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ACUTE-PHASE PROTEINS AND OTHER SYSTEMIC RESPONSES TO INFLAMMATION

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A LARGE number of changes, distant from the site or sites of inflammation and involving many organ systems, may accompany inflammation. In 1930 interest was focused on these changes by the discovery of C-reactive protein (so named because it reacted with the pneumococcal C-polysaccharide) in the plasma of patients during the acute phase of pneumococcal pneumonia.[1] Accordingly, these systemic changes have since been referred to as the acute-phase response,[2] even though they accompany both acute and chronic inflammatory disorders. New acute-phase phenomena continue to be recognized, and the mechanisms mediating them are becoming better understood. This review summarizes much of the knowledge that has been acquired about the acute-phase response since this subject was last reviewed in the *Journal* in 1984.[3]

ACUTE-PHASE RESPONSES

Acute-phase changes may be divided into changes in the concentrations of many plasma proteins, known as the acute-phase proteins (Table 1), and a large number of behavioral, physiologic, biochemical, and nutritional changes (Table 2). An acute-phase protein has been defined as one whose plasma concentration increases (positive acute-phase proteins) or decreases (negative acute-phase proteins) by at least 25 percent during inflammatory disorders.[4] The changes in the concentrations of acute-phase proteins are due largely to changes in their production by hepatocytes. The magnitude of the increases varies from about 50 percent in the case of ceruloplasmin and several complement components to as much as 1000-fold in the case of C-reactive protein and serum amyloid A, the plasma precursor of amyloid A (the principal constituent of secondary amyloid deposits) (Fig. 1).

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Conditions that commonly lead to substantial changes in the plasma concentrations of acute-phase proteins include infection, trauma, surgery, burns, tissue infarction, various immunologically mediated and crystal-induced inflammatory conditions, and advanced cancer. Moderate changes occur after strenuous exercise, heatstroke, and childbirth. Small changes occur after psychological stress and in several psychiatric illnesses.[6] Although the concentrations of multiple components of the acute-phase response commonly increase together, not all of them increase uniformly in all patients with the same illness. Thus, febrile patients may have normal plasma concentrations of C-reactive protein, and discordance between the plasma concentrations of different acute-phase proteins is common. These variations, which indicate that the components of the acute-phase response are individually regulated, may be explained in part by differences in the patterns of production of specific cytokines or their modulators in different pathophysiologic states.

REGULATION OF ACUTE-PHASE CHANGES

Induction of Acute-Phase Proteins by Cytokines and Other Extracellular Signaling Molecules

Cytokines are intercellular signaling polypeptides produced by activated cells. Most cytokines have multiple sources, multiple targets, and multiple functions. The cytokines that are produced during and participate in inflammatory processes are the chief stimulators of the production of acute-phase proteins. These inflammation-associated cytokines include interleukin-6, interleukin-1β, tumor necrosis factor α, interferon-γ, transforming growth factor β,[2] and possibly interleukin-8.[7] They are produced by a variety of cell types, but the most important sources are macrophages and monocytes at inflammatory sites.

Interleukin-6 is the chief stimulator of the production of most acute-phase proteins,[8] whereas the other implicated cytokines influence subgroups of acute-phase proteins. However, in mice rendered incapable of expressing interleukin-6 (knockout mice), the role of interleukin-6 in stimulating the production of acute-phase proteins depends on the nature or site of the inflammatory stimulus; the response is largely inhibited in interleukin-6 knockout mice injected with turpentine but is normal when bacterial lipopolysaccharide is the inflammatory stimulus.[9] This finding indicates that lipopolysaccharide causes the production of other cytokines capable of stimulating the production of acute-phase proteins.[9] The responses are similar in interleukin-1β knockout mice, presumably because interleukin-1β is required to stimulate the production of interleukin-6 after the administration of turpentine.[10] These studies provide further evidence that patterns of cytokine production and the acute-phase response differ in different

TABLE 1. HUMAN ACUTE-PHASE PROTEINS.

