Aaron S. Dumont, M.D.
Departments of Neurological Surgery and Neuroscience, University of Virginia School of Medicine, Charlottesville, Virginia

Randall J. Dumont, M.Sc.
Department of Neurological Surgery, University of Virginia School of Medicine, Charlottesville, Virginia, and Faculty of Medicine, University of British Columbia, Vancouver, British Columbia, Canada

Michael M. Chow, M.D.
Department of Neurological Surgery, University of Virginia School of Medicine, Charlottesville, Virginia

Chi-lung Lin, M.D.
Department of Neuroscience, University of Virginia, School of Medicine, Charlottesville, Virginia, and Department of Neurological Surgery, Kaohsiung Medical University, Kaohsiung, Taiwan

Tarkan Calisaneller, M.D.
Departments of Neurological Surgery and Neuroscience, University of Virginia School of Medicine, Charlottesville, Virginia

Klaus F. Ley, M.D.
Departments of Biomedical Engineering and Molecular Physiology and Biophysics, and Cardiovascular Research Center, University of Virginia School of Medicine, Charlottesville, Virginia

Neal F. Kassell, M.D.
Department of Neurological Surgery, University of Virginia School of Medicine, Charlottesville, Virginia

Kevin S. Lee, Ph.D.
Departments of Neuroscience and Neurological Surgery, University of Virginia School of Medicine, Charlottesville, Virginia

Reprint requests:
Aaron S. Dumont, M.D., Department of Neurological Surgery, University of Virginia Health Sciences Center, Box 212, Charlottesville, VA 22908.
Email: asd2f@virginia.edu

Received, July 17, 2002.
Accepted, March 11, 2003.

CEREBRAL VASOSPASM AFTER SUBARACHNOID HEMORRHAGE: PUTATIVE ROLE OF INFLAMMATION

CEREBRAL VASOSPASM IS a common, formidable, and potentially devastating complication in patients who have sustained subarachnoid hemorrhage (SAH). Despite intensive research efforts, cerebral vasospasm remains incompletely understood from both the pathogenic and therapeutic perspectives. At present, no consistently efficacious and ubiquitously applied preventive and therapeutic measures are available in clinical practice. Recently, convincing data have implicated a role of inflammation in the development and maintenance of cerebral vasospasm. A burgeoning (although incomplete) body of evidence suggests that various constituents of the inflammatory response, including adhesion molecules, cytokines, leukocytes, immunoglobulins, and complement, may be critical in the pathogenesis of cerebral vasospasm. Recent studies attempting to dissect the cellular and molecular basis of the inflammatory response accompanying SAH and cerebral vasospasm have provided a promising groundwork for future studies. It is plausible that the inflammatory response may indeed represent a critical common pathway in the pathogenesis of cerebral vasospasm pursuant to SAH. Investigations into the nature of the inflammatory response accompanying SAH are needed to elucidate the precise role(s) of inflammatory events in SAH-induced pathologies.

KEY WORDS: Cerebral vasospasm, Gene expression, Inflammation, Subarachnoid hemorrhage

Neurosurgery 53:123-135, 2003 DOI: 10.1227/01.NEU.0000068863.37133.9E www.neurosurgery-online.com

Stroke is the third leading cause of death and the leading cause of disability in contemporary society (3). Subarachnoid hemorrhage (SAH) accounts for approximately 6 to 8% of all strokes and 22 to 25% of cerebrovascular deaths (45). Between 1 million and 12 million people in the United States harbor intracranial aneurysms (119), and the annual prevalence of aneurysmal SAH in this country is believed to be in excess of 30,000 persons (45). The population-based incidence rate is estimated at 7 to 20 per 100,000 per year (111). Although the overall incidence of stroke is declining (9), the incidence of aneurysmal SAH does not seem to be on the wane (50). Despite considerable advances in the diagnosis and treatment of SAH, the outcome remains poor. Half of all patients who sustain an SAH die, approximately 15% are left severely disabled, and only 20 to 35% attain a moderate or good recovery (112, 116). Cerebral vasospasm has been demonstrated to be a significant predictor of adverse outcome and the leading potentially treatable cause of death and disability in patients with aneurysmal SAH (55, 56).

Cerebral vasospasm is a common and potentially incapacitating complication of SAH. Angiographic evidence of arterial spasm is seen in up to 70% of patients, and clinical manifestations are witnessed in 20 to 30% of patients (55, 145). Despite maximal therapy, nearly 50% of patients with symptomatic vasospasm will develop infarction (83). Fifteen percent to 20% of patients will sustain a disabling stroke or die of progressive ischemia (35). No consistently efficacious therapies have as yet been identified and implemented in clinical practice.

Although cerebral vasospasm after SAH has been the subject of substantial research interest, the underlying pathogenic mechanisms remain obscure. This fact has hindered the development of rational and specific treatment paradigms. The presence of a subarachnoid blood clot is sufficient to produce arterial spasm in the absence of additional arterial injury, intracranial hypertension, or cerebral

ischemia or infarction (although these conditions often coexist) (145). It is not known precisely how the presence of subarachnoid blood evokes delayed constriction of cerebral arteries. Although the production of arterial spasm is probably complex and multifactorial, identification of the key pathogenic pathways would be of immense benefit. Partial success with a variety of experimental treatments may reflect the fact that such interventions are targeted at one of potentially many processes upstream from the final common and integral pathway. If indeed such an entity exists, it would advance our current understanding of and therapeutic approaches to cerebral vasospasm. Inflammation in response to subarachnoid blood is a plausible candidate pathway leading to cerebral vasospasm. A burgeoning but currently incomplete body of evidence lends credence to this assertion.

Accrued data indicate that antecedent inflammation of the subarachnoid space elicits arterial constriction. Cerebral vasospasm is thought to complicate certain infectious processes of the subarachnoid space (110). For instance, cerebrovascular complications have frequently been found to accompany bacterial meningitis (110). In addition, nonspecific inflammation of the subarachnoid space produced by substances such as talc (88) or beads (latex or dextran) (104) results in marked arterial constriction and vessel morphological changes mimicking those seen after SAH. A recent surge of studies examining many facets of the inflammatory response accompanying experimental and clinical SAH has emerged. The present discussion critically evaluates the existing body of literature implicating inflammation as a mediator of cerebral vasospasm and attempts to highlight important avenues of investigation for future study.

IMMUNOLOGY AND THE INFLAMMATORY RESPONSE: AN INTRODUCTION

The immune system is composed of a carefully orchestrated repertoire of cells and molecules designed to defend against and ultimately eliminate foreign antigens. Cellular and molecular components play important roles in the immune response. Phagocytic cells, including neutrophils, monocytes, and macrophages, and lymphocytes, including B and T cells, are important cellular constituents. Molecular components, including complement, acute-phase proteins, and cytokines, are also important effectors of the immune response.

Active immune responses consist of two main constituents, called humoral and cellular. The humoral arm is mediated primarily by antibody-secreting B cells, whereas the cellular arm depends on T cells binding directly to foreign antigens on target cells. An active immune response may be divided into four distinct stages: 1) recognition and activation, 2) proliferation, 3) effector, and 4) memory (*Fig. 1*) (99).

The recognition and activation stage of the immune response relies on a complex interaction of multiple cell types. For lymphocyte activation, at least two signals are required, antigen-binding and additional signal derived from T cells. Peptide antigens are presented to T cells in the context of

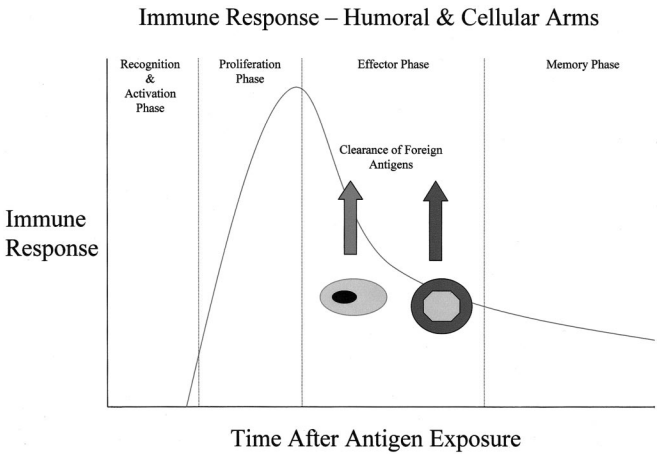

FIGURE 1. *Diagram showing immune response as a function of time after exposure to antigen. Both the humoral and cellular arms of the immune response can be subdivided into four distinct phases. Exposure to antigen elicits the recognition/activation phase, which is followed by an active proliferative phase during which the effector cell population expands. The effector phase is heralded by the elimination of foreign antigen by the effector cells. The number of effector cells is diminished through apoptosis, leaving a repertoire of memory cells capable of responding more rapidly and robustly if exposed to the same antigen again.*

major histocompatibility complexes located on the surface of antigen-presenting cells (including microglia, dendritic cells, and monocyte/macrophages). Furthermore, T cells require an additional stimulus to circumvent anergy, and this is usually provided via a costimulatory signal derived from B7-1 or B7-2 (receptors found on B lymphocytes, monocytes/macrophages, and dendritic cells) binding to CD28 (located on T cells) (31). Microglia, dendritic cells, and monocyte/macrophages (professional antigen-presenting cells) are integral to this aforementioned process (26, 81, 82, 89, 102, 109). Cytokines also actively participate in lymphocytic activation, with some subserving immunological activation (e.g., interleukin [IL]-2 [143]), whereas others participate in immunosuppression (transforming growth factor-β) (25). Furthermore, helper T cells may be classified according to cytokine expression into IL-12- and interferon-expressing helper T1 cells (associated with cell-mediated immunity) and IL-4-, IL-6-, and IL-10-secreting helper T2 cells (associated with humoral immunity) (86).

Proliferation, the second stage of the active immune response, ensues after T- and B-cell activation, producing expanded populations of mature effector lymphocytes. In addition, the cascade of events composing the effector stage is initiated both contemporaneously and subsequently. Effector killer T cells target cells expressing specific antigens, producing apoptotic (programmed) cell death via the Fas/Fas-ligand or perforin/granzyme pathways (5, 52). Effector B cells mature into plasma cells and produce and secrete antibodies that bind to foreign antigens, facilitating phagocytosis and subsequent elimination. The final phase of the immune response, denoted as the memory phase, results in the persistence of a

small population of immune cells that can respond rapidly to future challenges with the same antigen.

