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Local Intraarterial Fibrinolysis in the Carotid Territory

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A series comprising 12 patients who had intraarterial local fibrinolysis in the carotid territory is reported. A classification is proposed that divides the different types of occlusions into three groups on the basis of angiographic location. Group 1 (two cases) comprises occlusion of the extra- and/or intracranial carotid artery with patency of the circle of Willis and the lenticulostriate arteries. In this group, there is no brain infarction, the CT findings are normal, and the clinical signs are mainly hemodynamic and intermittent. Fibrinolysis may be performed late and rather safely and completed by surgery or angioplasty of the neck vessel stenosis responsible for the occlusion. Group 2 (five cases) comprises occlusions of the cortical arteries without involvement of the lenticulostriate arteries. The mechanism of the occlusion can be hemodynamic or embolic. Group 3 (five cases) comprises occlusions of intracerebral arteries involving the lenticulostriate arteries. In groups 2 and 3 with brain infarction, fibrinolysis will only be able to restore viability of the area of cerebral tissue surrounding the infarction (penumbra). The time factor is particularly critical in group 3 because lenticulostriate arteries are terminal vessels whose revascularization may induce hemorrhages with increasing frequency as the occlusion time is prolonged. The time factor is less critical in group 2 because collaterals make the ischemia less severe in the infarcted area and the vital and functional consequences of hemorrhage are not as serious as in group 3 because of the location. In this series, all the symptomatic complications of hemorrhage (two cases) occurred in group 3, in patients treated later than 6 hr after clinical onset. Given the time delay inherent in performing CT and angiography and in making the medical decision, it is considered dangerous to undertake fibrinolytic therapy in group 3, unless it can be started before 4 or 5 hr after clinical onset.

Cerebral vascular disease is the third leading cause of death in the United States [1] and the leading neuropathologic cause of death [2–4]. Survivors with major sequelae constitute a considerable burden for their families and society [5]. Most strokes are located in the carotid territory and are related to either cerebral hemorrhage or, more often, cerebral infarction. The latter may be embolic (coagulated blood and/or atherosclerotic) or hemodynamic, and is due to reduction in cerebral blood flow distal to an arterial occlusion, in most cases involving a neck vessel. Cerebral angiography has demonstrated occlusive lesions whose locations have correlated with clinical signs in more than 90% of cases when the angiography was performed within the first 12 hr after the onset of symptoms [6, 7]. The techniques of cerebral revascularization may be surgical (endarterectomy, embolectomy) or endovascular (angioplasty, fibrinolysis). By reducing the duration of ischemia, they aim to ameliorate the functional recovery of a maximum of cerebral tissue.

Pilot work done by Fletcher et al. [8] on systemic injection of urokinase has been disappointing, owing to the frequent hemorrhagic complications that occurred (25%). More recently, local intraarterial therapy has been more encouraging [9–14]: the published reports and unpublished experience collected by Del Zoppo et al. [13] in 1986 suggest an incidence of postperfusion hemorrhage of 13%. The

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hemorrhagic risk and the persisting confusion about how to select the patients currently limit the widespread use of the local intraarterial approach.

We report 12 new patients who had local intraarterial fibrinolysis in the carotid territory and try to clarify when this therapy can be beneficial or hazardous, depending mainly on the site of the arterial occlusion, its extent, and the delay between clinical onset and therapy.

Materials and Methods

Twelve patients with vascular occlusive lesions in the carotid territory were treated by local intraarterial fibrinolysis. There were six men and six women with a mean age of 56 years (range, 32–83 years) (Table 1). In all cases, CT and cerebral angiography via a femoral approach were performed before treatment. Two patients had had recurrent unilateral neurologic symptoms for 3 weeks (case 1) and 5 days (case 2) with normal CT. One patient (case 3) was treated 30 min after hemiplegia, which occurred during an angiogram obtained to investigate transient lateral hemianopsia of 48 hr duration. The other nine patients were treated 2–10 hr after clinical onset. The decision to treat the patient usually was made when (1) no hemorrhage was seen on CT, (2) angiography could be performed immediately after CT and showed an occlusive lesion, and (3) the radiologist and referring physician were both convinced that revascularization could be beneficial to the patient.

The fibrinolytic drug was delivered into the internal carotid or middle cerebral artery. A propulsion chamber* or Tracker catheter† was used for catheterization of the middle cerebral artery. Injection in the internal carotid alone was performed in four cases (cases 1–3 and 10), in the middle cerebral artery alone in four cases (cases 4, 5, 9, and 11), and in both arteries in four cases (cases 6–8 and 12). To standardize the results, it was decided to use only streptokinase in 11 patients in this series. In one patient (case 3), after it was decided to use fibrinolysis because of a complication during diagnostic angiography, urokinase was used because it was the only drug readily available in the angiographic suite.

Doses of streptokinase ranged from 25,000 to 150,000 units and were given in 25,000-unit boluses. An angiographic series was performed after each injection of 25,000 or 50,000 units. The total dose never exceeded 150,000 units to reduce the risk of systemic hemorrhagic complications. The dose of urokinase in case 3 was 150,000 units, followed by 75,000 units, injected intraoperatively. When the injection was performed in the middle cerebral artery, the dose injected directly was never more than 50,000 units, even when angiography did not show a dramatic modification of the occlusive pattern.

At the end of the procedure, an introducer was left in place, attached to the skin, and continuously flushed to prevent hemorrhagic complications due to decreased fibrinogen levels after fibrinolysis. Usually, another angiogram was obtained the next day, and the introducer was removed after the procedure. Adjunctive carotid endarterectomy was performed in two cases (cases 1 and 3) and carotid angioplasty in one case (case 2).

Results

Restoration of normal neurologic status was obtained in six patients (cases 1–3, 5, 8, and 9). Minor neurologic sequelae persisted in two patients (cases 4 and 7), a complete (case 11) or partial (case 6) hemiplegic deficit in two patients, and partial monoplegia of the upper limb in one patient (case 10). In the two patients (cases 3 and 8) who had complementary surgery, neurologic symptoms cleared before surgery was performed.

No systemic hemorrhagic complications were encountered. Intracranial hemorrhage during fibrinolysis occurred in two patients (cases 11 and 12); in one of these (case 12), the hemorrhage was followed by cerebral edema resulting in death. An asymptomatic limited hemorrhage was demonstrated on CT in one patient (case 9) the day after clinically successful fibrinolysis. More detailed information on the pre- and postfibrinolysis clinical status of the patients is given in Table 1. Figure 1 illustrates the different types of occlusion that occur in the carotid system.

Representative Case Reports

Case 1 (Fig. 1A Type)

A 54-year-old man was referred because of recurrent right brachial monoplegia and speech difficulties. The first episode occurred 3 weeks earlier and cleared in 3 days without residua. Monoplegic episodes recurred with normal intervening neurologic status despite antiplatelet therapy. CT on admission was normal. Cerebral angiography showed complete occlusion of the left internal carotid artery with revascularization of the left hemispheric vessels by the external carotid and vertebral system (Figs. 2A and 2B). Four boluses of 25,000 units of streptokinase were injected into the thrombosed internal carotid artery. Angiography performed between each bolus showed progressive thrombolysis and demonstrated underlying stenosis of the origin of the internal carotid branch responsible for the occlusion. Postfibrinolysis angiography showed complete revascularization of the internal carotid supplying the left hemisphere (Fig. 2C). Thereafter, the neurologic examination and CT findings remained normal. Endarterectomy of the ulcerated stenotic internal carotid was performed 1 week later. The patient has remained asymptomatic.

