



Review

From Inflammation to Sickness: Historical Perspective

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Abstract. The concept of the four cardinal signs of acute inflammation comes from antiquity as *rubor et tumor cum calore et dolore*, (redness and swelling with heat and pain) extended later by *functio laesa* (loss of function). The contemporary understanding of this process we owe to 19th-century milestone discoveries by Rudolph Virchow, Julius Cohnheim and Elie Metchnikoff. In the 20th century, the development of potent technological tools allowed the rapid expansion of knowledge of the cells and mediators of inflammatory processes, as well as the molecular mechanisms of their interactions. It turned out that some mediators of inflammation have both local and distant targets, among them the liver (responding by the production of several acute phase reactants) and neurohormonal centers. In the last decades it has become clear that the immune system shares mediators and their receptors with the neurohormonal system of the body; thus, they form a common homeostatic entity. Such an integrative view, introduced by J. Edwin Blalock, when combined with Hans Selye's concept of stress, led to the contemporary understanding of sickness behavior, defined by Robert Dantzer as a highly organized strategy of the organism to fight infections and to respond to other environmental stressors.

Key words: local inflammatory response; acute phase response; sickness behavior; immune-neuroendocrine network.

Basic Concepts

Most people have personal experience with inflammation: a red, swollen, hot and painful finger with pus formation from a thorn prick, or very similar symptoms after a mosquito bite; in more serious cases of trauma and/or infection, fever and general malaise. Thus, inflammation is a rather stereotypical response to a variety of stimuli, such as tissue injury and/or infection, and involves both localized and systemic effects.

The hallmarks of a localized acute inflammatory response were described in the medical section of a large encyclopedia almost 2000 years ago by the Roman writer Cornelius Celsus as “*rubor et tumor cum calore*

et dolore” meaning “redness and swelling with heat and pain”. It was not until the 19th century, that Rudolph Virchow extended this definition by “loss of function” (“*functio laesa*”), which occurs in more severe instances. Microscopic observations performed for the first time by R. Virchow and, independently, by one of his most famous pupils, Julius Cohnheim, allowed an explanation of the cardinal signs of inflammation in scientific terms. The redness and heat reflect an increased blood flow, the swelling is connected with the exudation and accumulation of cells and fluid, and pain follows³⁶.

The next great contribution to our understanding of inflammatory processes came from Elie Metchnikoff's

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comparative observations of phagocytic cells from a variety of animals, including unicellular amebas, several invertebrate species (e.g. transparent starfish larvae and a tiny transparent crustacean, *Daphnia*), and representatives of various vertebrates: fish, amphibians, reptiles, and mammals. He concluded that “the purpose of inflammation was to deliver phagocytes to a site of injury”. In his book “Comparative Pathology of Inflammation”, METCHNIKOFF³⁹ offers the following definition: “Inflammation is a local reaction, often beneficial, of living tissue against an irritant substance. This reaction is mainly produced by phagocytic activity of the mesodermic cells. In this reaction, however, may participate not only changes in the vascular system, but also the chemical action of the blood plasma and tissue fluids...”.

With minor modifications, this definition is still valid today. It introduces the main components of an inflammatory reaction: a) “the irritant substance”, which we now know to be, in most cases, microorganisms, dead or injured cells, or products of an adaptive immune reaction; b) “the mesodermic cells”, which we now call tissue macrophages, mast cells, blood-borne granulocytes and monocytes; c) “the vascular system”, more specifically the endothelium of small venules and capillaries; and d) “the chemical action of the blood plasma and tissue fluid”, including present-day entities such as cytokines, complement, arachidonic acid metabolites, enzymes, and many more.

Inflammation is also part of the adaptive immune response as a nonspecific but very effective ally in recognizing and destroying selected targets. The cost is when the immune response reacts excessively to innocent targets (such as pollens which cause allergy and, in extreme instances, anaphylactic response) or selects inappropriate targets (such as normal tissue in autoimmune disease, e.g. rheumatoid arthritis, when chronic inflammation develops). Chronic inflammation is an entirely different entity both in terms of pathogenesis, time course and clinical manifestations, and will only be touched upon briefly in this text.