Proteins whose plasma concentrations increase
Complement system
C3
C4
C9
Factor B
C1 inhibitor
C4b-binding protein
Mannose-binding lectin
Coagulation and fibrinolytic system
Fibrinogen
Plasminogen
Tissue plasminogen activator
Urokinase
Protein S
Vitronectin
Plasminogen-activator inhibitor 1
Antiproteases
α_1-Protease inhibitor
α_1-Antichymotrypsin
Pancreatic secretory trypsin inhibitor
Inter-α-trypsin inhibitors
Transport proteins
Ceruloplasmin
Haptoglobin
Hemopexin
Participants in inflammatory responses
Secreted phospholipase A_2
Lipopolysaccharide-binding protein
Interleukin-1–receptor antagonist
Granulocyte colony-stimulating factor
Others
C-reactive protein
Serum amyloid A
α_1-Acid glycoprotein
Fibronectin
Ferritin
Angiotensinogen
Proteins whose plasma concentrations decrease
Albumin
Transferrin
Transthyretin
α_2-HS glycoprotein
Alpha-fetoprotein
Thyroxine-binding globulin
Insulin-like growth factor I
Factor XII

TABLE 2. OTHER ACUTE-PHASE PHENOMENA.

Neuroendocrine changes
Fever, somnolence, and anorexia
Increased secretion of corticotropin-releasing hormone, corticotropin, and cortisol
Increased secretion of arginine vasopressin
Decreased production of insulin-like growth factor I
Increased adrenal secretion of catecholamines
Hematopoietic changes
Anemia of chronic disease
Leukocytosis
Thrombocytosis
Metabolic changes
Loss of muscle and negative nitrogen balance
Decreased gluconeogenesis
Osteoporosis
Increased hepatic lipogenesis
Increased lipolysis in adipose tissue
Decreased lipoprotein lipase activity in muscle and adipose tissue
Cachexia
Hepatic changes
Increased metallothionein, inducible nitric oxide synthase, heme oxygenase, manganese superoxide dismutase, and tissue inhibitor of metalloproteinase-1
Decreased phosphoenolpyruvate carboxykinase activity
Changes in nonprotein plasma constituents
Hypozincemia, hypoferremia, and hypercupremia
Increased plasma retinol and glutathione concentrations

inflammatory conditions. Interleukin-11, leukemia inhibitory factor, oncostatin M, ciliary neurotrophic factor, and cardiotrophin 1 may have actions similar to those of interleukin-6.[11]

Cytokines operate both as a cascade and as a network in stimulating the production of acute-phase proteins. Many cytokines can regulate the production of other cytokines and cytokine receptors. For example, tumor necrosis factor α is the main stimulator of interleukin-1 production in patients with rheumatoid arthritis[12]; interleukin-1β may increase or decrease expression of its own receptors[13]; the interleukin-6 response to the injection of turpentine in mice requires interleukin-1β; and interleukin-6 inhibits the expression of tumor necrosis factor α.[14]

In addition, cytokines are components of a large, complex signaling network. Most likely, cells are seldom exposed to only a single cytokine. Instead, combinations of mediators convey biologically relevant information. The effects of cytokines on target cells may be inhibited or enhanced by other cytokines, by hormones, and by cytokine-receptor antagonists and circulating receptors. Combinations of cytokines have been found to have additive, inhibitory, or synergistic effects.[15] Thus, the induction of C-reactive protein and serum amyloid A in some models requires both interleukin-6 and either interleukin-1 or tumor necrosis factor α, and the induction of fibrinogen by interleukin-6 is inhibited by interleukin-1, tumor necrosis factor α, and transforming growth factor β.[15] Interleukin-6 enhances the effect of interleukin-1β in inducing the expression of interleukin-1–receptor antagonist,[16] and interleukin-4 inhibits the induction of some acute-phase proteins by other cytokines.[17] Soluble interleukin-6 receptor α molecules increase the effects of the ligand,[18] whereas other soluble receptors, such as those for tumor necrosis factor α and interleukin-1, are inhibitory. Glucocorticoids generally enhance the stimulatory effects of cytokines on the production of acute-phase proteins,[19] whereas insulin decreases their effects on the production of some acute-phase proteins.[20]

