increasing evidence shows that the central nervous system and the immune system interact in complex ways, and better insight into these interactions may be relevant to the treatment of patients with stroke and other forms of central nervous system injury. Atherosclerosis, autoimmune disease, and physiological stressors, such as infection or surgery, cause inflammation that contributes to vascular injury and increases the risk of stroke. In addition, the immune system actively participates in the acute pathogenesis of stroke. Thrombosis and hypoxia trigger an intravascular inflammatory cascade, which is further augmented by the innate immune response to cellular damage occurring in the parenchyma. This immune activation may cause secondary tissue injury, but it is unclear whether modulating the acute immune response to stroke can produce clinical benefits. Attempts to dampen immune activation after stroke may have adverse effects because central nervous system injury causes significant immunodepression that places patients at higher risk of infections, such as pneumonia. The activation of innate immunity after stroke sets the stage for an adaptive immune response directed against brain antigens. The pathogenic significance of adaptive immunity and its long-term effects on the posts ischemic brain remains unclear, but it cannot be ruled out that a persistent autoimmune response to brain antigens has deleterious and long-lasting consequences. Further research will be required to determine what role, if any, immunity has in long-term outcomes after stroke, but elucidation of potential mechanisms may open promising avenues for the development of new therapeutics to improve neurological recovery after brain injury.
notoriously prone to confounding, and animal models of stroke in these patients. However, observational data are necessary to detect the jury and subsequent stroke, which would open the door to the inflammatory component, and inhibition of the immune response to lipoproteins seems to reduce the proportion to traditional vascular risk factors, implying an additive effect of underlying inflammation. Furthermore, animal models demonstrate that atherosclerosis has an inflammatory component, and inhibition of the immune response to lipoproteins seems to reduce the progression of atherosclerosis. These observations suggest that inflammation may have a causal role in vascular injury and subsequent stroke, which would open the door for immunomodulatory agents as new tools to prevent stroke in these patients. However, observational data are notoriously prone to confounding, and animal models often do not apply well to humans. Clearly, a more detailed understanding of the complex relationship between inflammation and stroke is required to better assess the feasibility of immunomodulation as a potential tool for stroke prevention.

Inflammation is increasingly recognized as a possible pathway in the pathogenesis of atrial fibrillation, which is a leading cause of stroke. Levels of C-reactive protein are elevated in patients with atrial fibrillation and are associated with incident atrial fibrillation and with its recurrence after ablation or cardioversion. Inflammatory pathways may promote atrial fibrillation by interacting with cell signaling cascades, causing ion channel dysfunction, impairing myocyte gap junctions, promoting atrial fibrosis, and recruiting leukocytes to cardiac tissue. The relationship between inflammation and atrial fibrillation is most likely bidirectional, with atrial fibrillation causing some degree of immune activation and inflammation. The prothrombotic state seen in atrial fibrillation may reflect this inflammation, and anticoagulation with heparinoids seems to reduce biomarkers of inflammation in patients with atrial fibrillation. On the other hand, perioperative treatment with glucocorticoids reduces the incidence of atrial fibrillation after cardiac surgery, which suggests that inflammation may also have a causal role in the pathogenesis of atrial fibrillation. Once patients develop atrial fibrillation, their risk of stroke varies in proportion to known clinical risk factors, such as congestive heart failure, hypertension, age, diabetes mellitus, prior stroke, and peripheral vascular disease. However, levels of the proinflammatory cytokine interleukin 6 are also associated with stroke risk, suggesting that inflammation is an additional biomarker of stroke risk within this population. Given these data, physicians should be mindful that periods of heightened