Local Events during Acute Inflammatory Reactions

Several reviews have attempted to cover the rapidly expanding knowledge of the course of acute inflammation^{26, 31, 32, 36, 44–46}. Put most simply, may be said that in response to an inflammation-inducing agent several mechanisms are triggered in parallel, coming both from cells (mainly resident mast cells, macrophages and

local endothelium) and from potent plasma enzymatic systems, such as the kinin, the clotting, the fibrinolytic, and complement cascades. These early alarm signals induce pain (bradykinin acts on prostaglandin-sensitized nerve endings), profound vascular changes (increased permeability and expression of a variety of signal molecules on endothelial cells), and deliver several chemotactic factors (complement components, arachidonic acid metabolites, chemokines, and some of the other cytokines). Vascular permeability plus the orchestrated actions of newly induced epithelial molecules and chemotactic factors leads to extravasation of blood plasma and leukocytes, the latter being related to the extensive cross-talk between the blood leukocytes and endothelial cells, with participation of their membrane-bound cell-adhesion molecules, such as selectins and integrins. The early wave of neutrophils, ultimately dying in the focus of inflammation, is accompanied by and then followed by a longer-lasting influx of monocytes (transforming into the highly active macrophages) and, in some cases, lymphocytes. These exudatory cells are the main source of new waves of cytokines, with a switch of proinflammatory (TNF- α , IL-1, IL-8, IL-6, IFN- γ) to anti-inflammatory cytokines (e.g. IL-4, IL-10, IL-13, TGF- β). These and other local anti-inflammatory agents (such as cytokine antagonists and soluble cytokine receptors) lead to resolution of the acute inflammation and tissue healing^{32, 46}. In the last few years it has been demonstrated that the exudatory cells synthesize and release opioid peptides participating in local analgesia^{13, 15, 18, 35}.

Modern molecular technology has forced a reinterpretation of dogmas concerning the so-called “immune-privileged sites”, such as the eye, brain, and others (testis, ovary, the pregnant uterus, and adrenal cortex), where histo-incompatible tissue grafts could be placed with little or no threat of immune rejection. According to MEDAWAR³⁸, who was the first to define immune-privilege sites, antigenic materials placed into them are sequestered from the immune system due to the absence of lymphatic draining and the existence of blood/organ barriers³⁸. However, the phenomenon of immune privilege is much more complicated. STREILEIN et al.⁵¹ stated recently: “As we learn more about biology, absolutes almost never exist...” and “... studies over the last 30 years have indicated that active processes... govern the creation and maintenance of immune privilege”. In particular, the results of Streilein’s and other groups of scientists (e.g. ^{25, 28, 51, 52}) have firmly established that the immune privilege of the anterior chamber of the eye depends upon immunomodulatory factors present in the ocular microenviron-

ment and are expressed on the surface of ocular parenchymal cells. This makes it possible for the eye to receive immune protection against pathogens while avoiding damage to the delicate visual axis (which allows sharp light images to fall on the retina) from destructive, intense inflammation with edema and cellular infiltration⁵¹.

Systemic Effects of Acute Inflammatory Reactions

From the biological point of view, there is a full spectrum of inflammatory reactions, from the small-scale local phenomena accompanying our everyday life, to life-threatening pathological conditions such as appendicitis, peritonitis, and so on. Most of the former reactions are resolved locally. However, in more severe instances, certain parenchymal organs, mainly the liver and neuroendocrine centers, are “informed” about the ongoing inflammatory processes and can participate in them. One clear indication of the systemic response is the increase in the synthesis and secretion of several plasma proteins by the liver with simultaneous decreases in others, triggered mainly by IL-6. These acute-phase proteins function in a variety of defence-related activities, such as limiting the dispersal of infectious agent, repairing tissue damage, the killing of microbes and other potential pathogens, and restoring the healthy state^{3, 4, 46, 50}. On the other hand, IL-1 activates the hypothalamo-pituitary-adrenal axis leading to the resolution of inflammation by the anti-inflammatory action of glucocorticoids, but this also induces sickness^{9, 53}. At the molecular level, the sickness symptoms develop due to the brain's response to proinflammatory cytokines such as IL-1 and TNF- α . Peripherally released cytokines act on the brain via the fast transmission pathway, involving primary afferent nerves innervating the bodily site of inflammation, and a slow transmission pathway, involving cytokines originating from the choroid plexus and circumventricular organs and diffusing into the brain parenchyma by volume transmission^{22, 23, 37}.