The central nervous system (CNS) has traditionally been heralded as a special immunological environment in that it has been viewed as a so-called "privileged" site. Several distinct lines of evidence lend credence to this hypothesis. Pioneering work by Medawar (84) seemed to indicate that allogeneic tissue grafts were not rejected when implanted in the brains of experimental animals. This paucity of immune response was ascribed to the lack of lymphocyte entry into the CNS because of the blood-brain barrier and as a consequence of the lack of connection of the CNS with the lymphatic system (7). Furthermore, others have asserted that the CNS does not possess native antigen-presenting cells (133).

More recently, the extent to which the CNS is truly immunologically privileged has been scrutinized. A substantial body of evidence indicates that xenograft and allograft rejection occurs in implanted grafts of the CNS unless immunosuppression and/or immunoincompetence is implemented (10, 33, 61, 108, 117, 118). In contrast to previous assumptions, some lymphocyte trafficking does occur into the CNS. Under resting conditions, CXCR3-expressing T cells gain access to the cerebrum. Under pathological conditions (such as SAH), leukocyte trafficking is increased because of blood-brain barrier breakdown (11, 19–21, 29, 103, 141). In addition, connections between cerebrospinal fluid (CSF) compartments and cervical lymphatics do seem to exist (17, 147). Microglia have been unequivocally established as resident antigen-presenting cells of the CNS, casting further doubt on the extent to which the CNS is an immunologically privileged environment.

Globally, humoral responses tend to be normal or increased and cell-mediated responses less profound in the CNS than in other sites (17). This may stem from the relatively diminished expression of major histocompatibility complex molecules on most neurons and glia (except microglia) (64, 65). Cytokines also seem to modulate the immune response within the CNS (107, 137). Taken collectively, the CNS seems to be a potentially active immunological environment, albeit with its own characteristic immune profile.

SAH, INFLAMMATION, AND CEREBRAL VASOSPASM

Inflammation is a complex and multifaceted response aimed to ultimately defend against foreign antigens. In the instance of SAH, a complex series of cellular and molecular events is elicited by the presence of blood clot in the subarachnoid space, culminating in a robust inflammatory response. Although the possible role of inflammation in the genesis of cerebral vasospasm has been recognized for some time, its cellular and molecular basis and putative importance have not been more clearly defined until recently.

Adhesion Molecules, Cytokines, and Leukocytes

In the acute stages of inflammation, the local homeostatic milieu is altered, resulting in expression of adhesion molecules that evoke leukocyte adherence to the endothelium, with subsequent migration, activation, and release of effector substances. Leukocyte adhesion is a hallmark of the inflammatory process that is necessary to specifically arrest leukocytes on the vascular endothelium and orchestrate their efficient and appropriate transmigration (4, 12, 67, 68, 72, 126, 140).

There is a well-characterized sequence of events by which the leukocyte approaches the vessel wall and adheres firmly to the endothelial surface before transmigration can occur. These successive events have been called margination, capture, rolling, and adhesion (*Fig. 2*). Margination, the process by which the leukocyte is brought into close proximity with the endothelium, was the subject of early investigation into leukocyte recruitment (138). This process is governed exclusively by rheological forces, such as the higher speed at which red blood cells travel relative to leukocytes, thereby directing the leukocytes toward the vessel wall, among other rheological mechanisms (32, 91, 120). Despite even maximal margination, the leukocyte is still traveling above the critical or hydrodynamic velocity that distinguishes rolling from freely flowing leukocytes (66, 69, 71). For leukocyte rolling to occur, there must first be an initiating event, called tethering or capture (70, 151). Capture is defined as the formation of the first molecular bond between the vascular endothelium and the flowing leukocyte. Capture is a process distinct from stable leukocyte rolling and is indeed mediated by an overlapping but characteristic repertoire of adhesion molecules. Stable leukocyte rolling occurs if leukocyte capture is followed by the formation of new molecular bonds before the initial molecular bonds dissociate (36, 134). Rolling is defined as movement below the critical velocity of a cell in continuous contact with the vessel wall. Rolling seems to have two important consequences: facilitation of stable leukocyte arrest (firm adhesion) and the marked

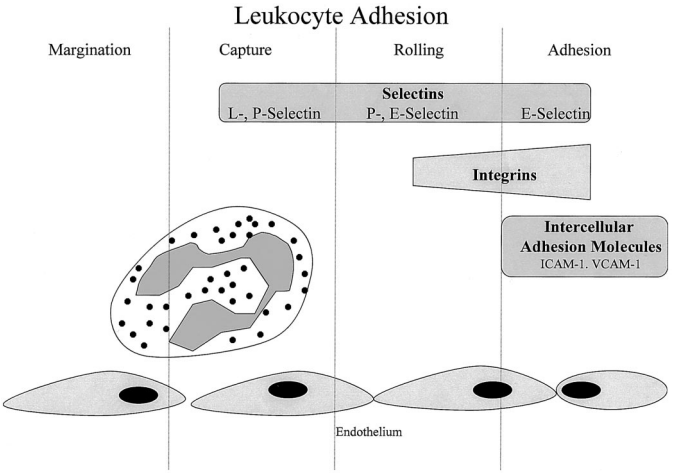

FIGURE 2. *Diagram showing leukocyte adhesion. Leukocyte adhesion is composed of an orchestrated and specific series of events that ultimately culminates in leukocyte trafficking to sites of active inflammation. The selectins mediate capture, rolling, and adhesion, and the integrins are involved intimately with rolling and adhesion. Intercellular adhesion molecules are concerned primarily with the achievement of firm adhesion.*

reduction of leukocyte velocity, thereby increasing transit time and the duration of the exposure of the cell to chemoattractants presented on the endothelial surface. After a rolling leukocyte encounters an appropriate stimulatory signal (usually a chemoattractant or chemokine molecule binding to a leukocyte surface receptor), leukocyte activation occurs, which is a prerequisite for firm adhesion (12, 67, 73). Firm adhesion is postulated to require the interaction of activated integrin receptors and their complementary endothelial ligands.

The selectins are a family of three receptors expressed on the surface of leukocytes, endothelial cells, and platelets (8, 54, 139) and are the main adhesion receptors mediating leukocyte capture and rolling in vitro and in vivo. The three selectins have been labeled leukocyte (L)-selectin, platelet (P)-selectin, and endothelial (E)-selectin. Both L- and P-selectin initiate capture, P- and E-selectin mediate rolling, and E-selectin supports the transition to firm adhesion. In addition, other leukocyte receptors, including the integrins, are important in leukocyte adherence. For example, some integrins (such as lymphocyte function-associated antigen-1 and macrophage antigen-1 (Mac-1 [$\alpha_M b_2$; CD11b/CD18]) reduce rolling velocity and are critical for firm adhesion (68). Intercellular adhesion molecules, members of the immunoglobulin (Ig) superfamily, are also important in leukocyte recruitment. These include intercellular adhesion molecule-1 (ICAM-1) (CD54), an Ig-like molecule that exhibits low constitutive presentation on endothelial cells but is markedly induced by exposure to inflammatory cytokines (30, 49, 60, 121, 142), and vascular cell adhesion molecule-1 (VCAM-1). Of significance, ICAM-1 is an important complementary endothelial ligand for lymphocyte function-associated antigen-1 and Mac-1 that is expressed on leukocytes (142). Hence, a host of cellular and molecular events coordinate the recruitment of leukocytes to sites of inflammation. Capture and rolling are mediated primarily by the selectins (L-, P-, and E-selectin), with firm adhesion relying most heavily on the integrins (such as Mac-1) and intercellular adhesion molecules (ICAM-1, VCAM-1). A clear understanding of these events is critical for mechanistic and therapeutic exploitation in cerebral vasospasm after SAH. Indeed, leukocyte recruitment has been the subject of both clinical and experimental investigations of SAH and remains a promising avenue for future investigation (6, 16, 24, 39, 48, 62, 104, 107, 131, 132).

Cytokines compose a group of protein hormones that are produced during the activation and effector phases of the immune response. Cytokines are powerful mediators and regulators of immune responses. Some of the cytokines that have been characterized and found to be up-regulated in experimental and/or clinical cerebral vasospasm after SAH include tumor necrosis factor-α (TNF-α), IL-1α, IL-1β, IL-6, and IL-8 (2, 22, 44, 130). TNF-α is produced by mononuclear phagocytes and T cells and activates neutrophils and endothelial cells (producing inflammation and coagulation), in addition to stimulating the hypothalamus (producing fever) and liver (producing acute phase reactants) and shifting the body toward catabolism (1). IL-1 is produced predominantly by mononuclear phagocytes but also by other cells; it acts on endothelial cells (promoting inflammation and coagulation), the hypothalamus (producing fever), and the liver (increasing elaboration of acute-phase reactants) and also promotes catabolism (1). IL-6 is produced by mononuclear phagocytes, T cells, and endothelial cells; it stimulates the growth of mature B cells and also promotes the synthesis of acute-phase proteins by the liver (1). IL-8 is a chemokine (a family of cytokines that share the ability to stimulate leukocyte motility [chemokinesis] and directed movement [chemotaxis]) (1). It is produced by mononuclear phagocytes, T cells, platelets, endothelial cells, and fibroblasts and acts on leukocytes. giving rise to chemotaxis, chemokinesis, adhesion, and activation (127).

Leukocytes are also critical constituents of the inflammatory response. Leukocytes may act by direct effects on the vasculature or indirectly through the elaboration and propagation of the inflammatory response. For example, neutrophils may produce and release reactive metabolites of oxygen that evoke endothelial dysfunction and calcium influx (34, 127). Furthermore, leukocytes may release a variety of other substances (including leukotrienes and other lipid mediators) that have powerful vascular effects. In addition, leukocytes produce a host of factors (such as cytokines) that further activate and propagate immune responses.