The expression of genes for acute-phase proteins is regulated mainly at the transcriptional level, but post-transcriptional mechanisms also participate.[21,22]

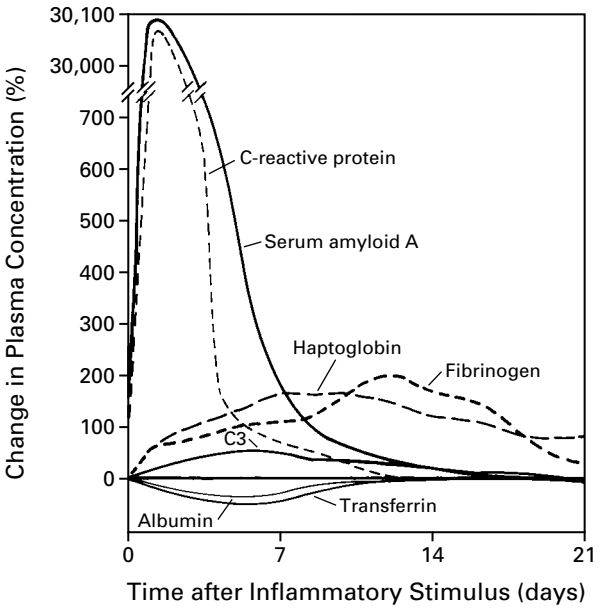

Figure 1. Characteristic Patterns of Change in Plasma Concentrations of Some Acute-Phase Proteins after a Moderate Inflammatory Stimulus.

Modified from Gitlin and Colten[5] with the permission of the publisher.

Post-translational changes in the glycosylation of plasma proteins during inflammatory states include alterations in oligosaccharide branching,[23] increased sialylation of orosomucoid,[24] and decreased galactosylation of IgG.[25] Changes in oligosaccharide branching are induced by inflammation-associated cytokines, independently of their effects on the production of acute-phase proteins. Finally, the efficiency of secretion of C-reactive protein, a process distinct from its synthesis, is greatly increased during the acute-phase response.[26]

Regulation of Other Acute-Phase Changes by Inflammation-Associated Cytokines

Fever is representative of the neuroendocrine changes that characterize the acute-phase response. Although several cytokines may induce fever, interleukin-6 produced in the brain stem is required for the final steps leading to fever.[27] However, cytokines are not the sole inducers of fever; the recent finding that subdiaphragmatic vagotomy blocks fever after intraperitoneal (but not intramuscular) injection of lipopolysaccharide implicates neural transmission in the febrile response.[28] Other neuroendocrine changes reflect complex interactions among cytokines, the hypothalamic–pituitary–adrenal axis, and other components of the neuroendocrine system.[29] For example, inflammation-associated cytokines stimulate the production of corticotropin-releasing hormone, with consequent stimulation of corticotropin and cortisol production, and also directly stimulate the adrenal gland. Stimulation of the production of arginine vasopressin by interleukin-6 can explain the hyponatremia that occurs during some inflammatory disorders.

The behavioral changes that often accompany inflammation, including anorexia, somnolence, and lethargy, are similarly induced by cytokines. Neural mechanisms have also been implicated in anorexia; as with fever, vagal afferents are required for the induction of anorexia after intraperitoneal injection of interleukin-1β and lipopolysaccharide. Increased plasma leptin concentrations occur in inflammation, probably in response to stimulation of adipocytes by cytokines, and may also contribute to anorexia.[30]

Inflammation-associated cytokines have been implicated in the pathogenesis of anemia in chronic disease; examples of their involvement include the decreased responsiveness of erythrocyte precursors to erythropoietin, decreased production of erythropoietin, and impaired mobilization of iron from macrophages.[31] Hypoferremia results largely from the sequestration of iron in macrophages by apoferritin produced in response to the inflammation-associated cytokines interleukin-4 and interleukin-13.[32] The thrombocytosis of inflammation appears to be caused by interleukin-6.[33] Finally, cachexia, the loss of body mass that occurs in severe chronic inflammatory disease, results from decreases in skeletal muscle, fat tissue, and bone mass. Interleukin-1β, interleukin-6, tumor necrosis factor α, and interferon γ all contribute to these processes.[34-36]

