Chapter 78

Inflammatory and Infectious Disorders

Although apparently different with respect to the underlying cause, inflammatory and infectious diseases have much in common. In both conditions the human defense system plays an active role, counteracting the cause of the disturbance, killing the intruder, and repairing the tissue damage.

Inflammation has principally a protective role. Paradoxically, in a large number of human diseases inflammatory reactions are part of the pathogenetic mechanisms causing tissue damage. Inflammatory reactions can be not only protective but also histotoxic. The inflammatory process is characterized by a complex interplay between blood cells, blood vessels, and tissue. Although the process is complex, it follows well-orchestrated patterns.

Many components of the defense system have to come into action to destroy the invading micro-organism or counteract adverse interactions. The defense system depends largely on the immune system, which can be subdivided into an *innate (nonadaptive)* and an *acquired (adaptive)* part. Repeated infections do not improve the innate system, whereas the adaptive immune system has a "memory bank" with improved resistance after repeated attacks. In both systems a *molecular* (solvable, humoral) component can be distinguished from a *cellular* component.

In the *innate system* the *soluble factors* are *lysozyme*, *complement*, *acute phase proteins*, and *interferon*.

The enzyme *lysozyme* is a soluble bactericidal substance, abundantly present in body fluids. It is capable of splitting the exposed peptidoglycan wall of susceptible bacteria.

Complement consists of a complex series of many proteins, and forms one of the enzyme systems in plasma triggered during inflammation. Once activated, the complement system produces a rapid, highly amplified response to a trigger stimulus, mediated by a cascade reaction, in which the product of one reaction is the enzyme catalyst of the next reaction. Components of complement are designated by the letter "C" followed by a number related to the chronology of its discovery. Unfortunately, the sequence in which the complement components come into action is not identical to the sequence of their discovery. The actions of activated complement range from increasing vascular permeability to mast cell degranulation, opsonization and phagocytosis of bacteria, neutrophil activation, chemotaxis, and lysis of bacteria and foreign cells. Two ways of activating complement are distinguished. One is the so-called alternative pathway, which is activated by a microbial polysaccharide. This pathway belongs to the innate, nonspecific immune system. The other, the classical pathway, is a specific response triggered by antibody–antigen complexes. Both systems work closely together.

Acute phase proteins are plasma proteins which undergo a dramatic increase in concentration in response to infection or injury. A number of factors belong to this group, including C-reactive protein (CRP) and fibrinogen. C-reactive protein has the ability to bind to a number of micro-organisms which contain phosphorylcholine on their membranes. The complex formed is able to activate complement by the classical pathway, resulting in opsonization of the microbe for adherence to phagocytes.

Interferons are broad-spectrum antiviral agents. Different molecular forms of interferon have been identified. There are at least 14 different interferons-α (IFN-α), produced by leukocytes, while fibroblasts and other cells produce interferon-β (IFN-β), interferon-γ (IFN-γ), and macrophage activating factors, which switch on the microbicidal mechanisms of the macrophage. A subpopulation of T lymphocytes, T helper cells, will produce lymphokines, amongst them IFN-γ, if bound to an antigen in association with a major histocompatibility complex (MHC) class II molecule on a macrophage surface. IFN-γ is also produced by cytotoxic T lymphocytes which recognize antigen in association with MHC class I molecules.

The *major histocompatibility complex* (MHC) is a complex of proteins which is of predominant importance in the transplant rejection process. In man the MHC is the *human leukocyte antigen* (HLA) cluster encoded for by chromosome 6. It has been recognized that proteins encoded in this particular region of chromosome 6 are involved in many aspects of immunological recognition, including both interaction between lymphoid cells and interaction between lymphocytes and antigen presenting cells. Three classes of MHC molecules are distinguished. Class I molecules associate with antigen on the surface of virally infected cells to signal cytotoxic T lymphocytes. Class II molecules signal T helper cells to activate B cells and macrophages. T helper cells are only activated when both antigen and MHC class II molecules are presented on the antigen-presenting cell. Class III genes encode components of the complement.