Many of the aforementioned factors have been investigated in both clinical and experimental studies of cerebral vasospasm after SAH (*Fig. 3*). Perturbations in levels of soluble adhesion molecules and cytokines have been noted in the CSF and plasma of patients. In addition, changes in adhesion molecules and cytokines have been noted in experimental models of cerebral vasospasm. Our laboratory has shown that levels

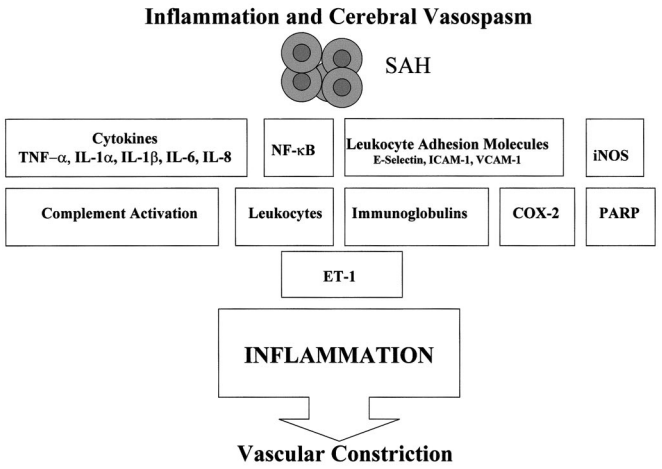

FIGURE 3. *Diagram showing inflammatory components and cerebral vasospasm. The inflammatory response is a complex and carefully orchestrated reaction to blood (and its breakdown products) located within the subarachnoid space after aneurysmal rupture. Factors that have been investigated in both clinical and laboratory studies as potential inflammatory contributors to the development and maintenance of cerebral vasospasm after SAH are summarized.*

of soluble E-selectin, soluble ICAM-1, and soluble VCAM-1 are elevated in the CSF of patients with SAH compared with matched controls (107). Furthermore, the level of these molecules decayed over time in a manner that suggested a correlation with the pathogenesis of cerebral vasospasm. Similarly, inflammatory cytokines and platelet-activating factor (PAF) were found to be elevated in jugular venous blood of patients who have sustained an SAH (44). Specifically, IL-6 and PAF concentrations increased within the first 4 days after SAH and remained elevated up to 14 days, and IL-1β demonstrated a transient increase between 5 and 9 days after SAH. More recently, Fassbender et al. (22) reported an association between cytokines in patients with SAH and abnormal blood flow velocities measured in basal cerebral arteries. These authors demonstrated that IL-1β, IL-6, and TNF-α were increased after SAH and that this response was closely correlated in time and extent with increased blood flow velocities in the basal cerebral arteries as assessed by transcranial Doppler ultrasonography. These authors were also able to correlate an increased intrathecal secretion of inflammatory cytokines with poor clinical outcome. In experimental models, soluble ICAM-1 has been shown to be up-regulated after SAH (39, 124). Our laboratory and others have shown that treatments such as monoclonal antibodies against ICAM-1 (with or without CD18) can reduce or inhibit cerebral vasospasm (6, 96).

Nuclear factor-κB (NF-κB), a ubiquitous transcription factor, regulates a number of processes and plays a critical role in inflammation (18, 41). NF-κB may modulate some of these aforementioned changes in adhesion molecules and cytokines and hence may be important in cerebral vasospasm (93). The role of NF-κB in cerebral vasospasm requires further characterization. The nuclear enzyme poly(ADP-ribose) polymerase (PARP) may also be important in the modulation of the course of inflammation by regulating the expression of adhesion molecules, neutrophil infiltration, NF-κB, and inducible nitric oxide synthase (iNOS). Satoh et al. (115) recently demonstrated that inhibition of PARP (a nuclear enzyme that modulates the expression of adhesion molecules, neutrophil infiltration, and iNOS) attenuates cerebral vasospasm after SAH in rabbits. Collectively, elevation of adhesion molecules and cytokines is postulated to recruit leukocytes and otherwise potentiate and perpetuate the mounting immune response.

The role of leukocytes in cerebral vasospasm has also been examined. Leukocyte accumulation has been noted after SAH in human and experimental arteries (16, 24, 38, 39, 48, 62, 104, 131), although a recently conducted preliminary study could not corroborate this (95). Leukocytosis has been correlated with ischemic complications after SAH (125). Although the admission white blood cell counts did not differ between patients who subsequently deteriorated because of ischemic complications and those who did not, the white blood cell count rose significantly in those who manifested clinical signs and symptoms of ischemia. A well-conducted study by Kubota et al. (62) characterized the kinetics of lymphocyte subsets and macrophages in the subarachnoid space after SAH in rats. They found that the peak appearance of T cells and macrophages occurred 2 days after SAH. In addition, the CD4:CD8 T-cell ratio also reached a peak 2 days after SAH. They proposed that an initial response in cellular immunity is followed by a response in the humoral arm of immunity accompanied by eicosanoid production. These responses may play a role in the development of cerebral vasospasm (62). A recent, elegant study by Fassbender et al. (23) introduced an interesting facet of the inflammatory response accompanying SAH. They illustrated that activated mononuclear cells in the CSF of patients who had sustained an SAH synthesized and released endothelin-1 (ET-1) in parallel with known acute-phase reactants (IL-1β, IL-6, and TNF-α). In addition, in a complementary line of in vitro experiments, these authors confirmed the leukocytic origin of ET-1 and showed that aging and subsequent hemolysis of the blood clot was sufficient to induce ET-1 production. It was then postulated that ET-1 produced by activated CSF mononuclear leukocytes suggests that subarachnoid inflammation may represent a therapeutic target to prevent vasospasm and delayed cerebral ischemia pursuant to SAH. ET-1 has been deemed a prime suspect as a pathogenic factor in the development and propagation of cerebral vasospasm after SAH. The fact that ET-1 production occurs by activated leukocytes accompanying an inflammatory response offers the first suggestion of a link between inflammation, ET-1 production/action, and the development of cerebral vasospasm. This supports the assertion that inflammation may represent a common pathogenic pathway in the development of cerebral vasospasm.

Igs and Complement

Igs and complement have also been studied as possible contributors to cerebral vasospasm. Some studies have found increased levels of Igs and complement constituents in the serum and vessel walls during vasospasm (47, 57, 97, 100, 101). Complement activation has been shown to accelerate erythrocyte lysis (thereby contributing to vasospasm by enhancing erythrocyte breakdown and liberating spasmogenic contents) (106), whereas complement depletion attenuates vasospasm (28). Oligoclonal IgG bands were found in serum and CSF of some patients with SAH (136). The authors suggested that there are two different mechanisms and sites of IgG synthesis, including an inflammatory process after an acute stage of vascular damage and a latent immunological process (polyclonal B-cell activation by cerebral insult). Collectively, these data support the concept that SAH is accompanied by an inflammatory response that may play a role in the development of cerebral vasospasm. However, the need for further study of these facets of the immune response is apparent.

Changes in Expression of Inflammation-related Genes

Gene expression analyses of complex processes, such as cerebral vasospasm, can help characterize the pathogenesis of specific disorders and can assist in the delineation of appropriately targeted preventive and therapeutic strategies. Preliminary characterization of altered gene expression accompa-

nying cerebral vasospasm has been performed (*Table 1*). It is known that ribonucleic acid synthesis is necessary for the development of arterial spasm after SAH, because inhibitors of ribonucleic acid synthesis prevent the development of vasospasm (85, 122). Inducible cyclooxygenase (COX-2) is up-regulated after SAH in canine basilar arteries in both the acute and chronic stages of SAH (98). In addition, intracisternal injection of IL-1β, IL-6, or IL-8 also induced COX-2 expression in the basilar artery. Up-regulation of COX-2 was also reported by Tran Dinh et al. (135) in rabbit basilar artery endothelial cells after SAH. COX-2 is known to be important in many inflammatory responses and may represent a therapeutic target worthy of further characterization. A recent study by Onda et al. (92) using complementary deoxyribonucleic acid expression arrays examined genes differentially expressed in vasospastic canine arteries. Expression of 18 genes (from 588 known human genes screened) was found to be up-regulated and two genes were found to be down-regulated in vasospastic relative to control arteries. Interestingly, five of the known genes up-regulated were found to be inflammation-related genes, including monocyte chemotactic protein-1, cystatin B, inter-α-trypsin inhibitor family heavy chain-related protein, serum amyloid A protein, and glycoprotein 130. Once again, these authors suggested that inflammation may be involved in the development of cerebral vasospasm. Preliminary data from Macdonald et al. (74, 75) have also demonstrated up-regulation of certain inflammation-related genes in a primate model of vasospasm. Recently, Aihara et al. (2) endeavored to analyze quantitatively the expression of a prespecified collection of genes related to inflammation in canine spastic artery after SAH. This group demonstrated significant differences in messenger ribonucleic acid expression in the basilar artery for IL-1, IL-6, IL-8, ICAM-1, and collagen Type I at Days 0, 2, 7, and 14 relative to controls. The average level of messenger

TABLE 1. Changes in gene expression after subarachnoid hemorrhage[a]

Series (ref. no.)	Model	Changes in gene expression
Aihara et al. (2)	Canine	Up-regulation of IL-1α, IL-6, IL-8, ICAM-1, and collagen Type I
Handa et al. (39)	Rat	Up-regulation of ICAM-1
Hino et al. (42)	Primate	Up-regulation of endothelin-B receptors
Kasuya et al. (59)	Rat	Up-regulation of procollagen Type I and III and transforming growth factor-β
Kasuya et al. (58)	Canine	Down-regulation of soluble guanylate cyclase
Kuroki et al. (63)	Rat	Heme oxygenase-1 (HSP32) up-regulation (no change in HO-2 or HSP70)
Macdonald and Weir (74, 75)	Primate	Changes in expression of 373 of 5184 genes (10%); related to inflammation, regulation of gene expression, cell proliferation, membrane proteins and receptors, and various kinases and phosphatases
Matz et al. (77, 79)	Rat	Heme oxygenase-1 (HSP32) up-regulation (no change in HO-2 or HSP70)
Matz et al. (78, 80)	Rat	HSP70 up-regulation
Onda et al. (92)	Canine	18 genes up-regulated (5 inflammation related), 2 down-regulated (12 known genes); inflammation-related genes up-regulated: monocyte chemotactic protein-1, cystatin B, inter-α-trypsin inhibitor family heavy chain-related protein, serum amyloid A protein, glycoprotein 130; stress-related proteins up-regulated: vascular endothelial growth factor, BiP protein, growth-arrest and DNA-damage-inducible protein
Ono et al. (94)	Primate	Heme oxygenase-1 and ferritin up-regulation
Osuka et al. (98)	Canine	Up-regulation of COX-2
Suzuki et al. (129)	Rat	Heme oxygenase-1 up-regulation; 282 of 9542 mRNA bands (3%) changed in basilar artery
Wang et al. (144)	Rat (aorta smooth muscle cells)	Up-regulation of c-fos, jun B, c-jun (transcription factors, early immediate genes)

[a] IL, interleukin; ICAM, intracellular adhesion molecule; HO, heme oxygenase; HSP, heat-shock protein; COX, cyclooxygenase; BiP, heavy chain binding protein; DNA, deoxyribonucleic acid; mRNA, messenger ribonucleic acid.

ribonucleic acid was highest at Day 7 for IL-1, IL-6, IL-8, and ICAM-1 (17-, 16-, 131-, and 1.7-fold higher, respectively). It was suggested that increased expression of genes related to inflammation in the spastic basilar artery indicates that the inflammatory reaction of the cerebral artery is associated with sustained contraction. Collectively, these data reveal changes in gene expression in vasospastic arteries, including the upregulation of a number of inflammation-related genes. Incorporation of microarray technology and a more comprehensive study of genomic and proteomic alterations accompanying cerebral vasospasm would be of substantial benefit in furthering contemporary understanding of this problem. Specific examination of changes in inflammation-related genes and the delineation of the interaction of expression of these genes with other genes and their functional correlation with the development of cerebral vasospasm is necessary. Such a body of knowledge could then be applied to examine the effects of potential gene manipulations on the course and severity of vasospasm (53).