Case 3 (Fig. 1B Type)

A 74-year-old man was referred after 48 hr of altered mental status associated with transient right lateral hemianopia. CT showed a left parietooccipital hypodensity (Fig. 3A). An angiogram obtained 2 days later showed occlusion of the left internal carotid (Fig. 3B). Intracranial views showed revascularization of the carotid siphon via the ophthalmic artery. The right carotid system revascularized the left anterior and middle cerebral arteries. The middle cerebral artery of the site of origin of the lenticulostriate arteries was patent but the distal cortical branches were poorly demonstrated. During the course of the angiogram, complete right hemiplegia with aphasia occurred. The angiographic catheter was immediately positioned in the stump of the internal carotid and 150,000 units of urokinase were infused over 20 min. The right hemiplegia and aphasia cleared completely during infusion. A postfibrinolysis angiogram showed revascularization of the occluded carotid artery; however, a residual thrombus was present (Fig. 3C). Surgery was performed with endarterectomy of the carotid bifurcation and Fogarty thrombectomy. Progression of this catheter was stopped in the intrapetrous segment of the carotid artery and no reflux was obtained. Then, 75,000 units of urokinase were injected in the carotid artery during the endarterectomy; 25 min later, on release of the clamp, excellent reflux was obtained. Neuro-

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TABLE 1: Summary of Patients with Vascular Occlusive Lesions in the Carotid Territory Treated by Local Intraarterial Fibrinolysis

Group[a]/ Case No.	Age	Delay[b]	Occlusion	Presumed Mechanism	Prefibrinolysis, CT	Neurologic Status Before Fibrinolysis	Fibrinolysis[c]			Postfibrinolysis CT	Follow-up
							Dose[d]	ICA	MCA		
Group 1											
1	54	3 wk	CCA	Hemodynamic	Normal	Recurrent brachial monoplegia; speech difficulties	100,000	+	–	Normal	Adjunctive carotid endarterectomy; normal neurologic status
2	83	5 days	CCA	Hemodynamic	Normal	R hemiparesis; transient recurrent aphasia	150,000	+	–	Normal	Adjunctive carotid angioplasty; normal neurologic status
Group 2, subgroup 1											
3	74	48 hr, 30 min[e]	CCA, LSA, MCA (cortical branches)	Hemodynamic	Parietooccipital hypodensity	R lateral hemianopia; R hemiplegia with aphasia; altered mental status	150,000 + 75,000 intraop	+	–	Hypodensity attenuated 2 wk later[f]; residual hypodensity 3 yr later	Carotid endarterectomy + adjunctive fibrinolysis; complete neurologic recovery
Group 2, subgroup 2											
4	32	4 hr	MCA (cortical branches)	Embolic	Normal	R hemiplegia + Broca aphasia + minor alteration of mental status	25,000	–	+25,000	Small L rolandic and vertex hypodensities	Clearing of aphasia; minor deficit, R hand
5	74	6 hr	MCA (cortical branches)	Embolic	L superficial hypodensity	R hemiparesis + aphasia + minor alteration of mental status	25,000	–	+50,000	Hypodensity attenuated 90 min later; residual hypodensity 1 yr later	Clearing of hemiparesis and aphasia
6	43	6 hr	MCA (cortical branches), ACA	Embolic	L superficial hypodensity	R hemiplegia + aphasia + minor alteration of mental status	125,000	+75,000	+50,000	Hypodensity	Marked reduction of deficit and aphasia
7	42	10 hr	MCA (cortical branches), ACA	Embolic	R superficial hypodensity	L complete hemiplegia; minor alteration of mental status	125,000	+75,000	+50,000	Hypodensity	Minor deficit, L hand
Group 3, subgroup 1											
8	76	2 hr	CCA (mural thrombus), LSA (lateral)	Embolic	Normal	L monoplegia, upper limb	75,000	+25,000	+50,000	Small insular hypodensities	Normal neurologic status; delayed reexploration of carotid bifurcation
9	32	10 hr	LSA (lateral)	Embolic	Deep limited hypodensity	L hemiplegia	50,000	–	+	Small deep asymptomatic hemorrhage	Rapid clearing of all neurologic signs
Group 3, subgroup 2											
10	38	4 hr	LSA, MCA (cortical branches), ACA	Embolic	R faint, diffuse, frontal hypodensity	L hemiplegia; major alteration of mental status	150,000	+	–	R frontal hypodensity	Persistent L partial monoplegia, upper limb
11	73	6 hr	LSA	Embolic	R insular hypodensity	L hemiplegia	50,000	–	+	R insular hemorrhage	L brachial hemiplegia; limited activity without assistance
Group 3, subgroup 3											
12	50	10 hr	CCA, LSA, MCA (cortical branches)	Embolic	R diffuse hemispheric hypodensity	L hemiplegia; minor alteration of mental status	150,000	+100,000	+50,000	R insular hemorrhage; edema	Death

Note.—ICA = internal carotid artery; MCA = middle cerebral artery; CCA = cervical carotid artery; LSA = lenticulostriate arteries; R = right; L = left; intraop = intraoperatively.

[a] Groups and subgroups are defined in the text.

[b] Delay between clinical onset and actual time of injection of fibrinolytic drug.

[c] Complications occurred during fibrinolysis in only two patients: cerebral hemorrhage occurred in cases 11 and 12.

[d] All doses are in units of streptokinase, except in case 3; that patient was given urokinase.

[e] 48 hr after R lateral hemianopia; 30 min after R hemiplegia. (See text.)

[f] See text.

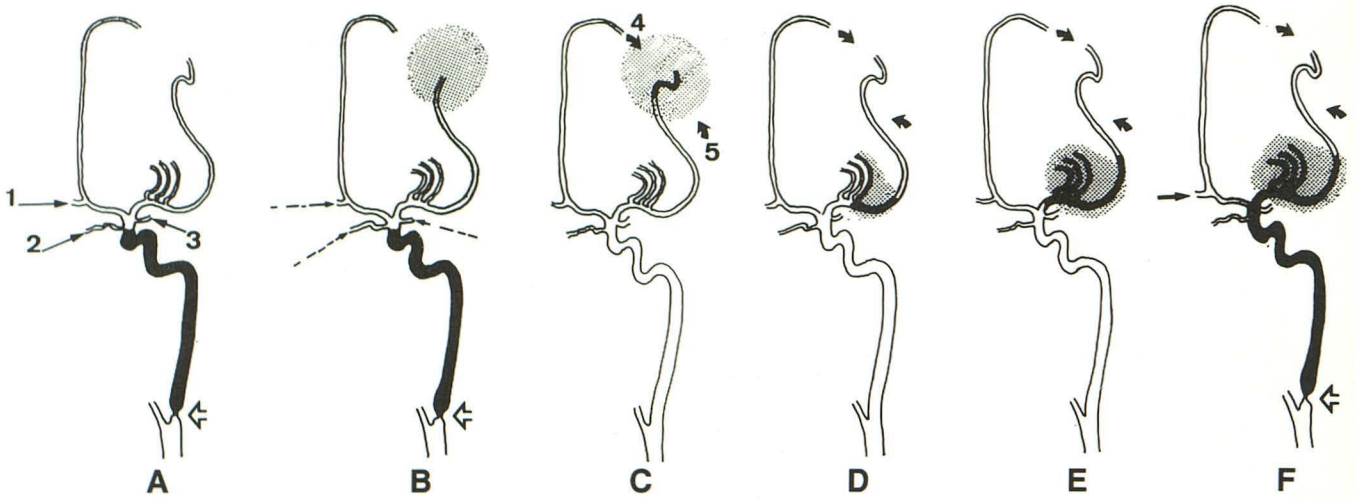

Fig. 1.—Schematic of different types of occlusion in carotid system. Only cerebral infarctions involving middle cerebral artery are represented to simplify classification.