**Table. Examples of Brain-Immune Interactions and Their Clinical Implications in the Care of Patients With Stroke**

<table>
<thead>
<tr>
<th>Examples</th>
<th>Interaction of Inflammation and Stroke Risk</th>
<th>Potential Clinical Implications</th>
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</thead>
<tbody>
<tr>
<td>Biomarkers of stroke risk include white blood cell count, fibrinogen, D-dimer, and C-reactive protein. Duration of systemic lupus erythematous and rheumatoid arthritis correlates with risk of stroke. A transient increased risk of stroke occurs after infection or surgery. A link exists between inflammation and atrial fibrillation.</td>
<td>Clinical implications include the following capabilities: predict favorable response to lipid-modifying agents, identify patients at high risk of stroke after cessation of antithrombotic drugs, stratify risk of stroke and determine appropriate antithrombotic strategy in patients with atrial fibrillation, use proven measures for stroke prevention in patients with underlying inflammatory disease and after infection or surgery, and control inflammation as a pathway to reducing vascular injury or occurrence of atrial fibrillation.</td>
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<td>Intravascular hypoxia from thrombosis activates complement and endothelial cells. Oxidative stress reduces nitric oxide, promoting platelet and leukocyte aggregation. Platelet activation generates proinflammatory signals. Spread of inflammation into perivascular space activates resident macrophages. Dying cells release signals that promote inflammation. Loss of neurons removes the anti-inflammatory check on adjacent microglia.</td>
<td>Inhibition of the complement cascade reduces ischemic brain damage. Lymphocyte depletion protects against penumbral ischemia in experimental animal models of stroke. Timely use of statin therapy during acute stroke seems to improve outcomes, potentially in part from anti-inflammatory properties.</td>
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<td>Stroke results in lymphopenia, upregulation of anti-inflammatory cytokines, and splenic atrophy. Pneumonia and urinary tract infections occur frequently after stroke. Cortisol and catecholamine levels correlate with susceptibility to infection after stroke.</td>
<td>Vigilance should be exercised for early signs of infection after stroke. Prophylactic antibiotic use after stroke may reduce infectious complications and improve outcomes. Modulation of sympathetic activation may reduce poststroke immunodepression.</td>
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<tr>
<td>Inflammatory brain infiltrates persist for years after stroke. Abnormal blood-brain barrier permeability may be associated with radiographic white matter disease.</td>
<td>Immunomodulation may reduce the burden of long-term sequelae of ischemic stroke.</td>
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inflammation (such as acute medical illness or recent surgery) place patients at higher risk of atrial fibrillation and stroke. With further development, biomarkers of inflammation may help to stratify patients' risk of developing atrial fibrillation and stroke, allowing targeted screening, risk factor modification, and timely treatment. A better understanding of the interactions among atrial fibrillation, inflammation, and thromboembolism may lead to the development of therapeutic agents that modulate inflammatory pathways to reduce the risk of atrial fibrillation and stroke.

**IMMUNE SIGNALING DURING ACUTE INFARCTION**

Besides its background role in stroke risk, the immune system actively participates in the acute pathogenesis of stroke (Figure). Independent of any immune response, brain ischemia quickly causes failure of ion pumps, overaccumulation of intracellular sodium and calcium, loss of membrane integrity, and necrotic cell death. In addition, arterial occlusion immediately leads to intravascular hypoxia, changes in shear stress, and the production of reactive oxygen species, all of which in turn activate the coagulation cascade, complement, platelets, and endothelial cells. This results in a vicious cycle, with fibrin formation entrapping platelets and leukocytes and causing further vascular occlusion. In addition, oxidative stress reduces the bioavailability of nitric oxide, undermining its protective role in promoting vasodilation and inhibiting platelet aggregation and leukocyte adhesion, causing further vascular occlusion and ischemia. Central in this cascade of events is the translocation of P-selectin, an adhesion molecule whose expression on the surface of platelets and endothelial cells rapidly leads to cell adhesion. Trafficking of inflammatory cells into the perivascular space is facilitated by downregulation of junctional proteins that maintain the integrity of the endothelial lining and the blood-brain barrier. Involvement of the perivascular space then activates resident macrophages and mast cells, leading to the release of vasoactive mediators and proinflammatory cytokines, which in turn recruit and promote the infiltration of more leukocytes.