Therapies Targeting the Inflammatory Cascade

The use of a number of anti-inflammatory treatments has been studied in cerebral vasospasm (*Table 2*). A multitude of therapeutic strategies, the majority being nonspecific in nature, have been investigated in both laboratory and clinical contexts. However, the outcomes of these studies have been equivocal. Such agents as cyclosporin A, FK-506, methylprednisolone, nonsteroidal anti-inflammatory agents, and other anti-inflammatory drugs have been used with variable success in limiting cerebral vasospasm (13–15, 76, 87, 123, 132). Corticosteroids possess some efficacy in the treatment of cerebral vasospasm, reducing vasospasm in animal models (13, 15, 148) and improving outcome in Phase II and III clinical trials in humans (14, 40, 114). Cyclosporin A attenuated vasospasm in primate and canine models (37, 105), although its efficacy in nonrandomized clinical studies was limited (76, 113). FK-506 did not diminish vasospasm in a canine model (87, 90). PAF Igs prevented neurological deterioration and vasospasm in a rabbit model of SAH; however, synthetic PAF antagonists prevented neurological deterioration but not vasospasm (43). As mentioned above, systemic complement depletion with cobra venom in a rabbit model diminished cerebral vasospasm (28). In addition, FUT-175 (nafamostat mesilate, a nonspecific serine protease inhibitor of activation of complement and plasma protein-mediated inflammation) reduced vasospasm in experimental and clinical studies (149, 150). Inhibition of leukocyte adhesion molecules has been demonstrated to be effective in some studies. Administration of monoclonal antibodies targeted against ICAM-1 has reduced vasospasm in a rabbit basilar artery model and a rodent femoral artery model of SAH (6, 132).

As previously discussed, the nuclear enzyme PARP may be important in the modulation of the course of inflammation by regulating the expression of adhesion molecules, neutrophil infiltration, NF-κB, and iNOS. Satoh et al. (115) recently demonstrated that inhibition of PARP attenuates cerebral vasospasm after SAH in rabbits. In addition, Ono et al. (93) demonstrated that intrathecal administration of antisense oligodeoxynucleotides to NF-κB prevented vasospasm and morphological changes in arteries in addition to decreasing activity of NF-κB as assessed by gel-shift assay. Changes in the balance of prostanoids and/or platelet function have been implicated in the pathogenesis of cerebral vasospasm. Accordingly, Juvela (51) retrospectively examined the use of aspirin

TABLE 2. Anti-inflammatory therapies for cerebral vasospasm[a]

Agent	Model	Efficacy
Corticosteroids (13–15, 40, 114, 148)	Animal, clinical	Some
Cyclosporin A (37, 76, 105, 113)	Animal, clinical	Yes animals, no clinical
FK-506 (87, 90)	Animal	No
Anti-platelet-activating factor antibodies (43)	Animal	Yes
Systemic complement depletion (28)	Animal	Yes
FUT-175 (nafamostat mesilate) (149, 150)	Animal, clinical	Yes
Anti-ICAM-1 antibodies (6, 132)	Animal	Yes
PARP inhibitor (115)	Animal	Yes
Antisense NF-κB oligonucleotides (93)	Animal	Yes
Aspirin (46, 51)	Clinical	Yes, preliminary
NSAIDs and thromboxane synthetase inhibitors (27, 128, 146)	Animal	Mixed; dependent on study and agent(s) used

[a] ICAM, intracellular adhesion molecule; PARP, poly(ADP-ribose) polymerase; NF, nuclear factor; NSAIDs, nonsteroidal anti-inflammatory drugs.

and the development of delayed cerebral ischemia after SAH. He found that there was a reduced risk of ischemic complications with aspirin use in those patients who had aspirin intake before the hemorrhage (an effect that remained significant after adjustment for multiple possible confounding factors). The results of a recent randomized pilot trial of postoperative aspirin in SAH were reported (46). This pilot study demonstrated that there was a nonsignificant trend toward improved functional outcome and quality-of-life scores in the aspirin-treated group and concluded that a clinical trial of aspirin in SAH is feasible and probably safe. Several other studies have demonstrated modest benefit of nonsteroidal anti-inflammatory drugs or thromboxane synthetase inhibitors (128, 146), although not uniformly so (27).

Currently, clinical treatment of cerebral vasospasm does not incorporate anti-inflammatory therapy. Studies taking into consideration the limitations of previous work are necessary to examine the efficacy of anti-inflammatory treatments. Furthermore, the development of specific anti-inflammatory therapy based on knowledge of precise candidate mechanisms underlying the inflammatory response accompanying SAH will provide a rational approach for future targeted therapy.

CONCLUSIONS

Cerebral vasospasm after SAH is common, potentially devastating, and incompletely understood. Inflammation accompanying SAH may be a critical pathway underlying the development of cerebral vasospasm. Further characterization of the role of inflammation in cerebral vasospasm is needed to fill the considerable gaps in our current knowledge. In addition, delineation of how other specific theories of pathogenesis (and non-inflammation-associated spasmogens) may relate to or contribute to the proposed final common pathway of inflammation is worthy of future study. Such knowledge may facilitate the development of novel therapies for prevention and/or treatment that may ultimately translate to clinical practice. An emphasis on the cellular and molecular substrates underlying the development and maintenance of cerebral vasospasm may be particularly important in solving this vexing problem that has plagued clinicians, scientists, and, most importantly, patients for decades. Because cerebral vasospasm is the leading potentially treatable cause of death and disability after SAH and current therapies are inadequate, efficacious treatment regimens would be a welcome and significant advancement in the provision of care for patients afflicted with ruptured intracranial aneurysms.

REFERENCES

1. Abbas AK, Lichtman AH, Pober JS: Cytokines, in Abbas AK, Lichtman AH, Pober JS (eds): *Cellular and Molecular Immunology*. Philadelphia, W.B. Saunders Co., 1997, pp 250–276.
2. Aihara Y, Kasuya H, Onda H, Hori T, Takeda J: Quantitative analysis of gene expressions related to inflammation in canine spastic artery after subarachnoid hemorrhage. **Stroke** 32:212–217, 2001.
3. American Heart Association: *1995 Heart and Stroke Facts*. Dallas, American Heart Association, 1996.
4. Arfors K-E, Lundberg C, Lindbom L, Lundberg K, Beatty PG, Harlan JM: A monoclonal antibody to the membrane glycoprotein complex CD18 inhibits polymorphonuclear leukocyte accumulation and plasma leakage in vivo. **Blood** 69:338–340, 1987.
5. Atkinson EA, Bleackley RC: Mechanisms of lysis by cytotoxic T cells. **Crit Rev Immunol** 15:359–384, 1995.
6. Bavbek M, Polin R, Kwan A, Arthur AS, Kassell NF, Lee KS: Monoclonal antibodies against ICAM-1 and CD18 attenuate cerebral vasospasm after experimental subarachnoid hemorrhage in rabbits. **Stroke** 29:1930–1936, 1998.
7. Bertrand I, Mannen H: Etude des réactions vasculaires dans les astrocytomes. **Rev Neurol (Paris)** 102:3–19, 1960.
8. Bevilacqua M, Butcher EC, Furie B, Furie BC, Gallatin WM, Gimbrone MA Jr, Harlan JM, Kishimoto TK, Lasky LA, McEver R, Paulson J, Rosen S, Seed B, Siegelman M, Springer T, Stoolman L, Tedder T, Varki A, Wagner D, Weissman I, Zimmerman G: Selectins: A family of adhesion receptors. **Cell** 67:233, 1991 (letter).
9. Bronner LL, Kanter DS, Manson JE: Primary prevention of stroke. **N Engl J Med** 23:1392–1400, 1995.
10. Bullard DE, Schold SC, Bigner SH, Bigner DD: Growth and chemotherapeutic responsiveness in athymic mice of tumors arising from human-glioma derived cell lines. **J Neuropathol Exp Neurol** 40:410–427, 1981.
11. Bundy GM, Merchant RE: Basic research applied to neurosurgery: Lymphocyte trafficking to the central nervous system. **Neurosurg Q** 6:51–68, 1996.
12. Butcher EC: Leukocyte-endothelial cell recognition: Three (or more) steps to specificity and diversity. **Cell** 67:1033–1036, 1991.
13. Chyatte D: Prevention of chronic vasospasm in dogs with ibuprofen and high-dose methylprednisolone. **Stroke** 20:1021–1026, 1989.
14. Chyatte D, Fode NC, Nichols DA, Sundt TM Jr: Preliminary report: Effects of high dose methylprednisolone on delayed cerebral ischemia in patients at high risk for vasospasm after aneurysmal subarachnoid hemorrhage. **Neurosurgery** 21:157–160, 1987.
15. Chyatte D, Rusch N, Sundt TM Jr: Prevention of chronic experimental cerebral vasospasm with ibuprofen and high-dose methylprednisolone. **J Neurosurg** 59:925–932, 1983.
16. Crompton MR: The pathogenesis of cerebral infarction following the rupture of cerebral berry aneurysms. **Brain** 87:491–510, 1964.
17. Cserr HF, Knopf PM: Cervical lymphatics, the blood-brain barrier and the immunoreactivity of the brain: A new view. **Immunol Today** 13:507–512, 1992.
18. de Martin R, Hoeth M, Hofer-Warinbek R, Schmid JA: The transcription factor NF-κB and the regulation of vascular cell function. **Arterioscler Thromb Vasc Biol** 20:E83–E88, 2000.
19. Doczi T: The pathogenetic and prognostic significance of blood-brain barrier damage at the acute stage of aneurysmal subarachnoid hemorrhage clinical and experimental studies. **Acta Neurochir (Wien)** 77:110–132, 1985.
20. Doczi T, Ambrose J, O'Laoire S: Significance of contrast enhancement after subarachnoid hemorrhage. **J Neurosurg** 60:335–342, 1984.
21. Doczi T, Joo F, Sonkodi S, Adam G: Blood-brain barrier damage during the acute stage of subarachnoid hemorrhage, as exemplified by a new animal model. **Neurosurgery** 18:733–739, 1986.
22. Fassbender K, Hodapp B, Rossol S, Bertsch T, Schmeck J, Schutt S, Fritzinger M, Horn P, Vajkoczy P, Kreisel S, Brunner J, Schmiedeck P, Hennerici M: Inflammatory cytokines in subarachnoid hemorrhage: Association with abnormal blood flow velocities in basal cerebral arteries. **J Neurol Neurosurg Psychiatry** 70:534–537, 2001.
23. Fassbender K, Hodapp B, Rossol S, Bertsch T, Schmeck J, Schutt S, Fritzinger M, Horn P, Vajkoczy P, Wendel-Wellner M, Ragoschke A, Kuehl S, Brunner J, Schurer L, Schmiedeck P, Hennerici M: Endothelin-1 in subarachnoid hemorrhage: An acute-phase reactant produced by cerebrospinal fluid leukocytes. **Stroke** 31:2971–2975, 2000.
24. Findlay JM, Weir BKA, Kanamaru K, Espinosa F: Arterial wall changes in cerebral vasospasm. **Neurosurgery** 25:736–746, 1989.