A, Group 1: Occlusion of extra- and/or intracranial internal carotid artery (cases 1 and 2). Occlusion of carotid artery is usually distal and related to stenosis at its origin (*arrow*). Hemispheric vessels are supplied by collaterals—anterior communicating artery (1), ophthalmic artery (2), and posterior communicating artery (3). These collaterals are partially efficient and there is no cerebral infarction. Patients present only with recurrent transient hemodynamic neurologic symptoms.

B, Group 2, subgroup 1: Occlusive lesion identical to that in group 1, except collaterals (*broken arrows*) and other compensatory systems, is insufficient to maintain necessary cerebral blood flow. Cerebral infarction (*stippled area*) usually arises in watershed area (case 3).

C, Group 2, subgroup 2: Embolic occlusions of distal cortical branches without involvement of lenticulostriate arteries. There is a cerebral infarction (*stippled area*) whose extension is limited by collaterals arising from anterior (4) and posterior (5) cerebral arteries (cases 4–7).

D, Group 3, subgroup 1: Occlusion of middle cerebral artery with partial occlusion of lenticulostriate arteries, caused by embolization. Extent of cerebral infarction (*stippled area*) depends on retrograde revascularization of cortical branches of middle cerebral artery via collaterals arising from anterior and posterior cerebral arteries (*arrows*) (cases 8 and 9).

E, Group 3, subgroup 2: Occlusion of middle cerebral artery with involvement of whole lenticulostriate territory. Variable revascularization of branches distal to occlusion by collaterals (*arrows*) changes extent of infarction (*stippled area*) (cases 10 and 11).

F, Group 3, subgroup 3: Same occlusion of middle cerebral artery as in subgroup 2, but located distal to occlusion of extra- and intracranial carotid artery and usually related to stenosis at its origin (*open arrow*). Variable revascularization via circle of Willis (*straight solid arrow*) and cortical collaterals (*curved arrows*) (case 12).

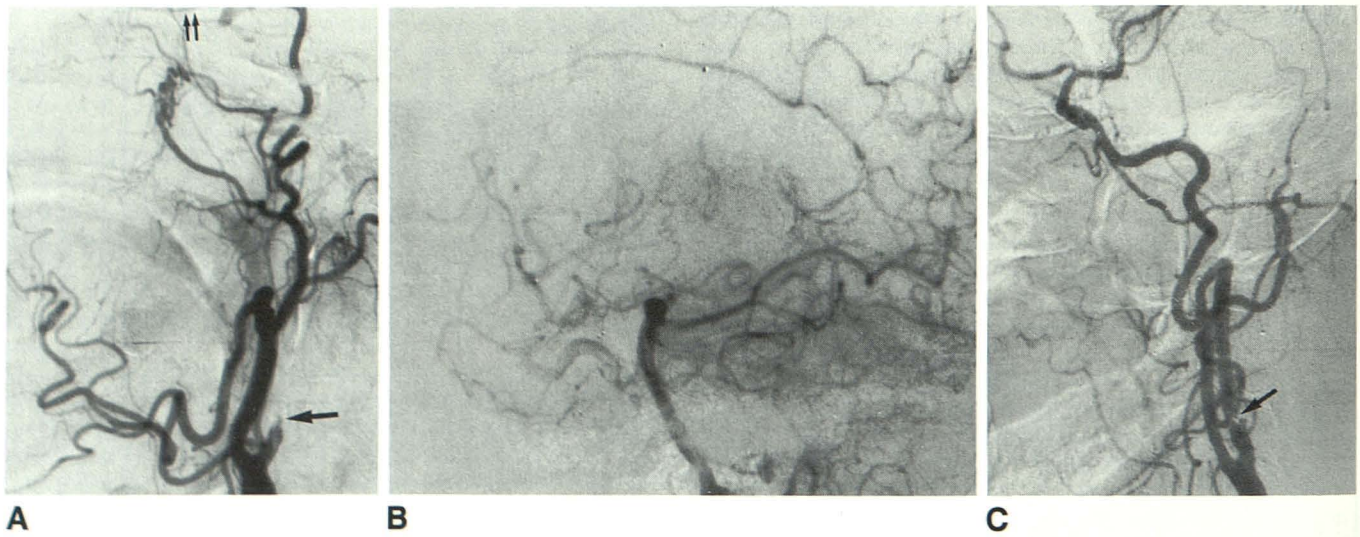

Fig. 2.—Case 1: 54-year-old man with recurrent transient right brachial monoplegia and speech disorder. First episode occurred 3 weeks earlier. Complete neurologic recovery between episodes. CT was normal (see Fig. 1A).

A, Left common carotid angiogram, lateral projection, shows occlusion at origin of internal carotid (*large arrow*). No string sign on late phase. Revascularization of carotid siphon and middle cerebral artery via retrograde filling of ophthalmic artery (*small arrows*) by external carotid.

B, Left vertebral angiogram, lateral projection, shows opacification of middle cerebral artery branches via cortical collaterals. Origins of middle cerebral and lenticulostriate arteries were not occluded. Contralateral carotid system only supplied left anterior cerebral artery.

C, Left common carotid angiogram after fibrinolysis. Complete revascularization of left internal carotid and left hemispheric vessels. The ulcerated stenosis of internal carotid (*arrow*) responsible for occlusion was surgically treated 1 week later. The patient remained asymptomatic; CT findings were normal.