Inflammation-associated cytokines also alter many intracellular hepatic constituents, including inducible nitric oxide synthase, manganese superoxide dismutase, and microsomal heme oxygenase. Interleukin-6 increases the production of the metal-binding protein metallothionein, with consequent increased zinc binding and hypozincemia. Interleukin-1β and tumor necrosis factor α decrease the expression of growth-hormone receptors on hepatocytes, with subsequent decreased responsiveness to growth hormone and low plasma concentrations of insulin-like growth factor I.[37] Transgenic mice that overexpress interleukin-6 have low plasma concentrations of insulin-like growth factor I and are smaller than normal mice. This finding suggests that increased production of inflammation-associated cytokines may explain, at least in part, impaired growth in children with chronic inflammatory conditions.[38]

POSTULATED FUNCTION OF THE ACUTE-PHASE RESPONSE

The assumption that the changes in plasma concentrations of acute-phase proteins are beneficial is based largely on the known functional capabilities of the proteins and on logical speculation as to how these might serve useful purposes in inflammation,

healing, or adaptation to a noxious stimulus. Inflammation is a complex, highly orchestrated process involving many cell types and molecules, some of which initiate, amplify, or sustain the process, some of which attenuate it, and some of which cause it to resolve. A number of the participating molecules are multifunctional and contribute to both the waxing and the waning of inflammation at different points in its evolution.[39]

Many of the acute-phase proteins have the potential to influence one or more of these stages of inflammation. A major function of C-reactive protein, a component of the innate immune system, is its ability to bind phosphocholine and thus recognize some foreign pathogens as well as phospholipid constituents of damaged cells.[40] It can activate the complement system when bound to one of its ligands and can also bind to phagocytic cells, an observation suggesting that it can initiate the elimination of targeted cells by its interaction with both humoral and cellular effector systems of inflammation.[40] Other proinflammatory effects of C-reactive protein include the induction of inflammatory cytokines and tissue factor in monocytes.[41,42] However, its net effect is antiinflammatory in transgenic mice that produce large amounts of C-reactive protein.[43,44] Such an effect of C-reactive protein may be explained by its ability to prevent the adhesion of neutrophils to endothelial cells by decreasing the surface expression of L-selectin,[45] to inhibit the generation of superoxide by neutrophils, and to stimulate the synthesis of interleukin-1–receptor antagonist by mononuclear cells. It seems likely that C-reactive protein has many pathophysiologic roles in the inflammatory process.

The actions of serum amyloid A, the other major acute-phase protein in humans, are largely unknown. Serum amyloid A consists of a family of apolipoproteins that rapidly bind to high-density lipoprotein after their synthesis and have the potential to influence cholesterol metabolism during inflammatory states.[46,47] Serum amyloid A has also been reported to cause adhesion and chemotaxis of phagocytic cells and lymphocytes and may contribute to the inflammation in atherosclerotic coronary arteries by increasing the oxidation of low-density lipoproteins.[48]

Several acute-phase proteins initiate or sustain inflammation. The classic complement components, many of which are acute-phase proteins, have central proinflammatory roles in immunity, as does mannose-binding lectin, a recently recognized acute-phase component of complement. Complement activation leads to chemotaxis, plasma protein exudation at inflammatory sites, and opsonization of infectious agents and damaged cells. Similarly, granulocyte colony-stimulating factor increases the inflammatory response by increasing the numbers of granulocyte precursors in bone marrow and by activating mature granulocytes.