25. Fontana A, Constam DB, Frei K, Malipiero U, Pfister HW: Modulation of the immune response by transforming growth factor beta. **Int Arch Allergy Immunol** 99:1–7, 1992.
26. Fuchs EJ, Matzinger P: B cells turn off virgin but not memory T cells. **Science** 258:1156–1159, 1992.
27. Fukumori T, Tani E, Maeda Y, Sukenaga A: Effects of prostacyclin and indomethacin on experimental delayed cerebral vasospasm. **J Neurosurg** 59:829–834, 1983.
28. German JW, Gross CE, Giclas P, Watral W, Bednar MM: Systemic complement depletion inhibits experimental cerebral vasospasm. **Neurosurgery** 39:141–146, 1996.
29. Germano A, Davella D, Cicciarello R, Hayes RL, Tomasello F: Blood brain barrier permeability changes after experimental subarachnoid hemorrhage. **Neurosurgery** 30:882–886, 1992.
30. Gerritsen ME, Bloor CM: Endothelial cell gene expression in response to injury. **FASEB J** 7:523–532, 1993.
31. Gimmi CD, Freeman GJ, Gribben JG, Gray G, Nadler LM: Human T-cell clonal anergy is induced by antigen presentation in the absence of B7 costimulation. **Proc Natl Acad Sci U S A** 90:6586–6590, 1993.
32. Goldsmith HL, Spain S: Margination of leukocytes in blood flow through small tubes. **Microvasc Res** 27:204–222, 1984.
33. Greene HSN: The transplantation of tumours to the brains of heterologous species. **Cancer Res** 11:529–534, 1951.
34. Grisham MB, Granger DN, Lefer DJ: Modulation of leukocyte-endothelial interactions by reactive metabolites of oxygen and nitrogen: Relevance to ischemic heart disease. **Free Rad Biol Med** 25:404–433, 1998.
35. Haley EJ, Kassell NF, Torner JC: The International Cooperative Study on the Timing of Aneurysm Surgery: The North American experience. **Stroke** 23:205–214, 1992.
36. Hammer DA, Apte SM: Simulation of cell rolling and adhesion on surfaces in shear flow: General results and analysis of selectin-mediated neutrophil adhesion. **Biophys J** 63:35–57, 1992.
37. Handa Y, Hayashi M, Takeuchi H, Kobayashi H, Kawano H, Kabuto M: Effect of cyclosporine on the development of cerebral vasospasm in a primate model. **Neurosurgery** 28:380–385, 1991.
38. Handa Y, Kabuto M, Kobayashi H, Kawano H, Takeuchi H, Hayashi M: The correlation between immunological reaction in the arterial wall and the time course of the development of cerebral vasospasm in a primate model. **Neurosurgery** 28:542–549, 1991.
39. Handa Y, Kubota T, Kaneko M, Tsuchida A, Kobayashi H, Kawano H, Kubota T: Expression of intercellular adhesion molecule 1 (ICAM-1) on the cerebral artery following subarachnoid hemorrhage in rats. **Acta Neurochir (Wien)** 132:92–97, 1995.
40. Hashi K, Takakura K, Sano K, Ohta T, Saito I, Okada K: Intravenous hydrocortisone in large doses for the treatment of delayed ischemic neurological deficits following subarachnoid hemorrhage: Results of a multicenter controlled double-blind clinical study [in Japanese]. **No To Shinkei** 40:373–382, 1998.
41. Hickenbottom SL, Grotta JC, Strong R, Denner LA, Aronowski J: Nuclear factor-κB and cell death after experimental intracerebral hemorrhage in rats. **Stroke** 30:2472–2478, 1999.
42. Hino A, Tokuyama Y, Kobayashi M, Yano M, Weir B, Takeda J, Wang X, Bell GI, Macdonald RL: Increased expression of endothelin B receptor mRNA following subarachnoid hemorrhage in monkeys. **J Cereb Blood Flow Metab** 16:688–697, 1996.
43. Hirashima Y, Endo S, Otsuji T, Karasawa K, Nojima S, Takaku A: Platelet-activating factor and cerebral vasospasm following subarachnoid hemorrhage. **J Neurosurg** 78:592–597, 1993.
44. Hirashima Y, Nakamura S, Endo S, Kuwayama N, Naruse Y, Takaku A: Elevation of platelet activating factor, inflammatory cytokines, and coagulation factors in the internal jugular vein of patients with subarachnoid hemorrhage. **Neurochem Res** 22:1249–1255, 1997.
45. Ho HW, Batjer HH: Aneurysmal subarachnoid hemorrhage: Pathophysiology and sequelae, in Batjer HH (ed): *Cerebrovascular Disease*. Philadelphia, Lippincott-Raven Publishers, 1997, pp 889–899.
46. Hop JW, Rinkel GJE, Algra A, Berkelbach van der Sprenkel JW, van Gijn J: Randomized pilot trial of postoperative aspirin in subarachnoid hemorrhage. **Neurology** 54:872–878, 2000.
47. Hoshi T, Shimizu T, Kito K, Yamasaki N, Takahashi K, Takahashi M, Okada T, Kasuya H, Kitamura K: Immunological study of late cerebral vasospasm in subarachnoid hemorrhage: Detection of immunoglobulins, C3, and fibrinogen in cerebral arterial walls by immunofluorescence method [in Japanese]. **Neurol Med Chir (Tokyo)** 24:647–654, 1984.
48. Hughes JT, Schianchi PM: Cerebral artery spasm: A histological study at necropsy of the blood vessels in cases of subarachnoid hemorrhage. **J Neurosurg** 48:515–525, 1978.
49. Iigo Y, Suematsu M, Higashida T, Oheda JI, Matsumoto K, Wakabayashi Y, Ishimura Y, Miyasaka M, Takashi T: Constitutive expression of ICAM-1 in rat microvascular systems analyzed by laser confocal microscopy. **Am J Physiol** 273[Suppl 1]:H138–H147, 1997.
50. Ingall TJ, Whisnant JP, Wiebers DO, O'Fallon M: Has there been a decline in subarachnoid hemorrhage mortality? **Stroke** 20:718–724, 1989.
51. Juvela S: Aspirin and delayed cerebral ischemia after aneurysmal subarachnoid hemorrhage. **J Neurosurg** 82:945–952, 1995.
52. Kagi D, Vignauz F, Ledermann B, Burki K, Depraetere V, Nagata S, Hengartner H, Golstein P: Fas and perforin pathways as major mechanisms of T cell-mediated cytotoxicity. **Science** 265:528–530, 1994.
53. Kamii H, Kato I, Kinouchi H, Chan PH, Epstein CJ, Akabane A, Okamoto H, Yoshimoto T: Amelioration of vasospasm after subarachnoid hemorrhage in transgenic mice overexpressing CuZn-superoxide dismutase. **Stroke** 30:867–872, 1999.
54. Kansas GS: Selectins and their ligands: Current concepts and controversies. **Blood** 88:3259–3287, 1996.
55. Kassell NF, Sasaki T, Colohan ART, Nazar G: Cerebral vasospasm following aneurysmal subarachnoid hemorrhage. **Stroke** 16:562–572, 1985.
56. Kassell NF, Torner JC, Haley EC Jr, Jane JA, Adams HP, Kongable GL: The International Study on the Timing of Aneurysm Surgery: Part 1—Overall management results. **J Neurosurg** 73:18–36, 1990.
57. Kasuya H, Shimizu T: Activated complement components C3a and C4a in cerebrospinal fluid and plasma following subarachnoid hemorrhage. **J Neurosurg** 71:741–746, 1989.
58. Kasuya H, Weir BK, Nakane M, Pollock JS, Johns L, Marton LS, Stefansson K: Nitric oxide synthase and guanylate cyclase levels in canine basilar artery after subarachnoid hemorrhage. **J Neurosurg** 82:250–255, 1995.
59. Kasuya H, Weir BK, Shen Y, Hariton G, Vollrath B, Ghahary A: Procollagen type I and III and transforming growth factor-beta gene expression in the arterial wall after exposure to periarterial blood. **Neurosurgery** 33:716–722, 1993.
60. Klein CL, Bittinger F, Kohler H, Wagner M, Otto M, Hermanns I, Kirkpatrick CJ: Comparative studies on vascular endothelium in vitro: Part 3—Effects of cytokines on the expression of E-selectin, ICAM-1 and VCAM-1 by cultured human endothelial cells obtained from different passages. **Pathobiology** 65:83–92, 1995.
61. Krushelnycky BW, Farr-Jones MA, Mielke B, McKean JD, Weir BKA, Petruk KC: Development of a large-animal human brain tumor xenograft model in immunosuppressed cats. **Cancer Res** 51:2430–2437, 1991.
62. Kubota T, Handa Y, Tsuchida A, Kaneko M, Kobayashi H, Kubota T: The kinetics of lymphocyte subsets and macrophages in subarachnoid space after subarachnoid hemorrhage in rats. **Stroke** 24:1993–2001, 1993.
63. Kuroki M, Kanamaru K, Suzuki H, Waga S, Semba R: Effect of vasospasm on heme oxygenases in a rat model of subarachnoid hemorrhage. **Stroke** 29:683–689, 1998.
64. Lampson LA: Immunobiology of brain tumors: Antigens, effectors, and delivery to sites of microscopic tumor in the brain, in Black PMcL, Loeffler JS (eds): *Cancer of the Nervous System*. Cambridge, Blackwell Science, 1997, pp 874–906.
65. Lampson LA, Hickey WF: Monoclonal antibody analysis of MHC expression in human brain biopsies: Tissue ranging from "histologically normal" to that showing different levels of glial tumor involvement. **J Immunol** 136:4054–4062, 1986.
66. Lawrence MB, Springer TA: Leukocytes roll on a selectin at physiologic flow rates: Distinction from and prerequisite for adhesion through integrins. **Cell** 65:859–873, 1991.
67. Ley K: Granulocyte adhesion to microvascular and cultured endothelium. **Studia Biophys** 134:179–184, 1989.