The *cellular part* of the *innate immune system* is formed by *phagocytes, natural killer cells*, and *mast cells.*

The *phagocytes* can be divided into monocytes and polymorphonuclear granulocytes. The latter can be further divided into neutrophils, eosinophils, and basophils, according to the histological staining of their granules. Granulocytes do not show any specificity for antigens, but together with antibodies and complement, they play an important role in protection against micro-organisms. Their predominant role is phagocytosis. In the process of phagocytosis both oxygen-dependent and oxygen-independent mechanisms play a role. The oxygen burst is the process in phagocytosis by which oxygen is converted to *free radicals*.

Oxygen radicals and their metabolites constitute an important class of inflammatory mediators. Free radicals are atoms or molecules containing an unpaired electron in the outer orbit. Phagocytic cells, when activated, exhibit a sharp increase in molecular oxygen consumption, the so-called respiratory burst, and produce a battery of biologically active oxygen radicals and derived metabolites. The stimuli for phagocyte-derived oxygen radical production are multiple, including endotoxins, γ-immunoglobulins, and cytokines. Reduction of molecular oxygen by addition of a single electron results in formation of the superoxide anion ($O_2^{\cdot}$). In aqueous environments, $O_2^{\cdot}$ exists in equilibrium with its protonated form, $H_2O^{\cdot}$ (perhydroxyl radical). In the presence of superoxide dismutase $O_2^{\cdot}$ can undergo dismutation, resulting in H_2O_2 formation. Hydrogen peroxide has the capacity to oxidize directly a wide spectrum of biological molecules. Phagocyte-derived oxygen radicals and their metabolites are important mediators of tissue damage in inflammatory disorders. The concurrent rise in pH due to free radical formation allows cationic proteins to function optimally, damaging the bacterial membrane. The process of phagocytosis is adequately supported by the complement system, which can prepare micro-organisms for phagocytosis by opsonization.

Natural killer cells are large granular lymphocytes with a characteristic morphology, capable of recognizing structures on high-molecular-weight glycoproteins which appear on the surface of virally infected cells and allow them to be differentiated from uninfected cells. At the binding site, pores are forced in the infected cell and the cell is then killed by nuclear fragmentation through calcium-dependent endonuclease. The various interferons produced by virally infected cells augment natural killer cytotoxicity and form an integrated feedback defense system.

Mast cells have a central role in the acute inflammation process. They are loaded with granules containing preformed mediators, which are released upon triggering. This triggering occurs by components of the complement system. Mast cell activation follows two major pathways. The first pathway involves the release of the preformed mediators from the granules, such as histamine, causing vasodilatation, increased capillary permeability, and chemokinesis; neutral proteases, which activate complement; eosinophil and neutrophil chemotactic factor; and platelet activating factor, which induces mediator release, including interleukins and tumor necrosis factor with multiple actions such as macrophage activation and triggering of acute phase proteins. The second pathway results in the release of newly synthesized mediators via the phospholipase A_2 pathway. This enzyme initiates arachidonic acid degradation. Breakdown of arachidonic acid is achieved by different enzymes. Lipoxygenase leads to the promotion of leukotrienes, which influence the microcirculation and enhance chemotaxis. Cyclo-oxygenase leads to the formation of prostaglandins and thromboxanes, which affect bronchial muscle, platelet aggregation, and vasodilatation.

Complex and efficient as the innate immune system appears, many micro-organisms find ways to circumvent these responses. Here the *adaptive immune system* is important, which also has humoral and cellular components. The *humoral adaptive immune system* leads to the formation of *antibodies*, which form specific responses to specific antigens. Antibodies form a highly specific answer to those micro-organisms which escape the innate immune system. Antibodies are capable of binding specifically to the attacking microbe, activating the complement system, and stimulating phagocytic cells. The antibody molecule therefore has three main regions, two regions concerned in communicating with complement and phagocytes, and one region for binding to an individual micro-organism. The latter region carries the external recognition function. The first two functions are constant. The recognition function, however, demands numerous adaptations of recognition sites. Antibodies, when bound to a microbe, will link to the first molecule in the classical complement sequence.

