative processes and proliferative (productive) processes.

The development of inflammation research

The theories of Rudolf Virchow and Julius Cohnheim on the process of inflammation come from the early period of scientific study of pathology.

According to Virchow (*Cellular pathologie*, 1858), inflammation was in essence an increase in the biological activity of cell parts that begin to show an intense nutrition and multiplication based on the liquid component of blood (the so called nutritional irritation), in response to excitation of tissue. Virchow explained the emergence of an increased number of cells in the inflammation area as an increase in local tissue elements [3].

Suppurative exsudate consisted of elements removed from the tissue. Other phenomena observed during inflammation, such as vascular or exsudative processes, played a secondary and subordinate role. All the inflammatory processes fell into two categories: interstitial inflammation, with predominant manifestations of the connective stroma and parenchymal inflammation, with manifestations of the specific elements of the organ.

The concomitant existence of altering, exsudative and proliferative processes in the affected tissue area was characteristic to the inflammatory reaction.

Each of the previously mentioned processes could not characterize the inflammatory reaction as a whole. There was no pure parenchymal inflammation, due to the fact that the inflammatory process involved more or less the connective tissue.

Virchow's conception on the essence of the inflammation fails to acknowledge the huge impact of the general status of the whole body in the pathogenesis of inflammation. Moreover, it denies the role of the nervous system as a key mechanism in regulating all biological functions. Among the limits of this approach are the obvious local character of cell theory on inflammation and unilateral explanation of the inflammatory process.

Once Cohnheim reported phenomena observed in an inflammation induced in a frog's mesentery, scientists began to focus on changes found in blood vessels and in the solid components of blood.

The *vascular theory* of Cohnheim (1885) places special emphasis on the vascular reaction that occurs during inflammation. The increase in vessel permeability, slowing of blood flow and local increase in blood pressure, determine exsudation and migration, which, according to this theory, occur passively. On the other hand, changes found during inflammation in the tissue itself are of minor importance. The reflex influences were not considered directly related to the occurrence mechanism of the inflammatory process. According to this theory, even the inflammatory process of the avascular tissues is determined by vessels, albeit from neighbouring tissues, from which the solid components of blood migrate towards the site of action of harmful agents [4].

However, subsequent research has not confirmed the paramount role of the vascular system of the damaged area in the development of inflammation. The inflammatory response is determined both by blood vessels and by the connective tissue or by the elements belonging to the reticular-histiocytic system.

Therefore, the theory of Cohnheim on inflammation is also unilateral, as it does not take into account all aspects of the observed phenomena, namely both the damaged area and the whole body.

After the infectious agents of inflammation were discovered, the biological theory on the process of inflammation occurred (1892). It revolutionized the concepts related to the mechanisms of the inflammatory reaction. The main role in inflammation was assigned to white blood cells, phagocytes, that are involved in all inflammatory processes. This is when the method of compared pathology was first used. A reasonable interpretation of the origin of inflammation and the research of this process by using phylogeny proved to be extremely valuable [5].

Thus, it was found that the response of protozoa to the action of biological, mechanical or chemical stimuli that usually cause an elaborate inflammatory reaction in organisms with a more complex structure; is a reaction of phagocytosis, meaning the embedding and digesting of irritants by cells of mesodermal origin.

The process of nutrition, i.e. embedding and digesting harmful agents, underlies the inflammatory response. In organisms with complex structure, cells of mesenchymal origin such as microphages and macrophages play this phagocytic function. Granulocytes migrated from the blood vessels into the inflammation area fall into the category of macrophages. They are able to incorporate and digest mostly microbes. Macrophages are large amoeboid cells, which are formed from the tissue cells, the so-called leucocytoid cells, during the inflammation process. They are able to incorporate and digest particles resulting from cell disintegration and even erythrocytes. Phagocytes help the body to dispose of harmful substances that permeate it. This is the defense mechanism of the inflammatory reaction, which developed as part of evolution and natural selection. All other phenomena observed during inflammation (eg. vascular reaction) are only of secondary importance, as they help phagocytes to enter the inflammation area.

Phagocytosis and chemotaxis that occur during inflammation give us a clue about the general responsiveness of the body when fighting infectious agents and links inflammation to immunity.

The evolutionary theory on inflammation based on Darwin's theory lasted for many decades and determined the development of the theory on inflammatory and the immune status. The method of comparative pathology helped to explain the role of inflammation as an adaptation and defense mechanism and also to associate the inflammatory reaction with the immune response.