As cells die of ischemia, they release signals that further activate the immune system. Extracellular accumulation of adenosine triphosphate released from dying cells activates microglia, which develop characteristics of macrophages and release proinflammatory mediators. Numerous normally intracellular components serve as danger-associated molecular pattern molecules on their release from dying cells, and these molecules activate toll-like receptors and scavenger receptors on microglia, perivascular macrophages, dendritic and endothelial cells, and infiltrating leukocytes. This activation induces the expression of proinflammatory molecules and primes dendritic cells for antigen presentation. Such proinflammatory changes are initially counterbalanced by the release of neurotransmitters, which activate anti-inflammatory receptors on microglia, and by the presence of cell-cell interactions between microglia and adjacent neurons, which usually keep microglia quiescent. However, as ischemic cell death progresses, neurons die and neurotransmitters are depleted, releasing this brake on proinflammatory signaling.

The clinical implications of the immediate immune involvement in the ischemic cascade are unclear. On the face of it, proinflammatory signals seem to promote mi-
crovascular occlusion and should tend to increase the size of the resulting infarct. In fact, in experimental models of stroke, mice deficient in adhesion receptors or complement subunits seem to be protected from acute ischemia, and healthy mice treated with inhibitors of adhesion molecules or the complement cascade also develop less ischemic brain injury. In addition, mice engineered to lack selected T-cell subgroups are protected from ischemic damage to the penumbral zone around areas of infarction. Available data indicate that the protective effect of lymphocyte suppression does not stem from an inability to propagate thrombus and that no significant differences in cerebral blood flow exist between healthy and lymphocyte-deficient mice. It is possible that lymphocytes instead produce cell damage directly or through proinflammatory signaling and activation of downstream microglia and macrophages. Or, the early damage associated with lymphocyte infiltration of the ischemic brain may be due to the natural killer T-cell subtype that harbors a simplified T-cell receptor and may not require antigen processing. The available data do not provide a clear picture of how lymphocytes participate in acute infarction.

Clinical attempts to explicitly modify the immune response after stroke (such as trials of recombinant neutrophil inhibitory factor or antibodies against adhesion molecules) have been ineffective to date, and these failures highlight the complexity and redundancy of the pathways involved in the immune response to stroke. On the other hand, observational data and a randomized clinical trial indicate that acute use of statin medications at the time of stroke improves long-term outcomes and reduces mortality. Because this time window is not consistent with the lipid-lowering effects of statin medications, the benefit of their use during the acute stage of stroke has been attributed to their anti-inflammatory properties. This suggests that, despite the absence of specific clinical strategies or drugs proven to beneficially modulate immune functioning during acute brain infarction, further elucidation of this complex interplay may yield more sophisticated and pleiotropic therapeutics to augment the limited repertoire of antithrombotic agents available to physicians today.

THE ROLE OF ADAPTIVE IMMUNITY AFTER STROKE

The inflammatory processes detailed thus far occur in a short time window after infarction and rely on the innate immune system, which involves the rapid activation of low-affinity receptors that recognize a wide range of targets. The immediate onset of this inflammatory cascade and the available experimental data on patterns of signaling during early immune activation do not support a substantial role in this process for the adaptive immune system, which relies on the clonal expansion of specific lymphocytes with high-affinity receptors to specific antigens. However, the general immune activation caused by cerebral ischemia raises the questions of whether the adaptive immune system is eventually activated and how it may contribute to the propagation and repair of brain injury after stroke.

After stroke, the number of antigen-presenting cells in the brain increases, along with costimulatory molecules required for antigen presentation to lymphocytes. This antigen presentation results in the production of antibodies against brain antigens and T cells sensitized to brain antigens. Furthermore, successive mucosal administration of myelin antigens in experimental models results in the development of immune tolerance and protection from subsequent ischemic injury, suggesting that this immune response involves adaptive immunity and that modulating it may be protective. On the other hand, although lymphocyte-deficient mice are protected from ischemic brain damage, reconstituting them with T cells directed against non-CNS antigens worsens ischemic damage. In addition, mice lacking the necessary costimulatory molecules for antigen-specific T-cell responses are nevertheless vulnerable to ischemic damage. Therefore, it is unclear whether the release and presentation of CNS antigens during and after stroke result in an adaptive immune response directed against the CNS.

