Knowledge about stroke continues to advance at a slow but unrelenting pace. In this issue of Stroke clinical and basic scientists highlight the progress made in 2005 in all areas of stroke.

The association of specific genes with a heterogeneous condition such as stroke can both delight and despair. Delight in identifying potential new causal factors and despair in the contradictory results of confirmatory studies. The identification of the phosphodiesterase 4D (PDE4D) and 5-Lipoxygenase activating protein (ALOX5AP) genes provide examples of associations with stroke risk, but subsequent studies both confirm and deny a relationship, despairing certainty seekers.

The recent completion of a halflotype map of the entire human genome (the Hap Map Project) may help narrow down the most relevant possibilities and accelerate the discovery and confirmation of disease-related genes. The alternative approach of monogenic disease continues to yield results. For example, a sickle cell disease model identified the 12 genes that interact with fetal hemoglobin to modulate risk of stroke, and allowed prediction of the occurrence of stroke with 95.2% accuracy.

Atherosclerosis may be the most common chronic inflammatory condition. Inflammation plays a role of both cause and effect in atherosclerosis. Inflamed vessels and inflamed blood interact, both affecting coagulation and blood flow.

Preconditioning affords the unique opportunity to study the repertoire of endogenous responses that confer neuroprotection after cerebral ischemia. One of the most encouraging recent developments has been the demonstration that preconditioning with lipopolysaccharide, a TLR4 ligand, interleukin-1 and tissue necrotic factor confer robust cytoprotection in experimental models of stroke.

Infections have been long established as frequent preludes to stroke. Now an Early Systemic Prophylaxis of Infection After Stroke (ESPIAS) Trial examines the role of antibiotics in acute stroke.

Five statins offer protection in a dose-dependent manner in ischemic models of normocholesterolemic animals. The mechanisms may be multiple, but include increasing endothelium-derived nitric oxide synthetase, which relaxes vascular smooth muscle, improving blood flow and having antiplatelet and antileucocyte effects.

A relationship between serum cholesterol levels and stroke has now been established. Meta-analyses confirm a reduction of stroke in coronary and diabetic patients treated with statins. We eagerly await the results of Stroke Prevention by Aggressive Reduction in Cholesterol Levels (SPARCL) study, the only trial examining the use of statins in stroke prevention in patients with cerebrovascular disease. The Heart Protection Study showed the effectiveness of statins in stroke patients, but the patients were randomized on average 5 years after their stroke. SPARCL will look at statins in patients with more recent ischemic events of the brain.

The symptoms of a transient ischemic attack may disappear, but the danger of stroke does not. Growing evidence suggests that all acute cerebrovascular events justify the term “brain attack”, with its implication of a threatened brain demanding emergent action. A simple ABCD score, computing age, blood pressure, clinical features and duration predicts stroke at 7 days. Evidence of infarction on computed tomography, diffusion-weighted imaging abnormalities predict an increased risk of stroke, especially if multiple. The relative and cumulative advantage of different imaging modalities in addition to the clinical score remains to be worked out. We are beginning to learn to assess risk and to develop risk graded responses.

One of the methods of assessing risk in asymptomatic carotid disease is by the detection of microemboli by transcranial Doppler. Although microembolization predicts higher risk and a combination of aspirin and clopidogrel reduces microembolization, it remains to be proven whether reducing microembolization decreases the risk of stroke.

2005 witnessed the approval of the Food and Drug Administration (FDA) of devices for carotid stenting and a clot retriever. This occurred despite lack of evidence of clinical efficacy for any of the devices. This highlights a double standard by the FDA when it comes to drugs and devices: perhaps too prohibitive for drugs and too permissive for devices. The issues are never simple and have been debated in the pages of Stroke. Although different criteria may apply to different therapeutic modalities, there can only be one standard of proof.

The time window of 3 hours dictates tissue plasminogen activator (tPA) administration in acute stroke. Efforts continue to replace it with a tissue window, based on imaging. The dose finding phase II Desmoteplase In Acute Ischemic Stroke (DIAS) trial used MRI-based criteria for patient selection. It found that desmoteplase dose had to be adjusted to body weight to decrease the likelihood of intracerebral hemorrhage. Increased reperfusion rates correlated with clinical outcomes. A phase III trial has begun.
The oral thrombin inhibitor Ximelagatran proved equal to warfarin in preventing stroke and systemic emboli with patients with atrial fibrillation. The combined major and minor bleeding complication record favored Ximelagatran. However, 6% of patients taking the drug had elevated serum transaminase enzymes and an increased rate of coronary events. The FDA denied approval.

