The possible value of fibrin-selective thrombolytic agents in acute stroke is the subject of significant current interest. In addition to their use in acute thrombotic and thromboembolic stroke, plasminogen activators have been used to achieve vascular recanalization in selected patients with superior sagittal sinus thrombosis and acute retinal vascular thrombosis.

Thrombus Formation

Arterial thrombosis and thrombus extension involve the overlapping systems of endothelial cell reactivity, platelet function, and coagulation. Thrombotic cerebrovascular occlusions arise secondary to thromboembolism from more proximal sites, e.g., the heart and proximal internal carotid artery, or from in situ thrombosis.

Thrombolysis and Cerebrovascular Ischemia

Thrombus Dissolution

Agents with thrombolytic activity are classified as endogenous or exogenous in origin. Thrombus dissolution results from the local generation and release of plasmin by endogenous fibrin-bound plasminogen activator (t-PA) and by single-chain urokinase plasminogen activator (scu-PA), where it is protected from the circulating inhibitors α2-antiplasmin and α2-macroglobulin. In contrast to the exogenous fibrin(ogen)olytic agents (see below), t-PA and scu-PA do not cause inactivation of factors V and VIII so that an anticoagulant state is generally not achieved.

The combination of thrombus-associated fibrinolysis and other forces in the microenvironment of the thrombus produce fragmentation and downstream embolism. Once a thromboembolism has lodged, the processes of thrombus growth and dissolution continue at the new site. These are of particular relevance to brain infarction since distal thromboembolic occlusion may account for symptom progression and may reflect spontaneous clot lysis and recanalization.

Vascular Recanalization

Endogenous (t-PA– and possibly scu-PA–mediated) fibrinolysis underlies spontaneous vascular recanalization. Both recombinant DNA-generated t-PA (rt-PA) and scu-PA have been used to achieve lysis of thrombi in arterial and venous disease by intravenous infusion. Pharmacological levels of rt-PA have been associated with dose-dependent hypofibrinogenemia. Clinical experience with scu-PA is quite limited.

Exogenous agents have been employed to achieve thrombus lysis in short-term, high-dose, direct intra-
arterial infusion and in long-term intravenous infusion regimens. Significant improvements in function have accompanied recanalization in acute coronary artery thrombosis, pulmonary embolism with hemodynamic compromise, and selective peripheral arterial occlusions. Hypofibrinogenemia and plasminogen depletion are common features of systemic fibrinogenolysis resulting from the use of exogenous agents.

Cerebral Ischemia

The molecular mechanisms of cerebral ischemic injury are complex and poorly understood. The contributions of cerebral vascular anatomy, focal versus global ischemia, and collateral flow are relevant to thrombolytic intervention in acute cerebral ischemia. Information about the importance of thrombus location and clinical outcome in untreated and treated acute carotid and acute vertebrobasilar territory stroke is being accumulated. Focal rather than global ischemia would seem a more appropriate setting for establishing arterial reflow because of the potential for salvage of perifocal ischemic tissue ("ischemic penumbra") following cerebral arterial occlusion. Salvage of tissue in the ischemic penumbra depends in part on nutrient support from collateral arterial channels recruited acutely or established during chronic arterial insufficiency. Functional end-arteriolar ischemia and thrombosis, e.g., lenticulostriate arterial thrombosis secondary to M1 middle cerebral artery occlusions, would seem less likely to undergo recanalization ("no-flow" phenomenon) than large-artery occlusions with adequate collaterals or distal runoff.

Consequences of Reperfusion

Arterial recanalization by thrombolytic agents in a region of cerebrovascular ischemia is accompanied by a risk of reperfusion injury and hemorrhagic transformation.

Recent investigation of the phenomenon of reperfusion injury suggests that the region of potential tissue salvage may be reduced by the generation of oxygen free radicals in the ischemic zone following reperfusion. The significance of this phenomenon and the effect of free radical quenching agents on the extent of cerebral tissue injury are under rigorous study in model systems.