The *cells* involved in the *adaptive immune system* are mainly *lymphocytes*. All the cells of the immune system are derived from pluripotent stem cells through two main lines of differentiation: the lymphoid lineage, producing lymphocytes, and the myeloid lineage, producing phagocytes and mast cells. There are three kinds of lymphocytes with different functions: T cells and B cells and the so-called third population cells. T cells differentiate initially in the thymus; B cells in fetal liver, spleen, and in adult bone marrow. Morphologically, T and B cells are identical; functionally they can be distinguished. B cells are classically defined by the production of immunoglobulins (antibodies), which are presented on

the cell surface. The T cells can be subdivided into T helper cells, T suppressor cells, and T killer cells. Their function is to recognize foreign intruders, to activate B cells, and to kill invading micro-organisms. The third population cells do not consistently carry markers of either T or B cells. They possess specific receptors for γ-immunoglobulins and form the greater part of natural killer and antibody-dependent cellular cytotoxic effectors. In another classification system, dependent on the surface proteins reacting to clusters of antigens (CD = cluster determinants), lymphocytes can be subdivided in terms of different cell types. The T helper cells are classified as CD4+ cells (formerly T4 cells); the T suppressor/killer cells as CD8+ cells (formerly T8 cells).

To orchestrate the actions of all the cells involved in the inflammatory process, a great variety of solvable mediators are used for communication between the cells. On the effector side, too, many solvable factors play an important role in the inflammatory reaction. An important group of such mediators has been given the name *cytokines*. Cytokines can be divided into monokines, produced by monocytes and macrophages, and lymphokines, produced by lymphocytes. Cytokines are hormone-like substances and are the most important mediators of the action of T lymphocytes. The immune functions of T lymphocytes are reflected by a specific set of cytokines, the lymphokines, produced by these cells after activation. Subpopulations of T cells, such as T1 and T2 helper cells, can be distinguished by the specific lymphokines they produce. Important lymphokines, some of which have been mentioned before, are interleukins, interferons, lymphotoxin, growth factors, and tumor necrosis factor. CD4+ cell has the cytokine profile of the T1 helper cell. The T1 helper cell activates the B lymphocytes to produce antibodies and it causes eosinophilia and mast cell hyperplasia. The CD8+ lymphocyte has T2 cell characteristics and is responsible for cytotoxicity, complement fixation, and macrophage activation. The CD8+ lymphocyte profile, therefore, protects against viruses, tumors, and infections. It is also responsible for transplant rejection, inflammation, and autoimmune reaction. Cytokines form a functional network. The various factors, messengers, and effectors act in a subtle interaction. These interactions may be synergistic, additive, or antagonistic, and function in order to maintain a balance of optimal efficacy in the protection of the host.

The cooperative cellular and mediator activity in *inflammatory (either infectious or noninfectious) disorders* of the CNS can be briefly summarized as follows:

Circulating T cells recognize the antigen concerned in combination with the major histocompatibility complex class II on antigen-presenting cells and start to proliferate. The antigen-presenting cells in the CNS may be perivascular macrophages, the gatekeepers of the CNS. Microglial cells may also act as antigen-presenting cells within the CNS. Sensitized or activated T cells start to release substances such as interferons (interferon-γ), which activate local cells such as microglia, astrocytes, and perivascular macrophages. This local activation results in upregulation of adhesion molecules on endothelial cells, enhanced expression of major histocompatibility complex, and release of chemoattractive substances, which attract and facilitate the entrance of more T cells, macrophages, and B lymphocytes. B cells are triggered to become plasma cells and produce antibodies. Macrophages, microcytes, astrocytes, and mast cells start to produce inflammatory mediators such as tumor necrosis factors, reactive oxygen species, interleukins, vasoactive amines, leukotrienes, complement, and hydrolytic enzymes. The result is, eventually, vascular dilatation, increased capillary permeability, exudation of fluid in tissue, and extravasation of numerous cells, leading subsequently to disruption of the blood–brain barrier, perivascular inflammation, formation of edema and demyelination. Phagocytosis of myelin by macrophages may be initiated by antimyelin antibodies, or by opsonization via their receptor for complement component.