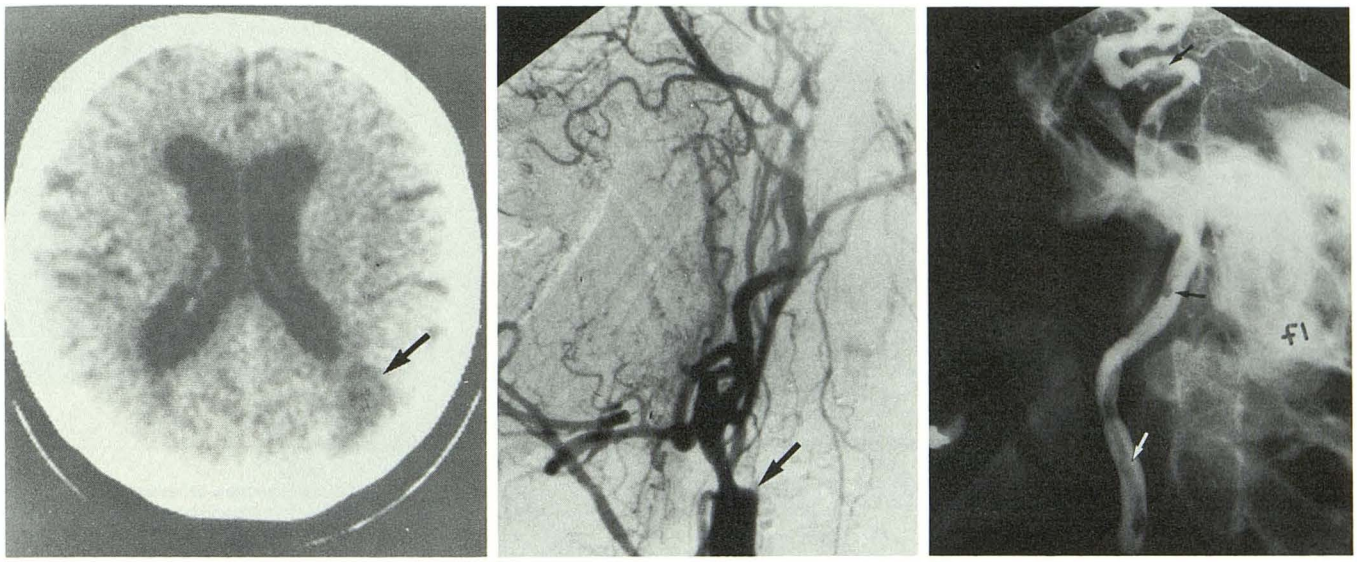

Fig. 3.—Case 3: 74-year-old man referred for altered mental status lasting 48 hr and associated with transient right lateral hemianopia (see Fig. 1B).
***A*, Admission CT scan shows parietooccipital hypodensity (*arrow*).**
***B*, Left common carotid angiogram, lateral projection. Internal carotid artery is occluded (*arrow*). On late phase, partial opacification of carotid siphon is seen without opacification of hemispheric branches. No string sign is present. Contralateral carotid angiogram showed revascularization of left middle cerebral artery, whose distal branches were poorly demonstrated.**
***C*, Complete right hemiplegia with aphasia occurred during angiography. Fibrinolysis of carotid occlusion (150,000 units urokinase) resulted in complete regression of deficit. Angiography shows revascularization of internal carotid with persistent intraluminal thrombus (*arrows*), which led to immediate endarterectomy and intraoperative fibrinolysis.**

logic status was normal over the following days, except for lateral hemianopia, which cleared completely within a few weeks. Postsurgery Doppler confirmed restoration of flow in the internal carotid artery. CT 17 days after surgery showed marked attenuation of the occipital hypodensity. Three years later, CT showed a residual hypodensity. The patient's neurologic status has remained normal.

Case 7 (Fig. 1C Type)

A 42-year-old man was referred because of complete left hemiplegia, which occurred during the course of an angiogram at another hospital. Angiography immediately after the onset of the deficit showed occlusion of one anterior cortical branch of the middle cerebral artery and some embolic material in the carotid siphon. The patient was referred to our institution. Admission CT 9 hr after onset (Fig. 4A) showed a superficial right hemispheric hypodensity. A right carotid angiogram showed multiple embolic occlusions of cortical branches of the middle and anterior cerebral arteries in the arterial phase (Fig. 4B); the lenticulostriate arteries were normal on the anteroposterior projection. In the capillary phase, an extensive avascular area was demonstrated. Fibrinolysis was performed 10 hr after clinical onset by injection of 75,000 units of streptokinase in the internal carotid and 50,000 units directly in the middle cerebral artery after repositioning the catheter. An immediate postfibrinolysis angiogram (Fig. 4C) showed revascularization of the anterior cerebral artery branch and of an anterior cortical branch of the middle cerebral artery, with marked reduction of the avascular area on the capillary phase. The patient improved rapidly in the following hours, with a marked reduction of deficit in the upper extremity. Two days later, he returned to the referring hospital. One year later, neurologic examination showed only a minor deficit in the left hand.

Case 9 (Fig. 1D Type)

A 32-year-old man was referred because of sudden left upper extremity paralysis. Admission CT (9 hr after onset) showed a limited deep right hypodensity (Fig. 5A). A right carotid angiogram showed a normal bifurcation. Intracranially, there was an embolic occlusion of the middle cerebral artery involving the external lenticulostriate arteries (Fig. 5B). During the late phase, the distal cortical branches of the middle cerebral artery were partially opacified retrograde via branches of the anterior cerebral artery. A catheter was positioned in the middle cerebral artery in contact with the occlusion (Fig. 5C). Fibrinolysis was started 10 hr after clinical onset, by delivery of two boluses of 25,000 units of streptokinase. Postfibrinolysis angiography (Fig. 5D) showed revascularization of the main branches of the middle cerebral artery and of all the lenticulostriate arteries, which appeared slightly dilated. The neurologic deficit cleared during angiography. CT the next day (Fig. 5E) showed a small asymptomatic hemorrhage at the site of the hypodensity seen on the admission CT. The patient was still asymptomatic after several months and CT findings were normal.

Case 10 (Fig. 1E Type)

A 38-year-old woman was referred because of sudden loss of consciousness. On admission, she presented with complete left hemiplegia. CT performed 3 hr after onset showed a diffuse, low

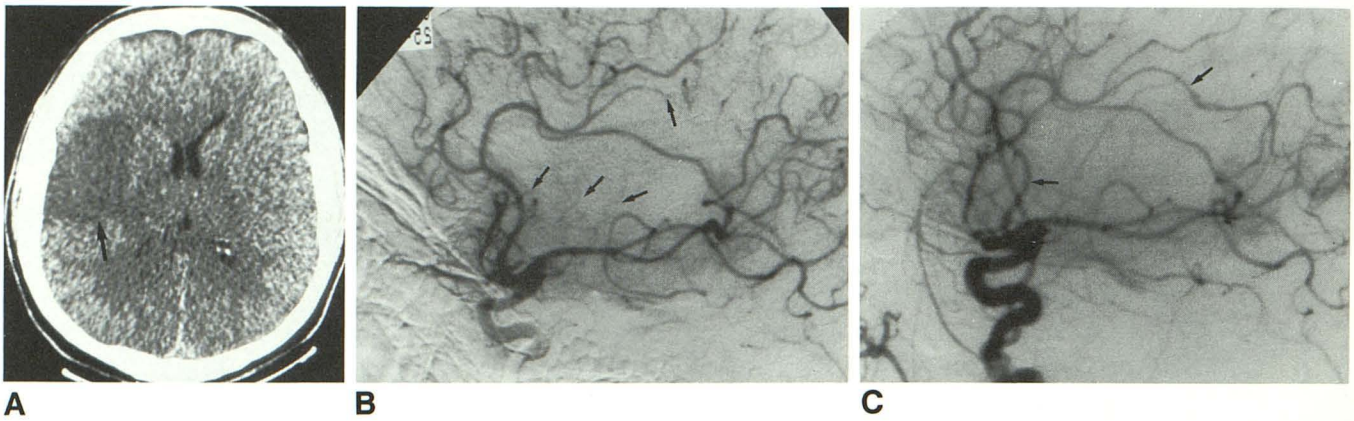

Fig. 4.—Case 7: 42-year-old man. Complete left hemiplegia occurred during course of angiography (see Fig. 1C).
***A*, CT scan 9 hr after onset (transfer of patient from another hospital). Superficial right hemispheric hypodensity (*arrow*).**
***B*, Right internal carotid angiogram, lateral projection, arterial phase, shows multiple embolic occlusions of cortical branches of anterior and middle cerebral arteries (*arrows*). On capillary phase, an extensive avascular area was demonstrated. On anteroposterior projection, lenticulostriate arteries were normal.**
***C*, Angiographic series immediately after fibrinolysis and 10 hr after onset (see text) shows revascularization of occluded branch of anterior cerebral artery and of one branch of middle cerebral artery (*arrows*). On capillary phase, avascular area appeared markedly reduced.**

hypodensity in the right frontorolandic area with attenuation of the cortical sulci (Fig. 6A). Right carotid angiography showed a normal cervical bifurcation and occlusion of the intracranial internal carotid artery, as well as of the origins of the middle and anterior cerebral arteries (Fig. 6B). The right posterior cerebral artery arose from the internal carotid artery and partly revascularized the pericallosal artery. During a later phase, there was retrograde revascularization of the branches of the middle cerebral artery distal to the occlusion, but no filling of the origin of this artery nor of the lenticulostriate arteries (Fig. 6C). No cross-filling was provided by the contralateral carotid system. Fibrinolysis was started 4 hr after the onset of symptoms by injection of six boluses of 25,000 units of streptokinase into the internal carotid artery. Rather rapid revascularization of the middle cerebral and lenticulostriate arteries was obtained. The latter appeared markedly dilated (Fig. 6D) with a hyperemic blush. During the ensuing hours after fibrinolysis, marked improvement was observed in the patient's state of consciousness; however, her motor deficit persisted. CT the day after fibrinolysis showed a right frontal hypodensity with moderate ventricular shift toward the left (Fig. 6E). A carotid angiogram 2 days later showed persistent dilatation of the lenticulostriate arteries, but no more surrounding hyperemic blush (Fig. 6F); the pericallosal artery remained occluded. An angiogram 13 days after fibrinolysis showed a marked decrease in the dilatation of the lenticulostriate arteries and revascularization of the pericallosal artery. The neurologic deficit progressively diminished during the following weeks. CT 18 months later showed a rather limited residual right frontal hypodensity when compared with the initial one. The patient still had partial monoplegia of the upper limb. Motor function of the lower limb was normal.