68. Ley K: Adhesion of leukocytes from flow: The selectins and their ligands, in Pearson JD (ed): *Vacular Adhesion Molecules and Inflammation*. Basel, Birkhäuser Verlag, 1999, pp 11–37.
69. Ley K, Gaehtgens P: Endothelial, not hemodynamic differences are responsible for preferential leukocyte rolling in venules. **Circ Res** 69:1034–1041, 1991.
70. Ley K, Tedder TF: Leukocyte interactions with vascular endothelium: New insights into selectin-mediated attachment and rolling. **J Immunol** 155:525–528, 1995.
71. Ley K, Cerrito M, Arfors K-E: Sulfated polysaccharides inhibit leukocyte rolling in rabbit mesentery venules. **Am J Physiol** 260[Suppl 5]:H1667–H1673, 1991.
72. Ley K, Lundgren E, Berger EM, Arfors K-E: Shear-dependent inhibition of granulocyte adhesion to cultured endothelium by dextran sulfate. **Blood** 73:1324–1330, 1989.
73. Lorant DE, Patel KD, McIntyre TM, McEver RP, Prescott SM, Zimmerman GA: Coexpression of GMP-140 and PAF by endothelium stimulated by histamine or thrombin: A juxtacrine system for adhesion and activation of neutrophils. **J Cell Biol** 115:223–224, 1991.
74. Macdonald RL, Weir B: Molecular biology and genetics, in Macdonald RL, Weir B (eds): *Cerebral Vasospasm*. San Diego, Academic Press, 2001, pp 476–508.
75. Macdonald RL, Zhang Z, Yamini B, Ono S, Marton LS, Komuro T, Weir B: Changes in gene expression do not mediate resolution of vasospasm after subarachnoid hemorrhage in primates. Presented at the 50th Annual Meeting of the Congress of Neurological Surgeons, San Antonio, Texas, September 23–28, 2000 (abstr).
76. Manno EM, Gress DR, Ogilvy CS, Stone CM, Zervas NT: The safety and efficacy of cyclosporine A in the prevention of vasospasm in patients with Fisher grade 3 subarachnoid hemorrhage: A pilot study. **Neurosurgery** 40:289–293, 1997.
77. Matz PG, Massa SM, Weinstein PR, Turner C, Panter SS, Sharp FR: Focal hyperexpression of hemeoxygenase-1 protein and messenger RNA in rat brain caused by cellular stress following subarachnoid injections of lysed blood. **J Neurosurg** 85:892–900, 1996.
78. Matz PG, Sundaresan S, Sharp FR, Weinstein PR: Induction of HSP70 in rat brain following subarachnoid hemorrhage produced by endovascular perforation. **J Neurosurg** 85:138–145, 1996.
79. Matz P, Turner C, Weinstein PR, Massa SM, Panter SS, Sharp FR: Heme oxygenase-1 induction in glia throughout rat brain following experimental subarachnoid hemorrhage. **Brain Res** 713:211–222, 1996.
80. Matz P, Weinstein P, States B, Honkaniemi J, Sharp FR: Subarachnoid injections of lysed blood induce hsp70 stress gene and produce DNA fragmentation in focal areas of the rat brain. **Stroke** 27:504–513, 1996.
81. Matzinger P: Tolerance, danger, and the extended family. **Ann Rev Immunol** 12:991–1045, 1994.
82. Matzinger P, Fuchs EJ: Beyond "self" and "non-self": Immunity is a conversation, not a war. **J Natl Inst Health Res** 8:35–39, 1996.
83. Mayberg MR, Batjer HH, Dacey RG Jr, Diringer M, Haley EC, Heros RC, Sternau LL, Torner J, Adams HP Jr, Feinberg W, Thies W: Guidelines for the management of aneurysmal subarachnoid hemorrhage: A statement for healthcare professionals from a special writing group of the Stroke Council, American Heart Association. **Stroke** 25:2315–2328, 1994.
84. Medawar PB: Immunity to homologous grafted skin: Part III—The fate of skin homografts transplanted to the brain, to subcutaneous tissue, and to the anterior chamber of the eye. **Br J Exp Pathol** 29:58–69, 1948.
85. Mima T, Mostafa MG, Mori K: Therapeutic dose and timing of administration of RNA synthesis inhibitors for preventing cerebral vasospasm after subarachnoid hemorrhage. **Acta Neurochir Suppl (Wien)** 70:65–67, 1997.
86. Mosmann TR, Sad S: The expanding universe of T-cell subsets: Th1, Th2 and more. **Immunol Today** 17:138–146, 1996.
87. Nagata K, Sasaki T, Iwama J, Mori T, Iwamoto S, Nirei H, Hamada K, Kirino T: Failure of FK-506, a new immunosuppressant, to prevent cerebral vasospasm in a canine two-hemorrhage model. **J Neurosurg** 79:710–715, 1993.
88. Nagata K, Sasaki T, Mori T, Nikaido H, Kobayashi E, Kim P, Kirino T: Cisternal talc injection in dog can induce delayed and prolonged arterial constriction resembling cerebral vasospasm morphologically and pharmacologically. **Surg Neurol** 45:442–447, 1996.
89. Ni K, O'Neill HC: The role of dendritic cells in T cell activation. **Immunol Cell Biol** 75:223–230, 1997.
90. Nishizawa S, Peterson JW, Shimoyama I, Iwasaki K, Uemura K: Therapeutic effect of a new immunosuppressant, FK-506, on vasospasm after subarachnoid hemorrhage. **Neurosurgery** 32:986–991, 1993.
91. Nobis U, Pries AR, Cokelet GR, Gaehtgens P: Radial distribution of white cells during blood flow in small tubes. **Microvasc Res** 29:295–304, 1985.
92. Onda H, Kasuya H, Takakura K, Hori T, Imaizumi T, Takeuchi T, Inoue I, Takeda J: Identification of genes differentially expressed in canine vasospastic cerebral arteries after subarachnoid hemorrhage. **J Cereb Blood Flow Metab** 19:1279–1288, 1999.
93. Ono S, Date I, Onoda K, Shiota T, Ohmoto T, Ninomiya Y, Asari S, Morshita R: Decoy administration of NF-κB into the subarachnoid space for cerebral angiopathy. **Hum Gene Ther** 9:1003–1011, 1998.
94. Ono S, Zhang ZD, Marton LS, Yamini B, Windmeyer E, Johns L, Kowalczuk A, Lin G, Macdonald RL: Heme oxygenase-1 and ferritin are increased in cerebral arteries after subarachnoid hemorrhage in monkeys. **J Cereb Blood Flow Metab** 20:1066–1076, 2000.
95. Oruckaptan HH, Caner HH, Kiline K, Ozgen T: No apparent role for neutrophils and neutrophil-derived myeloperoxidase in experimental subarachnoid haemorrhage and vasospasm: A preliminary study. **Acta Neurochir (Wien)** 142:83–90, 2000.
96. Oshiro EM, Hoffman PA, Dietsch GN, Watts MC, Pardoll DM, Tamargo RJ: Inhibition of experimental vasospasm with anti-intercellular adhesion molecule-1 monoclonal antibody in rats. **Stroke** 28:2031–2038, 1997.
97. Ostergaard JR, Kristensen BO, Svehag SE, Teisner B, Miletic T: Immune complexes and complement activation following rupture of intracranial saccular aneurysms. **J Neurosurg** 66:891–897, 1987.
98. Osuka K, Suzuki Y, Watanabe Y, Takayasu M, Yoshida J: Inducible cyclooxygenase expression in canine basilar artery after experimental subarachnoid hemorrhage. **Stroke** 29:1219–1222, 1998.
99. Parney IF, Hao C, Petruk KC: Glioma immunology and immunotherapy. **Neurosurgery** 46:778–792, 2000.
100. Pellettieri L, Carlson CA, Lindholm L: Is the vasospasm following subarachnoid hemorrhage an immunoreactive disease? **Experientia** 37:1170–1171, 1981.
101. Pellettieri L, Nilsson B, Carlsson CA, Nilsson U: Serum immunocomplexes in patients with subarachnoid hemorrhage. **Neurosurgery** 19:767–771, 1986.
102. Peters JH, Gieseler R, Thiele B, Steinbach F: Dendritic cells: From ontogenetic orphans to myelomonocytic descendants. **Immunol Today** 17:273–278, 1996.
103. Peterson EW, Cardoso ER: The blood brain barrier following experimental subarachnoid hemorrhage: Part I—Response to insult caused by arterial hypertension. **J Neurosurg** 58:338–344, 1983.
104. Peterson JW, Kwun B, Hackett JD, Zervas NT: The role of inflammation in experimental cerebral vasospasm. **J Neurosurg** 72:767–774, 1990.
105. Peterson JW, Nishizawa S, Hackett JD, Bun T, Teramura A, Zervas NT: Cyclosporine A reduces cerebral vasospasm after subarachnoid hemorrhage in dogs. **Stroke** 21:133–137, 1990.
106. Peterson JW, Searle R, Mandy FF, Teramura A, Hackett JD, Morgan JA, Nishizawa S, Bun T, Zervas NT: Immunological reaction against the aging human subarachnoid erythrocyte: A model for the onset of cerebral vasospasm after subarachnoid hemorrhage. **J Neurosurg** 71:718–726, 1989.
107. Polin RS, Bavbek M, Shaffrey ME, Billups K, Bogaev CA, Kassell NF, Lee KS: Detection of soluble E-selectin, ICAM-1, VCAM-1, and L-selectin in the cerebrospinal fluid of patients after subarachnoid hemorrhage. **J Neurosurg** 89:559–567, 1998.
108. Rana MW, Pinderton H, Thornton H, Nagy D: Heterotransplantation of human glioblastoma and meningioma to nude mice. **Proc Soc Exp Biol Med** 155:85–88, 1977.
109. Rescigno M, Winzler C, Delia D, Mutini C, Lutz M, Riciardi-Castagnoli P: Dendritic cell maturation is required for initiation of the immune response. **J Leukoc Biol** 61:415–421, 1997.