Knowledge of the factors mediating inflammation has stimulated attempts to undo undesired reactions by counteracting or blocking the involved pathways. Interferon-γ, for example, proved to have a negative influence on the course of secondary progressive multiple sclerosis. Interferon-β, known to counteract the action of interferon-γ, seems to have a beneficial effect on the course of this disease.

In *infectious disorders* several pathogenetic factors play a role in evoking the host response. Exotoxins, for example, are produced by micro-organisms during their growth. They have a proteinaceous nature and therefore act as antigens. They evoke an antibody response and in this way give rise to neutralizing antitoxins. Endotoxins are membrane molecules, lipopolysaccharides, present in the outer cell membrane of gram-negative bacteria. The polysaccharide chain is variable and determines the antigenic structure of the bacteria. The lipid fraction anchors the lipopolysaccharide in the outer bacterial membrane, is less variable, and is responsible for the toxic effects. After liberation of the lipopolysaccharides from the bacterial membrane they adsorb on the lipid membrane of many cells, especially neutrophils. This triggers a whole cascade of immune reactions. Another way to evoke immune reactions is by presentation of antigens by specialized cells, also called antigen-presenting cells, such as the Langerhans and dendritic cells. These cells recognize the foreign intruders, probably by lack of identifying cell surface membrane

MHC class I compounds. Viruses use the replication system of host cells and bring their antigens to expression on the surface of the host cells, activating natural killer cells.

The presence and multiplication of the original micro-organism sustains the disease or expands it. The micro-organisms produce a gamut of products to assist in their spread, including streptokinase, hyaluronidase, and neuraminidase. In many cases it is difficult to distinguish the direct influence of the micro-organisms on the tissue from the immunological reaction the attack provokes. A demonstration of this is found in subacute sclerosing panencephalitis, caused by the measles virus. In subacute sclerosing panencephalitis, as in other persistent viral infections, deposits of immune complexes can be demonstrated in the wall of small cerebral blood vessels. The presence of immune complexes and the histological findings of perivascular edema, inflammation, and demyelination provide strong evidence that, in addition to the actual invasion by the virus, there is a contemporaneous immune-mediated response to this virus which is responsible for much of the tissue damage. The same could be true for subacute AIDS encephalitis and tropical spastic paraparesis due to HTLV-1 infection.

Selective neuronal and/or glial damage in infectious disorders and the predilection for particular areas (topistic areas) is in most cases difficult to understand. Experience has taught that herpes simplex virus has an affinity for the frontal and temporal lobes; fungal infections attack primarily gray matter structures; *Haemophilus influenzae* has a preference for cortico-subcortical areas; cytomegalovirus (CMV) encephalopathy and AIDS encephalopathy in adults are predominantly located in the cerebral white matter and spare the U fibers. There is often a considerable difference between the course of a disease and the predilection sites between congenital infections and infections acquired later, after birth. A good example is the difference between congenital, connatal, and adult CMV infection, and between congenital and postnatal toxoplasmosis.

In some infections the preferential location is simply related to the porte d'entrée. For example, infections that involve the leptomeninges will enter the brain via the Virchow–Robin spaces and are located predominantly in the cortex (*Haemophilus influenzae*) and in the basal ganglia (*Cryptococcus neoformans*) or both. In herpes simplex virus, a primary infection in the throat or mouth is followed by the persistent presence of latent virus in sensory ganglia and possibly also in the brain, after entry via the olfactory route. Following activation of the latent virus, direct spread may explain the frontotemporal predominance. Within the affected area, herpes simplex virus infects all types of cells.