In contrast, other acute-phase proteins may have antiinflammatory actions. For example, the antioxidants haptoglobin and hemopexin protect against reactive oxygen species. Both α_1-protease inhibitor and α_1-antichymotrypsin antagonize the activity of proteolytic enzymes; α_1-antichymotrypsin also inhibits the generation of superoxide anion.[49] Wound healing can be influenced by two acute-phase proteins: fibrinogen can cause endothelial-cell adhesion, spreading, and proliferation, all critical to tissue repair, and haptoglobin aids in wound repair by stimulating angiogenesis.[50]

It is not clear what functional advantages may arise from decreases in plasma concentrations of the negative acute-phase proteins. It is logical to presume that the need to divert available amino acids to the production of other acute-phase proteins explains the decreased production of plasma proteins not required for host defense. Since transthyretin, a negative acute-phase protein, inhibits interleukin-1 production by monocytes and endothelial cells,[51] a decrease in its plasma concentration may be proinflammatory.

It is possible to speculate about the beneficial effects of other acute-phase phenomena. Somnolence associated with inflammatory states may reduce demands for energy. The adaptive value of fever has been attributed to both the enhancement of immunity and the stabilization of cell membranes.[52] Glucocorticoids have a major role in the maintenance of hemodynamic stability during severe illness and can modulate the immune and inflammatory responses to different noxious stimuli. The increase in plasma lipid concentrations may provide nutrients to cells involved in host defense and substrates for the regeneration of damaged membranes. In addition, circulating lipoproteins can bind to and decrease the toxic effects of lipopolysaccharide, thus participating in the defense against microbes.[36] Increased production of heme oxygenase and manganese superoxide dismutase may limit oxidant-mediated tissue injury, whereas tissue inhibitor of metalloproteinase-1 antagonizes the destructive effects of metalloproteinases.

As with all inflammation-associated phenomena, the acute-phase response is not uniformly beneficial. Anemia and impaired growth have been mentioned above. When extreme, cytokine-induced changes associated with the acute-phase response can be fatal, as in septic shock.[53] In addition, the persistence of the acute-phase response because of long-term stimulation, as in advanced cancer and the acquired immunodeficiency syndrome, can lead to metabolic disturbances that ultimately result in cachexia. Finally, secondary amyloidosis has long been recognized as a deleterious consequence of elevated serum amyloid A concentrations in some patients with chronic inflammatory conditions.

CLINICAL ASSESSMENT OF ACUTE-PHASE PROTEINS AND CYTOKINES

Both anemia and hypoalbuminemia due to inflammation are common among hospitalized patients. Estimation of other changes in acute-phase proteins, despite the lack of diagnostic specificity, is useful to clinicians because such changes reflect the presence and intensity of an inflammatory process. Thus, measurements of plasma or serum C-reactive protein can help differentiate inflammatory from noninflammatory conditions and are useful in managing the patient's disease, since the concentration often reflects the response to and need for therapeutic intervention. Finally, in some diseases, such as rheumatoid arthritis, serial measurements of C-reactive protein are of prognostic value.[54] In evaluating laboratory results, physicians should be aware that some laboratories report C-reactive protein concentrations in milligrams per liter and others in milligrams per deciliter. Serum amyloid A concentrations usually parallel those of C-reactive protein, although some studies indicate that serum amyloid A is a more sensitive marker of inflammatory disease.[46] At present, assays for serum amyloid A are not widely available.

Currently, the most widely used indicators of the response of acute-phase proteins are the erythrocyte sedimentation rate and the plasma C-reactive protein concentration. The rate at which erythrocytes fall through plasma — that is, the erythrocyte sedimentation rate — depends largely on the plasma concentration of fibrinogen. As a test, the erythrocyte sedimentation rate has the advantages of familiarity, simplicity, and an abundant literature compiled over the past seven decades. Nonetheless, measurement of C-reactive protein has several advantages over this method. The erythrocyte sedimentation rate is an indirect measurement of plasma acute-phase protein concentrations and can be greatly influenced by the size, shape, and number of erythrocytes, as well as by other plasma constituents such as immunoglobulins. Consequently, the results are imprecise and sometimes misleading. Although the erythrocyte sedimentation rate represented a great advance when it was introduced in the 1920s, this indirect method (which some regard as archaic) is no longer needed to assess plasma concentrations of fibrinogen, because they can now be determined directly. As a patient's condition worsens or improves, the erythrocyte sedimentation rate changes relatively slowly, whereas plasma C-reactive protein concentrations change rapidly. The range of abnormal values for C-reactive protein is broader than the range of abnormal values for the erythrocyte sedimentation rate, with accompanying clinical implications: among patients with plasma C-reactive protein concentrations greater than 100 mg per liter, 80 to 85 percent have bacterial infections.[4] The erythrocyte sedimentation rate increases steadily with age, but plasma C-reactive protein concentrations do not.