If such an autoimmune response was directed against the brain after stroke, its long-term implications would potentially be significant (Table). Such immune activity would be expected to impair neuronal plasticity and functional recovery and contribute to the frequent incidence of poststroke dementia. Such concerns are supported by the presence of inflammatory infiltrates in damaged areas of the brain years after stroke, as well as by persistently elevated titers of antibodies to brain antigens. Abnormal permeability of the blood-brain barrier has been linked to the radiographic white matter changes frequently associated with vascular disease and cognitive decline, and levels of inflammatory biomarkers such as C-reactive protein are associated with white matter changes, lacunar strokes, and loss of microstructural integrity as measured by diffusion-tensor imaging. Therefore, it cannot be discounted that immune activation contributes to the alterations in this endothelial permeability and vascular dysfunction. On the other hand, immune cells such as microglia may be important for clearing deleterious cellular debris that can cause neurodegeneration. Further research will be required to determine what role, if any, immunity has in long-term outcomes after stroke, but elucidation of any potential mechanisms may open promising avenues for the development of new therapeutics to improve neurological recovery after brain injury.

RESOLUTION OF INFLAMMATION AND THE ROLE OF THE IMMUNE SYSTEM IN TISSUE REPAIR

The inflammation unleashed by cerebral infarction is followed by a carefully orchestrated process to clear necrotic debris and foster tissue repair. This reparative process releases mediators that actively bring the inflammatory process to a close. Phagocytosis of dead cells by microglia and macrophages promotes the production of immunomodulatory cytokines, such as transforming growth factor β and interleukin 10. Although transforming growth factor β has numerous proinflammatory effects, in this context it helps to suppress inflammation by inhibiting helper T-cell responses and promoting regu-
latory T-cell development. Interleukin 10 has neuroprotective and anti-inflammatory properties, and its release helps to facilitate the resolution of inflammation and promotes the survival of remaining viable neurons.

In this evolving process, the same cells that were initially recruited in the inflammatory phase serve as important sources of growth factors required for neuronal sprouting, neurogenesis, angiogenesis, gliogenesis, and matrix reorganization. For example, microglia are required for the full expression of insulinlike growth factor 1, which promotes neuronal sprouting after injury. Reactive astrocytes produce vascular endothelial growth factor, which is required for angiogenesis. Circulating CD34+ immune progenitor cells promote revascularization in infarcted brain tissue. This reparative aspect of immune cells raises expectations that they can be harnessed to augment neuronal repair and recovery after CNS injury. However, experimental efforts so far provide cautionary tales; for example, increasing vascular endothelial growth factor levels early after ischemia or in excessive amounts actually worsens injury. Such findings highlight the complexity of the immune response to CNS injury and indicate that attempts to modify these interactions must be undertaken with care.

**BRAIN INJURY AND IMMUNOSUPPRESSION**

Thus far, we have focused on the effects exerted by the immune system on the CNS after stroke. However, this interaction is bidirectional, and CNS injury has profound effects on immune function (Table). Within days of stroke, patients develop significant immunodepression, marked by lymphopenia, upregulation of anti-inflammatory cytokines, and splenic atrophy. This immunodepression clinically manifests in the high rate of systemic infections seen in the immediate poststroke period. Patients with stroke are especially at risk of pneumonia and urinary tract infections, and such infections may independently worsen neurological outcomes and increase mortality. Immunodepression may account for the inability of other factors (such as dysphagia) to fully account for the high rates of pneumonia seen in survivors of stroke.