110. Ries S, Schminke U, Fassbender K, Daffertshofer M, Steinke W, Hennerici M: Cerebrovascular involvement in the acute phase of bacterial meningitis. **J Neurol** 244:51–55, 1997.
111. Ronkainen A, Miettinen H, Karkola K, Papinaho S, Vanninen R, Puranen M, Hernesniemi JA: Risk of harboring an unruptured intracranial aneurysm. **Stroke** 29:359–362, 1998.
112. Rosenorn J, Eskesen V, Schmidt K, Esperson JO, Haase J, Harmsen A, Hein O, Knudsen V, Midholm S, Marcussen E, Rasmussen P, Ronde F, Volby B, Hansen L: Clinical features and outcome in 1076 patients with ruptured intracranial aneurysms: A prospective consecutive study. **Br J Neurosurg** 1:33–46, 1987.
113. Ryba M, Grieb P, Pastuszko M, Bidzinski J, Andrychowski J, Dziewiecki, Bojarski P, Krolicki L: Successful prevention of neurological deficit in SAH patients with 2-chlorodeoxyadenosine. **Acta Neurochir (Wien)** 124:61–65, 1993.
114. Ryba M, Patuszko M, Iwanska K, Bidzinski J, Dziewiecki C: Cyclosporine A prevents neurological deterioration of patients with SAH: A preliminary report. **Acta Neurochir (Wien)** 112:25–27, 1997.
115. Satoh M, Date I, Nakajima M, Takahashi K, Iseda K, Tamiya T, Ohmoto T, Ninomiya Y, Asari S: Inhibition of poly(ADP-ribose) polymerase attenuates cerebral vasospasm after subarachnoid hemorrhage in rabbits. **Stroke** 32: 225–231, 2001.
116. Säveland H, Sonesson B, Ljundggren B, Brandt L, Uski T, Zygmunt S: Outcome evaluation following subarachnoid hemorrhage. **J Neurosurg** 64:191–196, 1986.
117. Scheinberg LC, Edelman FL, Levy WA: Is the brain "an immunologically privileged site?": Part I—Studies based on intracerebral homotransplantations and isotransplantation to sensitized hosts. **Arch Neurol** 11:248–264, 1964.
118. Scheinberg LC, Kotsilimbas DG, Karpf R, Mayer N: Is the brain "an immunologically privileged site?": Part III—Studies based on homologous skin grafts to the brain and subcutaneous tissues. **Arch Neurol** 15:62–67, 1964.
119. Schievink WI: Intracranial aneurysms. **N Engl J Med** 336:28–40, 1997.
120. Schmid-Schönbein GW, Usami S, Skalak R, Chien S: The interaction of leukocytes and erythrocytes in capillary and postcapillary vessels. **Microvasc Res** 19:45–70, 1980.
121. Scholz D, Devaux B, Hirche A, Potzsch B, Kropp B, Schaper W, Schaper J: Expression of adhesion molecules is specific and time-dependent in cytokine-stimulated endothelial cells in culture. **Cell Tissue Res** 284:415–423, 1996.
122. Shigeno T, Mima T, Yanagisawa M, Saito A, Goto K, Yamashita K, Takenouchi T, Matsuura N, Yamasaki Y, Yamada K, Masaki T, Yamada K: Prevention of cerebral vasospasm by actinomycin D. **J Neurosurg** 74:940–943, 1991.
123. Shigeru N, Peterson JW, Shimoyama I, Iwasaki K, Uemura K: Therapeutic efficacy of a new immunosuppressant, FK-506, on vasospasm after subarachnoid hemorrhage. **Neurosurgery** 32:986–992, 1993.
124. Sills AK, Clatterbuck RE, Thompson RC, Cohen PL, Tamargo RJ: Endothelial expression of intercellular adhesion molecule-1 (ICAM-1) in experimental vasospasm. **Neurosurgery** 41:453–461, 1997.
125. Spallone A, Acqui M, Pastore FS, Guidetti B: Relationship between leukocytosis and ischemic complications following aneurysmal subarachnoid hemorrhage. **Surg Neurol** 27:253–258, 1987.
126. Springer TA: Traffic signals on endothelium for lymphocyte recirculation and leukocyte emigration. **Annu Rev Physiol** 57:827–872, 1995.
127. Sullivan GW, Sarembock IJ, Linden J: The role of inflammation in vascular diseases. **J Leukoc Biol** 67:591–602, 2000.
128. Suzuki S, Iwabuchi T, Tanaka T, Kanayama S, Ottomo M, Hatanaka M, Aihara H: Prevention of cerebral vasospasm with OKY-046 an imidazole derivative and a thromboxane synthetase inhibitor: A preliminary cooperative clinical study. **Acta Neurochir (Wien)** 77:133–141, 1985.
129. Suzuki H, Kanamaru K, Tsunoda H, Inada H, Kuroki M, Sun H, Waga S, Tanaka T: Heme oxygenase-1 gene induction as an intrinsic regulation against delayed cerebral vasospasm in rats. **J Clin Invest** 104:59–66, 1999.
130. Takizawa T, Tada T, Kitazawa K, Tanaka Y, Hongo K, Kameko M, Uemura KI: Inflammatory cytokine cascade released by leukocytes in cerebrospinal fluid after subarachnoid hemorrhage. **Neurol Res** 23:724–730, 2001.
131. Tanabe Y, Sakata K, Yamada Y: Cerebral vasospasm and ultrastructural changes in cerebral arterial wall. **J Neurosurg** 49:229–238, 1978.
132. Thai Q, Oshiro EM, Tamargo RJ: Inhibition of experimental vasospasm in rats with the periadventitial administration of ibuprofen using controlled-release polymers. **Stroke** 30:140–147, 1999.
133. Theele DP, Streit WJ: A chronicle of microglial ontogeny. **Glia** 7:5–8, 1993.
134. Tözeren A, Ley K: How do selectins mediate leukocyte rolling in venules? **Biophys J** 63:700–709, 1992.
135. Tran Dinh YR, Jomaa A, Callebert J, Reynier-Rebuffel AM, Tedgui A, Savarit A, Sercombe R: Overexpression of cyclooxygenase-2 in rabbit basilar artery endothelial cells after subarachnoid hemorrhage. **Neurosurgery** 48:626–635, 2001.
136. Tsementzis SA, Chao SW, Hitchcock ER, Gill JS, Beevers DG: Oligoclonal immunoglobulin G in acute subarachnoid hemorrhage and stroke. **Neurology** 36:395–397, 1986.
137. Van Meir EG: Cytokines and tumors of the central nervous system. **Glia** 15:264–288, 1995.
138. Vejlens G: The distribution of leukocytes in the vascular system. **Acta Pathol Microbiol Scand Suppl** 33:1–239, 1938.
139. Vestweber D (ed): *The Selectins*. Amsterdam, Hardwood Academic Publishers, 1997.
140. von Andrian UH, Chambers JD, McEvoy LM, Bargatze RF, Arfors K-E, Butcher EC: Two step model of leukocyte-endothelial cell interaction in inflammation: Distinct roles for LECAM-1 and the leukocyte $beta_2$ integrins in vivo. **Proc Natl Acad Sci U S A** 88:7538–7542, 1991.
141. von Holst H, Ericson K, Edner G: Positron emission tomography with 68-Ga-EDTA and computed tomography in patients with subarachnoid hemorrhage. **Acta Neurochir (Wien)** 97:146–149, 1989.
142. Wagner JG, Roth RA: Neutrophil migration mechanisms, with an emphasis on the pulmonary vasculature. **Pharmacol Rev** 52:349–374, 2000.
143. Waldmann TA: The IL-2/IL-2 receptor system: A target for rational immune intervention. **Immunol Today** 14:264–270, 1993.
144. Wang X, Marton LS, Weir BK, Macdonald RL: Immediate early gene expression in vascular smooth muscle cells synergistically induced by hemosylate components. **J Neurosurg** 90:1083–1090, 1999.
145. Weir BK, Macdonald RL, Stoodley M: Etiology of cerebral vasospasm. **Acta Neurochir Suppl (Wien)** 72:27–46, 1999.
146. White RP, Robertson JT: Comparison of piroxicam, meclofenamate, ibuprofen, aspirin, and prostacyclin efficacy in a chronic model of cerebral vasospasm. **Neurosurgery** 12:40–46, 1983.
147. Yamada S, DePasquale M, Patlak CS, Cserr HF: Albumin outflow into deep cervical lymph from different regions of rabbit brain. **Am J Physiol** 261[Suppl 4]:H1197–H1204, 1991.
148. Yamakawa K, Sasaki T, Tsubaki S, Nakagomi T, Saito I, Takakura K: Effect of high-dose methylprednisolone on vasospasm after subarachnoid hemorrhage. **Neurol Med Chir (Tokyo)** 31:24–31, 1991.
149. Yanamoto H, Kikuchi H, Okamoto S, Nozaki K: Preventive effect of synthetic serine protease inhibitor, FUT-175, administered in the acute stage after subarachnoid hemorrhage. **Neurosurgery** 30:358–363, 1992.
150. Yanamoto H, Kikuchi H, Okamoto S, Nozaki K: Preventive effect of synthetic serine protease inhibitor, FUT-175, on cerebral vasospasm in rabbits. **Neurosurgery** 30:351–356, 1992.
151. Zimmerman GA, Prescott SM, McIntyre TM: Endothelial cell interactions with granulocytes: Tethering and signaling molecules. **Immunol Today** 13:93–100, 1992.