Systemic lupus erythematosus is one exception to the generalization that C-reactive protein concentrations correlate with the extent and severity of inflammation. Many patients with active systemic lupus erythematosus do not have high plasma concentrations of C-reactive protein (or serum amyloid A) but do have marked increases during bacterial infection.[55] Application of this knowledge to the differential diagnosis of fever in patients with systemic lupus erythematosus has been somewhat limited by the finding that plasma C-reactive protein concentrations are also high in patients with active lupus serositis[56] or chronic synovitis.[57]

Most normal subjects have plasma C-reactive protein concentrations of 2 mg per liter or less, but some have concentrations as high as 10 mg per liter. The latter finding, attributed to limited stimulation by minimally apparent low-grade processes such as gingivitis or trivial injury, has led to the suggestion that values of less than 10 mg per liter should be regarded as clinically unimportant.[4] However, C-reactive protein concentrations well below 10 mg per liter, but higher than those in most normal subjects, have been found in patients with osteoarthritis, particularly those with progressive joint damage.[58] This observation supports other data indicating the participation of inflammation in this disorder. In addition, slightly elevated concentrations of C-reactive protein, within the range in normal subjects, have been found to predict subsequent coronary events, often years later, in patients with angina and in healthy physicians.[59,60] These data may reflect the presence of low-grade inflammation in coronary arteries or elsewhere, or alternatively, they may reflect proinflammatory or prothrombotic effects of C-reactive protein itself.[41,42] These findings are not likely to prove clinically useful, since the mildly elevated concentrations in these studies fall well within the range in healthy subjects.

Plasma concentrations of cytokines and cytokine receptors have been studied in patients with inflammatory conditions. Measurement of cytokines in plasma is difficult, partly because of their short plasma half-lives and the presence of blocking factors.[61,62] Plasma interleukin-6 concentrations are elevated in patients with many inflammatory diseases, but except for the rapidity with which change occurs, measurement of plasma interleukin-6 concentrations has no apparent advantage over measurement of plasma C-reactive protein. Reports of different patterns of cytokine responses in different disease states raise the possibility that cytokine determinations may ultimately have diagnostic value.[63,64] Until further studies are available, the high cost, limited availability, and absence of standardization argue against the measurement of plasma cytokines and their receptors in clinical practice.

CONCLUSIONS

The acute-phase response, an important pathophysiologic phenomenon, replaces the normal homeostatic mechanisms with new set points that presumably contribute to defensive or adaptive capabilities. The functions of these changes are highly variable and diverse: some participate in initiating or sustaining the inflammatory process, others modulate it, and still others have adaptive roles. These changes are induced by a complex intercellular signaling system of which the chief constituents are inflammation-associated cytokines. Several cytokines, particularly interleukin-6, stimulate the production of acute-phase proteins in response to varied stimuli. The patterns of cytokine production and of the acute-phase response differ in different inflammatory conditions. Acute-phase changes reflect the presence and intensity of inflammation, and they have long been used as a clinical guide to diagnosis and management. For this purpose, determination of serum C-reactive protein has advantages over the traditional strategy of measuring the erythrocyte sedimentation rate.

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CORRECTION

Acute-Phase Proteins and Other Systemic Responses to Inflammation

Acute-Phase Proteins and Other Systemic Responses to Inflammation . On page 449, in Table 1, under the heading ``Proteins whose plasma concentrations decrease,´´ retinol-binding protein should have appeared. Also on page 449, in Table 2, the last entry should have been two entries reading, ``Decreased plasma retinol concentrations´´ and ``Increased plasma glutathione concentrations,´´ not one entry reading, ``Increased plasma retinol and glutathione concentrations,´´ as printed.