Poststroke immunodepression seems to be mediated by catecholamines and steroids released by sympathetic activation after stroke. Cortisol and serum catecholamine levels correlate with susceptibility to infection after stroke, and experimental models have shown that steroid and adrenergic antagonists counteract lymphocyte apoptosis and reduce rates of infection after brain injury. Intriguing clinical observations associate β-blocker use with lower rates of pneumonia and mortality after stroke, but given the sparse nature of these data and the pleiotropic effects of β-blockers, further research will be required to determine the usefulness of such widely available drugs to modulate the immune response after stroke.

Other efforts to counteract poststroke immunodepression have involved the prophylactic administration of antibiotics after stroke to protect patients from common infections. Several randomized trials investigated whether this strategy improves outcomes after stroke, and a meta-analysis of their results indicates that antibiotic use reduced the rate of infections but not mortality. However, these studies were underpowered to detect a meaningful difference in mortality rates, and further large trials will be required to answer this question. If antibiotic use is eventually shown to improve outcomes after stroke, questions will remain about the effects of such a strategy on microbial resistance patterns. Nevertheless, it is possible that a strategy of prudent poststroke antibiotic use may emerge as a cost-effective and safe strategy for improving outcomes in these vulnerable patients. In the meantime, physicians should be cognizant of the immunosuppressed state of their patients with stroke and should remain vigilant to expeditiously identify and appropriately treat infections in these patients.

**RELATIONSHIP BETWEEN POSTSTROKE IMMUNODEPRESSION AND ADAPTIVE IMMUNITY**

In speculating about why poststroke immunodepression occurs, on the surface it would seem to harm patients by increasing their risk of infectious complications. Although it may simply be a maladaptive response that stems from inherent aspects of the design of the CNS and immune system, immunodepression may serve to protect the CNS from the development of adaptive immune responses directed against self. Recent data indicate that the CNS undergoes regular immune surveillance by circulating lymphocytes. Central nervous system components are not routinely presented to these lymphocytes in such a way as to sensitize them and launch an immune response against the CNS. However, in the absence of countervailing factors, such antigen presentation would be expected to occur after CNS injury and compromise of the blood-brain barrier. Therefore, the immunodepression seen after stroke may serve a beneficial purpose in limiting the development of such autoimmunity. Such considerations suggest that a detailed understanding of the many facets of the interactions between the CNS and the immune system is needed to guide any interventions to modify these interactions and improve outcomes.

**CONCLUSIONS**

The relationship between the CNS and the immune system is complex and remains incompletely understood. It has particular salience after stroke and other forms of CNS injury, which trigger immune processes that seem to be both beneficial and harmful. A major frontier in stroke research involves efforts to better understand these interactions to develop new strategies and drugs that will prevent and reduce the burden of stroke. Based on current knowledge, physicians should be mindful that underlying inflammation is a biomarker of stroke risk and should carefully consider antithrombotic, statin, and antihypertensive therapy in vulnerable populations. Further work will be needed to delineate precise clinical strategies for risk factor modification based on specific biomarkers. In addition, it would be reasonable to administer statin drugs to patients with acute stroke given data suggesting that this improves outcomes, possibly as a result of anti-inflammatory properties. Furthermore,
physicians caring for patients with stroke should recognize that poststroke immunodepression increases the risk of infection and should adjust their clinical suspicion and treatment strategies accordingly. Whether a strategy of routine prophylactic antibiotic administration after stroke is beneficial remains unknown, but it holds promise as a simple method for improving poststroke outcomes. Finally, the care of patients with stroke may be improved by advances in specific areas, including investigation of whether modulating inflammatory pathways can reduce the risk of stroke and decrease penumbral ischemia during acute stroke, whether immunity has a role in poststroke functional recovery and dementia, and whether strategies to prevent poststroke immunodepression can reduce the incidence of infection after stroke without increasing dangerous autoimmunity against the brain. The immune system has not traditionally been the subject of therapeutic manipulation in patients with stroke, but given its intertwined relationship with the CNS, it promises to be an exciting avenue for future attempts to reduce the high burden of disability and death from stroke.

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