Acknowledgments

ASD receives research support from the American Heart Association, and KSL receives research support from the National Institutes of Health.

COMMENTS

In an era of increasing controversy over the most appropriate treatment for intracranial aneurysms, neurosurgeons must remember that more patients die of subarachnoid hemorrhage (SAH) than because of clipping or coiling of the culpable

aneurysm. Cerebral vasospasm remains one of the most important contributors to morbidity and mortality after aneurysmal SAH. Despite decades of outstanding basic research into the mechanisms and pathophysiology of cerebral vasospasm, a unified theory of pathogenesis and reliable therapeutic options remain elusive.

For many years, the putative role of inflammation in the initiation and maintenance of cerebral vasospasm has been suggested. Initially believed to be "immunologically privileged," it is now clear that the central nervous system is fully capable of initiating an inflammatory response, albeit with its own characteristic immune profile.

The authors have provided an outstanding review article for neurosurgeons and neuroscientists in which they have critically evaluated the existing literature implicating inflammation as a mediator of cerebral vasospasm. In addition, they have provided a concise and understandable overview of immunology and the inflammatory response. This body of evidence strongly suggests that inflammation may represent a common pathogenic pathway in the development of cerebral vasospasm. Although anti-inflammatory therapy has not been demonstrated to consistently provide efficacy in the treatment of cerebral vasospasm, much of the treatment to date has been nonspecific. We may hope that further understanding of the potential role of inflammation in cerebral vasospasm will provide for more specific and novel therapeutic options.

Daniel L. Barrow
Atlanta, Georgia

The inflammatory response is reviewed, and studies that examine the role of inflammation in vasospasm are discussed. Undoubtedly, the inflammatory response contributes in some way to vasospasm after SAH. The final common pathway of injury caused by vasospasm is cerebral ischemia and infarction, and this process is accompanied by inflammation. Inflammatory mechanisms in cerebral ischemia have been the subject of previous reviews that have noted that inflammation is a complex biological response that may have beneficial and/or detrimental effects depending on the specific type of inflammation that is induced and on the time after the insult (2). For example, after spinal cord injury in mice, the effect of the specific cytokines interleukin-1β, interleukin-6, and tumor necrosis factor-α was detrimental when administered 1 day after injury, whereas there was a suggestion that they were beneficial when administered 4 days after injury (4). Certain aspects of the inflammatory response may contribute to vasospasm. Peterson et al. (6) reported that lysis of subarachnoid erythrocytes, a process strongly suggested to be important in the pathogenesis of vasospasm, was mediated by the complement pathway of the inflammatory response. The authors of this review note that patients with meningitis may develop cerebral infarction. How this relates to vasospasm after aneurysmal SAH is unclear. Many inflammatory mediators are vasodilators, and acute inflammation in meningitis is associated with increased cerebral blood flow (1, 3). The pattern of cerebral infarction with meningitis is different from that caused by vasospasm. In addition, results derived from the study of systemic arteries are not generalizable to the cerebral arteries, in which the inflammatory response is quantitatively much less and inflammatory responses, as reviewed in this report, are different (7). Delayed hypersensitivity-type reactions do not seem to be involved, because vasospasm does not get worse when repeated injections of blood are given (8). The failure of anti-inflammatory agents to alleviate angiographic vasospasm, although only a crude test of the hypothesis, for reasons discussed above, has not provided particularly substantial evidence in support of the inflammatory hypothesis (5). In any case, the complexity of the immune and inflammatory response is such that it seems likely to be involved in both beneficial and detrimental responses to SAH that might even vary depending on the individual situation. The models currently used to investigate vasospasm have numerous shortcomings (chiefly the ability to replicate vasospasm in a species in which precisely targeted molecular manipulations can be performed) that will make it extremely difficult to dissect out the role of inflammation in the near future.

R. Loch Macdonald
Chicago, Illinois

1. Faraci FM, Heistad DD: Regulation of the cerebral circulation: Role of endothelium and potassium channels. **Physiol Rev** 78:53–97, 1998.
2. Feuerstein GZ, Wang X, Barone FC: The role of cytokines in the neuropathology of stroke and neurotrauma. **Neuroimmunomodulation** 5:143–159, 1998.
3. Haberl RL, Anneser F, Kodel U, Pfister HW: Is nitric oxide involved as a mediator of cerebrovascular changes in the early phase of experimental pneumococcal meningitis. **Neurol Res** 16:108–112, 1994.
4. Klusman I, Schwab ME: Effects of pro-inflammatory cytokines in experimental spinal cord injury. **Brain Res** 762:173–184, 1997.
5. Manno EM, Gress DR, Ogilvy CS, Stone CM, Zervas NT: The safety and efficacy of cyclosporine A in the prevention of vasospasm in patients with Fisher grade 3 subarachnoid hemorrhages: A pilot study. **Neurosurgery** 40:289–293, 1997.
6. Peterson JW, Kwun BD, Hackett JD, Zervas NT: The role of inflammation in experimental cerebral vasospasm. **J Neurosurg** 72:767–774, 1990.
7. Thai QA, Oshiro EM, Tamargo RJ: Inhibition of experimental vasospasm in rats with the periadventitial administration of ibuprofen using controlled-release polymers. **Stroke** 30:140–147, 1999.
8. Weir B, Erasmo R, Miller J, McIntyre J, Secord D, Mielke B: Vasospasm in response to repeated subarachnoid hemorrhages in the monkey. **J Neurosurg** 33:395–406, 1970.

Basic molecular and cellular research is demonstrating the emergence of two major hypotheses as key to the pathophysiological story of cerebral vasospasm. One is the role of nitric oxide and nitric oxide synthase. Second is the role of inflammation. Several groups are already demonstrating that the two hypotheses may in fact be intertwined. Dumont et al. provide a thorough review of the literature concerning one of the hypotheses: inflammation.

The authors make the case for inflammation being critical to the development of cerebral vasospasm. SAH triggers an inflammatory cascade, possibly from the hemolysis of the blood clot itself in the cerebrospinal fluid, as has been elegantly

demonstrated with endothelin-1, and may cause the release of cytokines. Cytokines cause an inflammatory cascade of events that include activation of B cells (humoral response) and T cells (cellular response). Adhesion molecules aid in the focal recruitment of leukocytes to the putative areas of vasospasm. Complement and immunoglobulins have also been suspected to play roles.

The proposition that inflammation plays some role in cerebral vasospasm will likely be borne out as basic research continues. It will be interesting to see how inflammation after SAH differs from other inflammation. The inflammatory elements being investigated in regard to vasospasm are known to occur in other instances of inflammation as well, such as cerebral neoplasm, cerebral infection (studied particularly in toxoplasmosis), cerebral trauma, and, most notably, cerebral ischemic stroke. Why do these inflammatory elements cause vasospasm of the cerebral vessels only in the circumstances of SAH?

The fact that we do not see clinical vasospasm until 4 days after SAH indicates an inflammatory process. However, we must be careful not to make the assumption that the expression of certain inflammatory elements at higher levels after SAH necessarily demonstrates some role for them in vasospasm. Certain cytokines or inflammatory events may occur as an acute-phase reaction to the SAH event and do not necessarily mean that they cause cerebral vasospasm. Thus, studies that demonstrate higher levels of an inflammatory element in the cerebrospinal fluid or in the serum after SAH do not sufficiently demonstrate a role in cerebral vasospasm.

Further research may help us to understand the process by which global systemic inflammatory events, such as the release of cytokines, translate to focal recruitment of leukocytes to specific segments of vessels and how the sequence of leukocyte margination–rolling–adhesion endoluminally then translates to vasoconstriction of the vessel wall. Furthermore, why do specific vessels and specific segments of vessels develop vasospasm, whereas others do not?

It is interesting that immunocompromised patients who do not mount a strong inflammatory response still experience cerebral vasospasm after SAH. We have found this in our cohort of acquired immunodeficiency syndrome patients with SAH. In addition, therapies aimed at countering inflammation in studies such as ours, in which we tested cyclosporin A (1), have not been promising.

We have found it interesting that there seems to be a natural progression in basic research that comes from concepts that our colleagues in cardiology investigate in coronary vessel disease, which lend themselves to cerebral ischemic stroke research by our colleagues in neurology, and finally lend themselves to applications in the study of cerebral vasospasm. Much of the work described in this review regarding the role of inflammatory elements in cerebral vasospasm credits work done in coronary vessel disease and cerebral ischemic stroke. It will be exciting to see how the inflammatory story in cerebral vasospasm unfolds as this research continues. It will be even more valuable if this can be translated to a therapeutic measure.

Brian L. Hoh
Christopher S. Ogilvy
Boston, Massachusetts

---

1. Manno EM, Gress DR, Ogilvy CS, Stone CM, Zervas NT: The safety and efficacy of cyclosporine A in the prevention of vasospasm in patients with Fisher grade 3 subarachnoid hemorrhage: A pilot study. **Neurosurgery** 40: 289–293, 1997.

The authors review evidence supporting the concept that inflammation is involved in vasospasm after aneurysmal SAH. Considerable data demonstrate that many molecular and cellular agents known to participate in inflammation also participate in vasospasm. Furthermore, the authors hypothesize that inflammation may be the final common pathway by which these agents exert a vasospastic effect. It remains unclear whether subarachnoid blood induces an inflammatory response that triggers vasospasm or whether subarachnoid blood triggers vasospasm directly by use of some of the same agents that participate in inflammation. Unfortunately, the current body of knowledge does not elucidate an underlying mechanism. This review leaves little doubt that further investigation is necessary. The endeavor to understand vasospasm and develop targeted therapies against it has been frustratingly tedious and slow. The authors have exhibited perseverance and commitment to improving the fate of patients with this devastating sequela of aneurysmal SAH.

Michael T. Lawton
San Francisco, California