Case 12 (Fig. 1F Type)

A 50-year-old man was referred for sudden complete left hemiplegia. On admission, 6 hr after onset, he had a mildly altered mental status. Nonenhanced CT showed spontaneous opacification of the first segment of the right middle cerebral artery (Fig. 7A) and diffuse faint hypodensity of the right hemisphere on higher slices (Fig. 7B). The angiogram showed complete occlusion of the right internal carotid at the bifurcation, without revascularization of the carotid siphon via the ophthalmic artery (Fig. 7C). The right intracranial carotid and the anterior cerebral arteries were revascularized via the posterior communicating artery, but there was no revascularization of the middle cerebral artery (Fig. 7D). A catheter was positioned in the thrombus in the internal carotid, and five boluses of 25,000 units of streptokinase were injected. This resulted in revascularization of the cervical carotid and carotid siphon. A catheter was then positioned at the origin of the still-occluded middle cerebral artery. Fibrinolysis was performed with two boluses of 25,000 units of streptokinase. Because of the time required for revascularization of the neck vessel, intracerebral fibrinolysis was not started until 10 hr after clinical onset. Partial revascularization of the lenticulostriate arteries was obtained. These freshly revascularized arteries appeared markedly dilated proximal to the still-occluded middle cerebral artery (Fig. 7E). On the last postfibrinolysis angiographic series, diffuse extravasation of contrast material from the internal lenticulostriate arteries was demonstrated (Fig. 7F). CT confirmed the cerebral hemorrhage (Fig. 7G). Clinically, the patient rapidly deteriorated with significant edema on CT and died the following day.

Discussion

Occlusion of a cervical vessel supplying the brain or an intracerebral artery decreases arterial perfusion distal to the site of occlusion (Fig. 8). This simultaneously activates compensatory mechanisms [15]: (1) collaterals, which revascularize the ischemic cerebral territory distal to the occlusion and sometimes are sufficient to reestablish quasinormal cerebral blood flow, and (2) increased oxygen extraction in the ischemic cerebral territory. The efficacy of these compensatory mechanisms is quite variable from one patient to another and depends on (1) the location of the arterial occlusion; (2) its extent; (3) anatomic variations of the collateral system; and (4) individual reactivity to ischemia, which is itself dependent on the patient's age, his or her pathologic antecedents, and multiple biochemical factors still incompletely understood

[16]. This unpredictable efficacy explains why some intracerebral or cervical arterial occlusions remain asymptomatic while others, apparently less extensive, rapidly assume clinical significance. Compensatory mechanisms may be only partly efficient and the patient may have transient clinical signs (as in group 1). These patients are close to having cerebral infarction. Techniques of revascularization are directed toward preventing cerebral infarction. The battery of therapeutic tools now includes surgery [17, 18], fibrinolysis, and angioplasty [14]. When decreased cerebral blood flow persists or

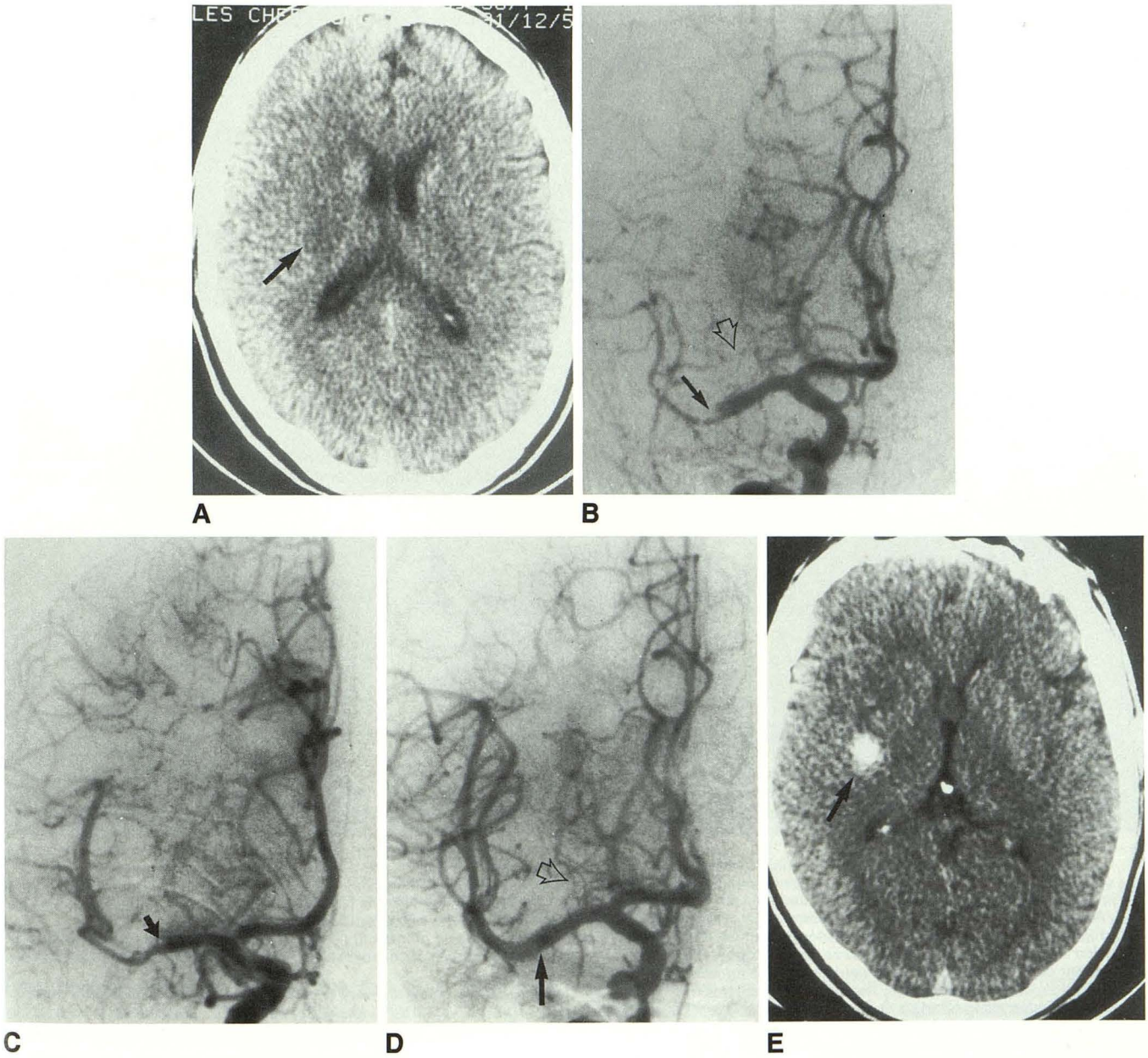

Fig. 5.—Case 9: 32-year-old man with sudden left hemiplegia prevailing in upper limb (see Fig. 1D).