The risk of hemorrhage is characteristic of all thrombolytic agents. In the central nervous system, parenchymal hemorrhage probably occurs secondarily to lysis of fibrin-stabilized hemostatic plugs and exposure of damaged vessels to increased perfusion pressure. It has been suggested that in cerebrovascular ischemia there may be little advantage to the use of fibrin-selective agents over fibrinogenolytic agents if thrombus lysis is achieved. The risk and severity of hemorrhage is undoubtedly increased by systemic fibrinogen depletion and the anticoagulant effect characteristic of exogenous agents. The comitment use of agents with antiplatelet (acetylsalicylic acid, hemodialutional agents) or anticoagulant properties (heparin) may contribute to the hemorrhagic risk.

Of relevance in acute stroke is the distinction between hemorrhagic transformation of an ischemic infarcted zone without clinical change and intracerebral hemorrhage with clinical deterioration. The spontaneous hemorrhagic conversion rate in cerebral infarction has been reported to be between 0% and 43% and is related to variables such as infarct size and mechanism (embolic versus thrombotic). Fibrinogenolytic agents have been associated with a 0–1.3% risk of intracerebral hemorrhage in patients without known cerebrovascular disease. The risk of hemorrhage in carotid and vertebrobasilar territory ischemia following thrombolytic agents remains unknown. Even though hemorrhage into a nonreversible ischemic zone may have little clinical significance, measures to minimize the incidence of intracerebral hemorrhage with clinical deterioration must be an integral part of clinical studies with fibrinolytic agents.

Timing of Reperfusion

While models of global or hemispheric ischemia indicate that irreversible neuronal death occurs within 6–8 minutes, functional recovery may follow even 3–6 hours of focal ischemia. The maximum interval from symptom onset to successful vascular recanalization with significant tissue recovery is unknown. Coronary artery recanalization after 4 hours of ischemic symptoms is not associated with significant myocardial functional recovery.

Thrombolytic Therapy in Stroke

Various animal model systems have been used to demonstrate dissolution of cerebral arterial thrombi and thromboemboli following immediate intravenous or intra-arterial infusion of exogenous thrombolytic agents, while improved survival after immediate rt-PA infusion has been reported. Functional improvement and apparent reduction in infarct size accompanied delayed local intra-arterial infusion of urokinase in a primate model. Several reports suggest that at low doses of rt-PA, the incidence of infarction-related hemorrhage is not significantly different from control. However, species variability with regard to dose rate and plasminogen activation must be taken into account in assessing the above reports.

Intravenous Infusion: Completed Stroke

Eight clinical trials evaluating the effect of late intravenous infusion of thrombolytic agents in patients with completed stroke have been reported (Table 1). In an early study by Herndon and colleagues, clinical improvement occurred in 22 of 45 patients, while hemorrhagic complications (all extracerebral) occurred in 13. Meyer et al demonstrated angiographically that thrombi were dissolved more frequently in the group receiving intra-
venous streptokinase, but there was no clinical improvement over the control group. Fletcher et al observed no benefit in 31 patients with completed stroke receiving urokinase, and intracerebral hemorrhage occurred in seven patients. This observation supported a general contraindication to the use of fibrinolytic agents in stroke patients.26

**Intra-arterial Infusion: Acute Stroke**

Recanalization has accompanied local intra-arterial infusion of streptokinase or urokinase in patients with angiographically demonstrable acute arterial thrombotic occlusions in the carotid and vertebrobasilar territories (Table 2).47-55 Case reports and limited series have suggested neurological recovery following lysis in middle cerebral artery territory thrombotic occlusions47-48 and documented vertebrobasilar artery occlusions.49

Two prospective studies have used intra-arterial exogenous agents in consecutive acute stroke patients. Twenty patients with angiographically defined carotid territory occlusions were treated by intra-arterial local infusion of streptokinase/urokinase within 6 hours of symptom onset in a pilot study.50-52 Complete recanalization was achieved in 15 patients, of whom 10 displayed partial or complete symptom resolution. No improvement was observed in the absence of reperfusion. Hemorrhagic transformation was witnessed by serial cerebral computed tomograms (CT scans) in four patients (20%) although none deteriorated clinically. Resolution of the hemorrhage occurred in all patients, and two patients improved clinically. All hemorrhagic infarctions were confined to the ipsilateral subcortical white matter.