Everybody has experienced the non-specific symptoms of infection and inflammation collectively referred to as “sickness behavior”, which include fever and profound physiological and behavioral changes. Sick individuals experience weakness, malaise, listlessness, and an inability to concentrate. They become depressed, lethargic, show little interest in their surrounding, and stop eating and drinking. According to a contemporary view, such sickness behavior is the ex-

pression of a central motivational state that reorganizes the organism's priorities to cope with an infectious pathogen^{22, 23}.

Due to their commonality, sickness symptoms were ignored for centuries as uncomfortable, but rather banal, components of pathogen-induced debilitation. Only the imaginative curiosity of Hans Selye linked these symptoms with both infection/inflammation and the neurohormonal system of the body, which opened many new avenues of scientific research¹⁹.

Already as a young student of medicine, H. Selye made the simple observation that patients suffering from different diseases exhibited identical signs and symptoms: they simply “looked sick”. This observation was the first step towards the concept of “stress”^{47, 48}. Then, additional terms were introduced, according to which stress may be either “spice of life or kiss of death”^{34, 49}. Thus, “eustress” (i.e. good stress) arises in response to a variety of everyday stimuli, initiating responses beneficial to the human's or animal's comfort, well-being, and/or reproduction. In contrast, “distress” initiates a response that may interfere with the animal's comfort, well-being, and/or reproduction, with possible pathological consequences²⁰. Infection and clinical syndromes of inflammation evidently belong to the latter category. Organisms respond to infection with complex adaptations involving bidirectional communication between the immune and neuroendocrine systems, as these share mediatory molecules and their receptors¹³.

We owe this contemporary knowledge to the efforts of many scientific groups (e.g. see ^{1, 5-8, 11, 21, 24, 29, 30, 40}), but the milestone concepts came from J. Edwin Blalock, who already in 1984 considered “the immune system as a sensory organ” and, 10 years later, referred to it as “the immune system: our sixth sense” which detects antigenic molecules, otherwise undetectable by the conventional senses^{10, 12, 17}. In the review from 1995, concerning the association between the neuroendocrine and immune systems, WEIGENT and BLALOCK⁵⁴ wrote: “It is our hypothesis that the relay of information to the neuroendocrine system represents a sensory function for the immune system wherein leukocytes recognize stimuli that are not recognizable by the central and peripheral nervous systems (i.e. bacteria, tumors, viruses, and antigens). The recognition of such noncognitive stimuli by immunocytes is then converted into information and a physiological change occurs”. There is now overwhelming evidence that cytokines, peptide hormones and neurotransmitters, as well as their receptors, are endogenous to the brain, endocrine and immune systems. These shared ligands and receptors are used as a common chemical language for com-

munication within and between the immune and neuroendocrine systems. Such communication suggests both a sensory function for the immune system and an immunoregulatory role for the brain (see e.g. ^{2, 14, 33, 41–43}).

That the mind can influence the body during health and disease is an ancient notion which, in part because of its origins in anecdotal observations, has been an often and sometimes hotly debated concept. Over 20 years ago GOOD²⁷ formulated of this problem from an immunological perspective: “Immunologists are often asked whether the state of mind can influence the body’s defences. Can positive attitude, a constructive frame of mind, grief, depression, or anxiety alter ability to resist infections, allergies, autoimmunities, or even cancer? Such questions leave me with a feeling of inadequacy because I know deep down that such influences exist, but I am unable to tell how they work, nor can I in any scientific way prescribe how to harness these influences, predict or control them. Thus they cannot usually be addressed in scientific perspective”. In 2002, BLALOCK¹⁶ stated: “Today we have established that the phenomenon of central nervous system (CNS) regulation of immune function exists and, at least roughly, elucidated the how and why...”.

Acknowledgment. This work was supported in part by the State Committee for Scientific Research (KBN, Warsaw, Poland, grant No. 6P04C 047 21 and DS/IZ/2002).

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Received in August 2002

Accepted in September 2002