***A*, Admission CT scan (9 hr after onset). Limited hypodensity located deep in right hemisphere (*arrow*).**

***B*, Right internal carotid angiogram, anteroposterior projection, shows embolic occlusion of middle cerebral artery (*solid arrow*). Lateral lenticulostriate arteries are not opacified (*open arrow*). There is faint opacification of some cortical branches distal to occlusion. On late phase, faint retrograde opacification was seen on other cortical branches.**

***C*, Catheter is positioned in middle cerebral artery in contact with occlusion (*arrow*). Fibrinolysis was started 10 hr after onset. Angiographic series during fibrinolysis shows partial thrombolysis and better filling of cortical branches distal to occlusion.**

***D*, Postfibrinolysis series shows complete thrombolysis (*solid arrow*), clearing of deficit on angiographic table, and filling of mildly dilated lenticulostriate arteries (*open arrow*).**

***E*, CT scan the next day shows small hemorrhage at site of initial hypodensity (see *A*). The patient was asymptomatic.**

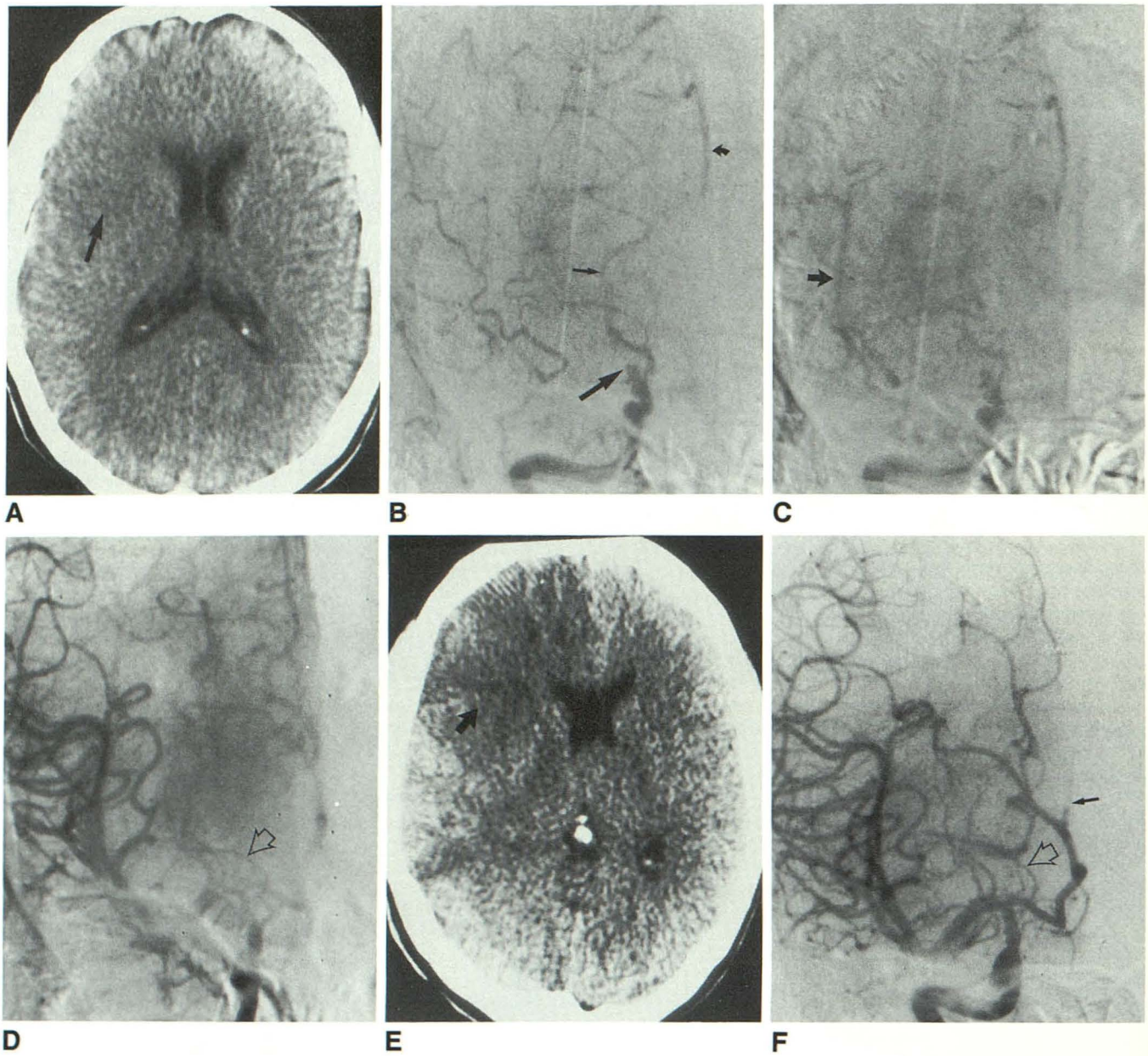

Fig. 6.—Case 10: 38-year-old woman with sudden loss of consciousness and complete left hemiplegia (see Fig. 1E).

***A*, Admission CT scan (3 hr after onset) shows faint, diffuse right frontal hypodensity (*arrow*) with attenuation of cortical sulci.**

***B*, Right carotid angiogram, anteroposterior projection, early arterial phase, shows occlusion of internal carotid at its bifurcation (*large straight arrow*), occlusion of origin of middle and anterior cerebral arteries, and revascularization of distal portion of pericallosal artery (*curved straight arrow*) via branches of posterior cerebral artery (*small straight arrow*) arising from internal carotid.**

***C*, Same angiogram, late phase. Retrograde opacification of cortical branches of middle cerebral artery (*arrow*) from branches of posterior cerebral artery. There is no filling of origin of middle cerebral and lenticulostriate arteries.**

***D*, Angiographic series after fibrinolysis, begun 4 hr after onset, shows revascularization of middle cerebral artery. Lenticulostriate arteries (*arrow*) appear markedly dilated and surrounded by hyperemic blush.**

***E*, CT scan the next day shows right frontal hypodensity with moderate ventricular shift (*arrow*).**

***F*, Carotid angiogram 2 days after fibrinolysis shows persistent occlusion of pericallosal artery (*solid arrow*). Lenticulostriate arteries are still dilated (*open arrow*), but hyperemic blush no longer surrounds them (compare with *D*). Lenticulostriate arteries were no longer dilated on angiogram obtained 13 days after fibrinolysis.**

worsens, the patient will develop a deficit that, initially, is only functional [19]. When it persists for 30 min to 1 hr, a portion of the ischemic territory progresses to infarction, where the neural cells die in a few minutes. This infarcted area extends progressively but remains surrounded by an area of cerebral tissue called the "penumbra" [20, 21], in which the palsy is only functional. After the third hour, only a limited portion of the penumbra persists for an undetermined time. Except in rare cases where revascularization can be obtained in the first hour after clinical onset, all the techniques of revascular-