Zeumer and colleagues53-54 have demonstrated recanalization in 19 of 43 (44.2%) consecutive patients with acute thrombotic occlusions in the vertebrobasilar artery territory by local intra-arterial streptokinase/urokinase within hours of symptom onset. A significant improvement in survival and favorable clinical status were apparent in patients undergoing recanalization compared with those not displaying recanalization or those in a group not receiving fibrinolytic agents. Hemorrhagic transformation occurred in four patients (9.3%) receiving fibrinolytic agents, two undergoing recanalization and two not displaying recanalization.53-54-56 Two patients died secondary to fibrinolysis-related hemorrhage.

The incidence of hemorrhage in the above pilot studies falls within the broad expected range published. Without exception, all patients who hemorrhaged received a hemodilutional agent and heparin in the postfibrinolytic period.

**Present Studies: Intravenous Infusion of rt-PA**

The fibrin-selective character of rt-PA, its efficacy in coronary artery recanalization in acute myocardial infarction, and the suggestion that early intervention may contribute to functional recovery have

### Table 1. Intravenous Fibrinolytic Therapy in Stroke Patients

<table>
<thead>
<tr>
<th>Study</th>
<th>Agent</th>
<th>Patients</th>
<th>Improved</th>
<th>Hemorrhage</th>
<th>Deaths</th>
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<tr>
<td>Clarke and Clifton40</td>
<td>F</td>
<td>7</td>
<td>5</td>
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<td>Herndon et al41</td>
<td>F</td>
<td>29</td>
<td>15</td>
<td>6</td>
<td>11</td>
</tr>
<tr>
<td>Meyer et al33</td>
<td>P</td>
<td>16</td>
<td>7</td>
<td>7</td>
<td>5</td>
</tr>
<tr>
<td>Meyer et al42</td>
<td>S</td>
<td>37</td>
<td>16</td>
<td>4</td>
<td>13</td>
</tr>
<tr>
<td>Fletcher et al43</td>
<td>C</td>
<td>36</td>
<td>21</td>
<td>0</td>
<td>4</td>
</tr>
<tr>
<td>Matsuo et al44</td>
<td>U</td>
<td>31</td>
<td>0</td>
<td>7</td>
<td>5</td>
</tr>
<tr>
<td>Abe et al45</td>
<td>U</td>
<td>49</td>
<td>39</td>
<td>1</td>
<td>2</td>
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<td>Abe et al46</td>
<td>U</td>
<td>57</td>
<td>48</td>
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<td></td>
<td>—</td>
<td>58</td>
<td>48</td>
<td>0</td>
<td>0</td>
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</tbody>
</table>

F, fibrinolysin; P, plasmin/plasminogen; S, streptokinase; U, urokinase; C, control.

### Table 2. Local Intra-arterial Thrombolytic Therapy in Acute Stroke

<table>
<thead>
<tr>
<th>Territory</th>
<th>Patients</th>
<th>Recanalization</th>
<th>Recovery</th>
<th>Hemorrhage</th>
<th>Deaths</th>
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<td>Carotid territory</td>
<td></td>
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<td>Miyakawa48</td>
<td>2</td>
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<td>0</td>
<td>0</td>
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<tr>
<td>Zeumer, Del Zoppo1255</td>
<td>20</td>
<td>18</td>
<td>12</td>
<td>4</td>
<td>3</td>
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<td>Vertebrobasilar territory</td>
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<td></td>
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<tr>
<td>Nenci et al49</td>
<td>4</td>
<td>4</td>
<td>3</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Zeumer, Hacke156</td>
<td>43</td>
<td>19</td>
<td>8 (6*)</td>
<td>2 (21)</td>
<td>29</td>
</tr>
</tbody>
</table>

*Partial recovery.
†Contributed to patient demise.
Concerns About Thrombolysis in Acute Stroke

A separate National Institutes of Health-sponsored contract study in progress examines the incidence of hemorrhage following rt-PA administered at several dose levels within 90 minutes of symptom onset. All patients are screened by CT scan to rule out intracerebral hemorrhage as a cause of the neurological deficits. Two additional studies, in the Netherlands and in Scandinavia, have been undertaken, the results of which are not yet available.

scu-PA has been used in limited preclinical studies in animal models and has been discussed as an alternative to rt-PA in acute stroke.

No data are available on intracerebral hemorrhagic risk versus dose rate of rt-PA, but these will be obtained from the preliminary studies. The concomitant use of anticoagulants may increase such risk.57,58

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