Although inflammation is not fully explained by this theory, the evolutionary concept is still very important, as it explains the role of the body's adaptation mechanism in the formation of an inflammatory response. Furthermore, the biological theory is the starting point of the modern theory on the role of mesenchymal tissues in inflammation.

The phagocytosis theory explained for the first time the interdependence between the inflammation area and the body seen as a whole. Inflammation was considered not only a local response, but also a general reaction of the body against the action of a harmful agent. It was the phagocytic theory that moved the focus of research towards changes in hematopoiesis and blood composition during inflammation and towards the influence exerted by the immunological properties of the organism on the development of the inflammatory process.

On the time scale of animal evolution, the reaction of phagocytosis forms complex relationships with various functional systems. In later stages of animal development, phagocytosis acts jointly with the nervous system. Inflammation should be considered a phagocytic reaction of the body against stimulating agents. This reaction is achieved either solely through mobile phagocytes or in association with vascular phagocytes or with the nervous system.

The emergence of physical chemistry and biochemistry and the use of their achievements in the field of pathology have enabled a deeper understanding of the inflammatory process. A physical chemical orientation was used in the research of inflammation, leading to concepts based on a physical chemical approach of inflammation (Schade).

The increased metabolism in the area of inflammation causes changes of the main physicochemical properties of the tissue: isoionic, isotonic, isooncotic and isothermic. There is an increase in the concentration of hydrogen ions (hyper-ionic), an increase in the osmotic pressure (hyper-tonic), an increase in the oncotic pressure (hiper-oncotic), an increase in temperature (hyper-thermic). All these changes, collectively called tissular hyper-plethism, lead to the development of hyperemia, exsudation, migration, proliferation and underlie the main symptoms of the inflammatory process.

The physical chemical orientation in the study of inflammation has explained several aspects playing a role in this process. This theory even proposed a link between different phenomena observed during the process of inflammation. But the question remains, if the physicochemical changes represent the primary contributing factor to inflammation. All the physico-chemical changes characteristic to the inflammation process can be described only if the inflammatory process has already occurred. Therefore, these observations are secondary.

Physicochemical theory has another major limitation in explaining inflammation in that it tries to subject the inflammatory process to the laws of physical chemistry and colloidal chemistry. This mechanistic approach ignores the biological aspect of the inflammatory response.

The physicochemical theory considers inflammation as a merely local process, disregarding the role of regulatory systems and mechanisms involved in inflammation and particularly the role of the nervous system.

As the normal and pathologic physiology of the nervous system determined the role of disturbances of the activity of the nervous system in the pathogenesis of various diseases, the neurogenic theories became increasingly important in explaining the inflammation process. Depending on the degree of excitation of vasomotor nerves, a vascular reaction of different intensity occurs, leading to hyperaemia and blood stasis, with all their consequences. They are followed by an inflammatory response. The tissue and the vasculature determine both the intensity and type of metabolic disorders (Ricker).

However, according to the so-called *vasomotor theory*, the rigorous limit between inflammation and non-inflammatory vascular disorders disappears. By emphasizing the crucial role of vasomotor nerves in the inflammatory process, this theory could not provide a qualitative description of the inflammatory reaction as a whole.

Some research highlighted the role played in inflammation by disturbances of the trophic function of the nervous system, in addition to changes in the modulation of the vascular lumen. When acting on the tissue, the harmful agent induces a reflex response in the form of disorders of tissue metabolism, such as dystrophy and acidosis, with all their consequences.

The importance of trophic reflexes in the development of the inflammatory process is also proved from the fact that their abolition prevent or mitigate inflammation. The argument that the inflammation may occur even in denervated tissues was brought against the neurogenic theory. Such observations can not be considered convincing, because surgery could not provide a complete denervation of tissues, due to the existence of nerve structures located in the vessel walls.

But even with an incomplete denervation of tissues, the inflammation has an unusual course. The complete elimination of receptor nerves by using anesthesia usually prevents an inflammatory process, during the period in which the anesthetic is effective.

The nervous system plays an essential role in the two processes of inflammation. Changes in the reflex activity caused by a pathogen agent lead to the emergence of neurodystrophic phenomena. The nervous system is also highly involved in developing adaptive mechanisms (exsudation, phagocytosis and proliferation), which help the organism to suppress the pathogen agents and to heal the injuries caused by these damaging factors during an inflammatory process.

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