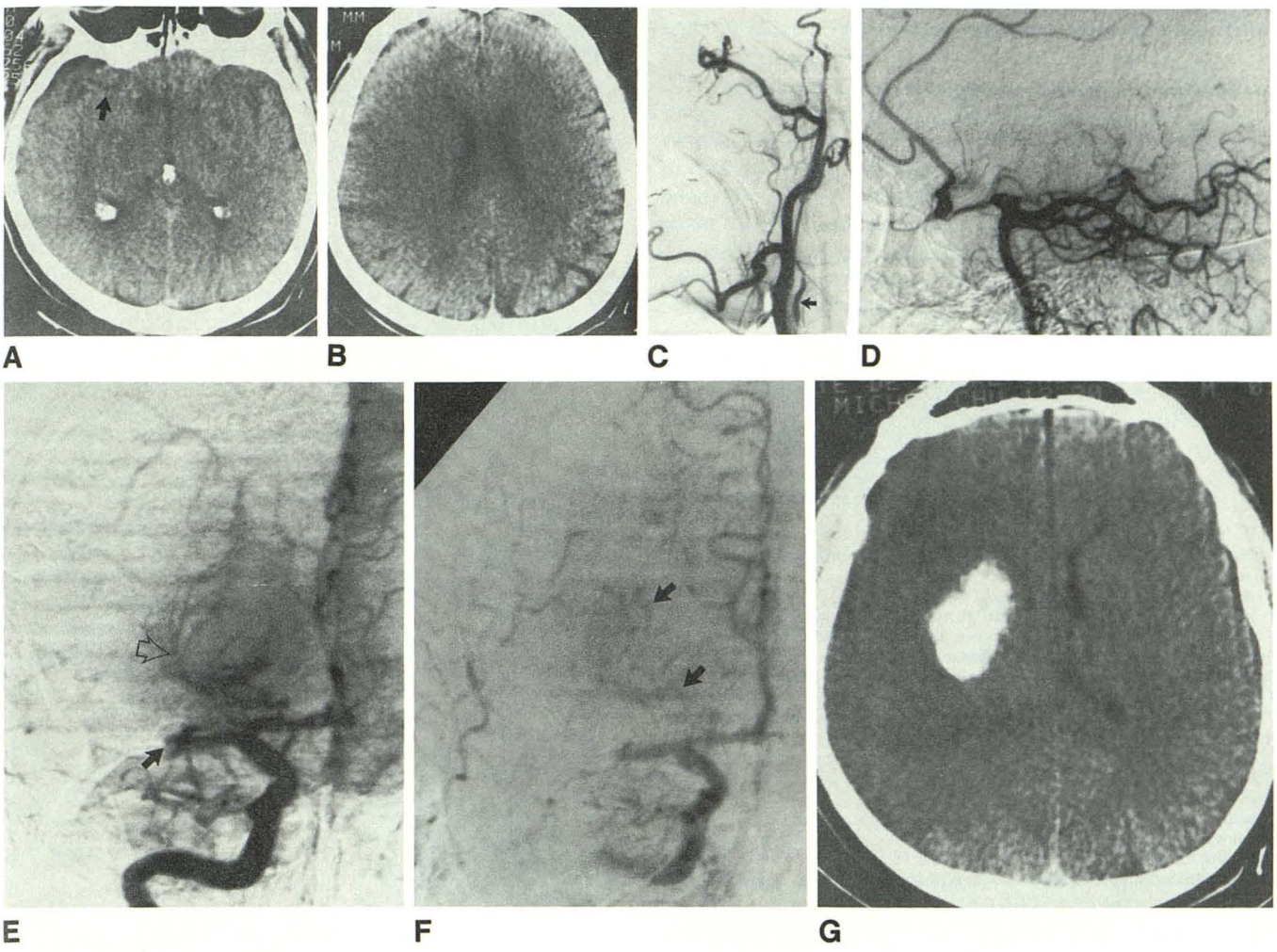

Fig. 7.—Case 12: 50-year-old man with complete left hemiplegia (see Fig. 1F).

***A*, CT scan 6 hr after onset. Opacity within middle cerebral artery (*arrow*) is suggestive of embolus.**

***B*, Higher CT slice. Faint diffuse hypodensity of right hemisphere is seen.**

***C*, Right common carotid angiogram, lateral projection, shows complete occlusion of internal carotid artery (*arrow*). There is no revascularization of siphon via ophthalmic artery. No string sign was seen on late phase.**

***D*, Right vertebral angiogram, lateral projection, shows opacification of supraclinoid internal carotid and anterior cerebral arteries via posterior communicating artery. There is no revascularization of middle cerebral artery. Contralateral carotid does not revascularize this artery.**

***E*, Angiographic series during course of fibrinolysis. Cervical internal carotid has been revascularized. Anteroposterior projection shows middle cerebral artery is still occluded (*solid arrow*). Fibrinolytic drug has reached only intracerebral vessels 10 hr after onset. Freshly revascularized internal lenticulostriate arteries are markedly dilated (*open arrow*) and surrounded by hyperemic blush.**

***F*, Later angiographic series shows extravasation of contrast material all along revascularized lenticulostriate arteries (*arrows*).**

***G*, CT scan 2 hr after fibrinolysis shows deep cerebral hemorrhage and hemispheric edema with ventricular shift. The patient deteriorated clinically and died the next day.**

ization will only be able to regain the viability of this limited portion of brain tissue. They also have a chance of limiting or preventing the risk of occurrence of vasogenic edema, which is responsible for the death of many patients through transtentorial herniation [22–25].

Location and Extent of Arterial Occlusion

In our opinion, angiography is still mandatory when deciding whether to use fibrinolysis. It allows us to schematically distinguish three main groups (Fig. 1).

Group 1: occlusion of the extra- and/or intracranial carotid artery with patency of the circle of Willis and the lenticulostriate arteries.—Clinical signs are mainly hemodynamic, consisting of transient deficits or a fluctuating deficit. There is no cerebral infarction and CT findings are normal. Revascularization of the hemisphere is provided in various proportions by the posterior communicating, anterior communicating, and ophthalmic arteries. However, this supply is insufficient, which explains the transient clinical signs. The angiographic workup of the patient, usually performed between transient ischemic attacks, will show the carotid occlusion (Fig. 2) and reveals the revascularization of the hemisphere distal to the occlusion. Intraarterial fibrinolysis may be used fairly safely in this group. Surgery alone cannot give access to the clot located in the carotid siphon. Carotid endarterectomy (case 1) or angio-

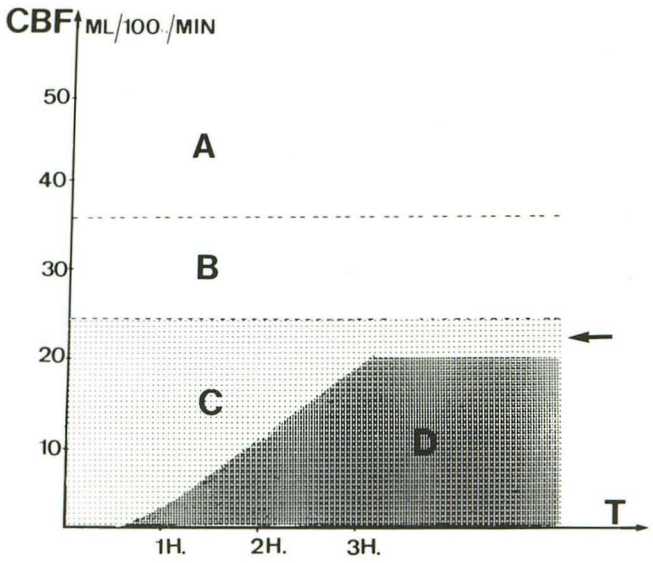

Fig. 8.—Diagram of cerebral blood flow (CBF) in ml/100 g/min vs time (T) in hours (H.).

***Area A* represents normal values.**

In *area B*, despite poor cerebral perfusion, there is still no infarction, thanks to compensatory systems (see text). These patients are at high risk for cerebral infarction and will present with transient recurrent hemodynamic deficits with normal neurologic status between episodes (see Fig. 1A).

In *area C*, cerebral perfusion has decreased even more and there are functional neurologic signs for 30–60 min.

An infarct (*area D*) will then appear and extend progressively; in infarcted area, nerve cells will die in a few minutes. However, after the third hour and for an undetermined time, an area called the penumbra will remain, surrounding the infarction (*arrow*). All revascularization techniques are directed toward reviving this penumbra to reduce the size of infarction and presumably the risk of massive edema.