The Abestt II trial of the GpIIb/IIIb/Ila antagonist Abciximab in acute ischemic stroke patients was halted after 808 patients had been enrolled, presumably for safety reasons. This calls into question other ongoing trials with the drug.

Thrombin is playing an increasingly important role in the development of edema after intracerebral hemorrhage. Perihematoma edema begins in the first 3 hours after an intracerebral hemorrhage and continues for at least 72 hours. First, the clot retracts and serum extrudes. Then, for the first 2 days thrombin forms, followed after 3 days by red blood lysis with hemoglobin-induced neuronal damage. Thrombin induces inflammation, cytotoxicity and disruption of the blood-brain barrier, whereas thrombin inhibitors reduce edema.

The STICH (International Trial in Intracerebral Hemorrhage) trial failed to show a beneficial effect for surgical intervention, but the nature of the research design leaves the door open to continue to operate on patients with subcortical or cerebellar hematoma at least 3 cm in diameter and impaired consciousness. Although the benefits of operating on putaminal intracerebral hemorraghes in stuporous patients remains uncertain, comatose patients with basal ganglia or thalamic hemorrhages are unlikely to benefit from surgery.

Although yet unproven, recombinant factor VIIa treatment resulted in decreased hematoma size and improved mortality and clinical outcomes in a phase IIb study. A phase III rFIIa Acute Hemorrhage Stroke Treatment interventional trial is underway.

Unlike other types of stroke, subarachnoid hemorrhage shows little geographic variation and no signs of decline. Inflicting death or dependence on two thirds of its patients, it remains a daunting challenge to diagnose and treat. About 12% of patients are still misdiagnosed initially. All patients with a thunderclap headache deserve an emergency CT scan without contrast and a lumbar puncture if normal.

A recent trial of the antifibrinolytic agent tranexamic acid showed a reduction of aneurysm rebleeding from 11% to 2.4%. A follow-up of the Interventional Subarachnoid Hemorrhage Trial (ISAT) showed that coiling yielded an absolute reduction of aneurysm rebleeding from 11% to 2.4%.

The Honolulu-Asia Aging Study showed that the presence of cerebrovascular lesions more than doubled dementia frequency in men with sparse neuritic plaques.

It has been known for some time that the same risk factors that predispose to stroke represent risk factors for “Alzheimer disease”. The whole field has been confounded by obsolete exclusionary definitions and criteria, largely untranslatable from one study to the other. A step forward was taken in April by an international group of investigators that came up with recommendations and minimal data sets for the use of clinicians and a minimal data set for the use of investigators with the aim of developing a common vocabulary of understanding. The recommendations will be published in 2006, in Stroke.

Because three fourths of strokes are first-ever strokes, primary prevention may accomplish more than everything that we do after a transient ischemic attack or a stroke. We need to practice secondary prevention in our patients and recommend primary prevention to their families. Lowering systolic blood pressure by 10 mm Hg reduces the risk of stroke by one third, regardless of the baseline blood pressure.

In 714 patients with atrial fibrillation followed for a median of 2.7 years, a combination of the anticoagulant acenocumarol and trifusal (an antiplatelet agent) was associated with a stroke or systemic embolism rate of 0.92%. This compared to 3.8% in the trifusal arm and 2.7% in the anticoagulant arm. The primary outcome plus severe bleeding was seen in 1.48% of cases for the combined therapy, 3.78% with anticoagulation and 3.82% with antiplatelet therapy. These findings are worthy of further exploration given the risks of combined warfarin plus aspirin therapy.

The Women’s Health Study has shown that 100 mg of aspirin every other day in women ≥45 years for 10 years reduces stroke by 17% (RR=0.83, 95% CI, 0.69% to 0.99%; P=0.04) and ischemic stroke by 24%. This was associated with an increased risk of gastrointestinal hemorrhage requiring transfusion (RR=1.40, 95% CI, 1.07% to 1.83%; P=0.02).

The answer to an important question, whether positive or negative, is by definition, important. The Warfarin-Aspirin Symptomatic Intracranial Disease (WASID) Trial provides a significant answer. Intracranial stenosis may be the most important cause of stroke worldwide. Warfarin proved no better than aspirin and was associated with higher rates of adverse events. These results encourage alternate approaches.

It is gratifying to see so many advances and humbling to realize how much more needs to be done. As judged by the annual reviews in Stroke, we are on the right track.
Introduction
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