For many viruses a necessary condition for the entry into cells is the availability of specific receptor molecules at the surface of such cells. The distribution of these receptor molecules will largely determine the specific regions of the brain preferentially attacked by the virus and the population of cells in the affected regions that are injured or destroyed. Some viruses like JC papovavirus, responsible for progressive multifocal leukoencephalopathy, infect oligodendrocytes with sparing of the neurons. This explains the affinity of this virus for white matter. Rabies virus has great affinity for the cerebellum and limbic system, whereas poliomyelitis affects the motor nuclei in the cortex, brain stem, and anterior horns of the spinal cord. Creutzfeldt–Jacob disease, caused by prions, has been shown by MRI to affect in particular the basal ganglia. These differences in topographical distribution are considered to be the result of specific receptor interactions.

Viruses enter the cells of the host either by fusing with the plasma membrane and discharging their contents directly in the cytosol, or by being internalized through the endocytotic pathway. The first way is used by herpes simplex and corona viruses. Internalization does not have special requirements in these cases. Other viruses do not have this option and have to follow the other path, involving binding to a receptor and collection of receptor–ligand complexes at the cell membrane. The viruses are then transported within endocytotic vesicles. After penetration of the cell membrane, the replicative machinery of the virus itself comes into play. Using the host cell system of nucleic acid (DNA/RNA) replication and transcription, viruses can replicate and transcribe their DNA or RNA and in so doing multiply themselves; the new virus particles leave the cell in search of new host cells. Ultimately the balance between the viral machinery and the host immune system will determine the outcome of the infection.

In the *noninfectious inflammatory disorders* other mechanisms play a role in invoking the host response, not all of which are well understood. The inflammatory reactions may be triggered by "primary" autoimmune reactions, in which autoantibodies are primarily directed against autoantigens, as is the case in vasculitis of the CNS, in systemic lupus erythematosus, Behçet disease, giant cell arteritis, and rheumatoid vasculitis. The hypothesis is that these primary autoimmune disorders are the result of a dysfunction of T cell regulation. The inflammatory response in the CNS may also be secondary to an infectious disease elsewhere in the body or a vaccination. Mycoplasma infections of the lung, for example, may lead to an acute disseminated encephalomyelitis, caused by the formation of antibodies that cross-react with CNS antigens on myelin membranes or surface molecules of CNS cells. This reaction resembles in many re-

spects the experimental allergic encephalomyelitis provoked by immunization with components of the myelin membrane (basic myelin protein, for example). Such a secondary autoimmune response probably also forms the basis of several paraneoplastic syndromes of the CNS, such as limbic encephalitis, and Purkinje cell degeneration. Here, too, the hypothesis is that antibodies formed against tumor antigens cross-react with structural components of the CNS.

As far as the involvement of myelin in inflammatory and infectious disorders is concerned, several biomechanisms can be distinguished:

- Immune reaction against one of the components of myelin. This occurs in acute disseminated encephalomyelitis. This condition can be simulated in an animal model, experimental allergic encephalomyelitis. In this experimental condition the animal has been sensitized against basic myelin protein.
- Specific infection of oligodendrocytes leading to cell death and subsequent loss of the myelin sheath extension of the oligodendrocytes. This is the case in progressive multifocal leukoencephalopathy.
- Myelin can also be an innocent bystander and become a victim in a process that hits all white matter components and possibly gray matter as well. This occurs in a multitude of infections, such as those caused by *Haemophilus influenzae* and herpes simplex virus, and in toxoplasmosis.
- Finally, dysmyelination may be the consequence of infectious or inflammatory changes to unmyelinated white matter, damaging the white matter matrix. Most of the congenital infections can have this effect, often in addition to other visible structural lesions.