(Modified from Baron [16] and Jones et al. [19].)

plasty (case 2) of the stenosis, usually responsible for the occlusion, is an efficient adjunct to fibrinolysis to prevent reocclusion.

Group 2: occlusion of the cortical arteries without involvement of the lenticulostriate arteries.—In this group, cerebral infarction does not involve the deep part of the insula. The mechanism may be either hemodynamic (subgroup 1) or, more often, embolic (subgroup 2). Here again, intraarterial fibrinolysis may be used rather safely.

1. Hemodynamic mechanism. When a decrease in cerebral blood flow persists and worsens (Fig. 8), the compensatory systems will not be able to prevent a cerebral infarction distal to the occlusion, usually in the watershed area (Fig. 3). A complete angiographic workup must demonstrate patency of the middle cerebral artery at the site of origin of the lenticulostriate arteries. When patency cannot be demonstrated, particularly after the fourth hour, it is prudent to consider these patients as in group 3, subgroup 3.

2. Embolic mechanism. Cortical arteries are not terminal arteries, and collaterals sometimes are able to prevent development of an infarction. However, when cortical occlusions are multiple, cerebral infarction occurs, particularly when distal occlusions also involve territories other than the middle cerebral artery. It is not unusual for angiography performed immediately after fibrinolysis to show only partial lysis of the emboli (Fig. 4). However, the ischemic area demonstrated on the late phase appears smaller.

Group 3: occlusion of intracerebral arteries involving the lenticulostriate arteries.—This type of occlusion corresponds to that found in case 1 of Zeumer et al. [9] and includes the group most at risk for fibrinolysis. Lenticulostriate arteries are terminal arteries whose walls are fragile because of prolonged ischemia. This carries a high risk of rupture revascularization. Here again, three subgroups can be recognized:

1. Partial embolic occlusion of lateral lenticulostriate arteries (Fig. 1D). Partial occlusion of the lenticulostriate arteries makes this subgroup slightly less vulnerable at revascularization. In the two patients in our series (cases 8 and 9), revascularization was obtained with an excellent clinical result. However, in case 9, treated 10 hr after clinical onset, an asymptomatic small hemorrhage was demonstrated on CT performed the following day (Fig. 5). Conversely, in case 8, treated 2 hr after onset, CT was normal the following day.

2 and 3. Complete occlusion of the lenticulostriate arteries. In subgroup 2 (Fig. 1E), the occlusion is embolic (cases 10 and 11) (Fig. 6). In subgroup 3 (Fig. 1F), there is occlusion of the extra- and intracranial carotid artery distal to a stenosis at the carotid bifurcation (case 12) (Fig. 7). In this case, occlusion of the middle cerebral artery was related to the cervical occlusion or to an embolus detached from it. These two subgroups are the most at risk during fibrinolysis. The two patients in our series who had cerebral hemorrhages during fibrinolysis are included in these subgroups (cases 11 and 12). Only the patient treated 4 hr after clinical onset did not develop cerebral hemorrhage.

Subgroup 3 is particularly at risk because fibrinolysis of the neck occlusion is required before the fibrinolytic agent can reach the lenticulostriate arteries. This delays revascularization and increases hemorrhagic risk (case 12) (Fig. 7). As previously stated, the angiographic workup should be as complete as possible before the decision to use fibrinolysis is made, because unilateral angiography in subgroup 3 can yield findings similar to those in group 2, subgroup 1 (Figs. 1, 3, and 7).

Revascularization of an Occlusive Vascular Cerebral Lesion

Revascularization occurs spontaneously in most cases, and fibrinolysis only accelerates this phenomenon. Revascularization is accompanied by dilatation of the revascularized arteries, as previously demonstrated in monkeys [26] and by nonadaptation of oxygen extraction to the hyperemia. This is known as luxury perfusion [27, 28]. In the best cases, the vascular network distal to the occlusion is reperfused after successful thrombolysis, but there is a possible "no reflow" phenomenon due to irreversible alteration of the vascular contents related to stagnation [29].

Postrevascularization hyperemia.—This is a general phenomenon that occurs after revascularization of an occluded artery anywhere in the human body. It is, in our opinion, a

major risk factor for hemorrhagic complications. Hyperemia seems particularly likely when the initial ischemia has been severe and prolonged, particularly in the lenticulostriate arteries, which are terminal vessels. In our series, this hyperemia was demonstrated with certainty in three cases (cases 10–12) in group 3 (Figs. 6 and 7) in the lenticulostriate arteries or in the perforating arteries proximal to a still-occluded middle cerebral artery.

Time factor.—It has been shown experimentally in the cat [30] that revascularization of a temporarily occluded middle cerebral artery induces hemorrhagic extravasation with increasing frequency as the occlusion time is prolonged. Extravasation starts at the sixth hour and is related to ischemic alteration of the endothelium of the lenticulostriate arteries. The two cases of cerebral hemorrhage in our series occurred at the sixth and 10th hours of occlusion, with significant hyperemia of the lenticulostriate territory proximal to the still partly occluded middle cerebral artery. When ischemia of the lenticulostriate territory was more limited (group 3, subgroup 1) (despite a good clinical result), an asymptomatic small hemorrhage occurred in one patient treated at 10 hr (Fig. 5), whereas CT remained normal in the patient treated at 2 hr.

The time factor, which seems essential when the lenticulostriate arteries are involved (group 3), appears to be less critical in group 2, presumably because the collaterals make the ischemia much less severe. However, the functional prognosis is obviously better if revascularization occurs earlier with more reclaimed penumbra. In this group, hemorrhage may occur, but presumably, its functional and vital consequences would not be as serious as in group 3, because of its location. When there is no cerebral infarction, as in group 1, the time factor is even less critical, and fibrinolysis may be performed late and rather safely.

In basilar artery occlusions, the problem appears to be different despite multiple perforating branches that arise from the artery. Satisfactory results have been reported, with few hemorrhagic complications, even in patients treated long after clinical onset [31, 32]. We presume that the permeability of the circle of Willis limits the ischemia in this type of occlusion.

In conclusion, it seems dangerous to undertake fibrinolytic revascularization after the fourth or fifth hour when the lenticulostriate arteries are involved in the occlusion. The time delay inherent in performing CT and angiography and making the medical decision does not support the use of fibrinolytic therapy in a territory at high risk for hemorrhagic complications, even though late fibrinolysis may yield good results.

Prefibrinolysis Radiologic Workup

Pilot work by Fletcher et al. [8] on systemic injection of a fibrinolytic drug (urokinase) was disappointing and showed no clinical benefit. In this study, seven intracerebral hemorrhages occurred in 31 patients after fibrinolysis. The conclusions of this study may be criticized because (1) CT was not performed before treatment to rule out a cerebral hemorrhage, (2) angiography was not performed before treatment and, (3) most of the patients were treated more than 6 hr after clinical onset.

In most institutions, the radiologic workup of stroke is limited to CT to rule out cerebral hemorrhage and tumor. When these are excluded, the patient is given anticoagulants to limit the extent of occlusion and reduce recurrent thromboembolic events. When the patient is seen very early after onset, CT findings are classically normal, although it is not exceptional for high-definition CT to show a moderate hypodensity due to cytotoxic edema (Figs. 6 and 7). In our opinion, early, extensive edema is related to a poor compensatory collateral system. This carries a bad prognosis and may justify more aggressive treatment, such as fibrinolysis (cases 10 and 12). In patients seen early on after clinical onset, injection of contrast material is unnecessary since there is no contrast enhancement on CT (or MR). In patients seen later, massive contrast enhancement suggests a greater risk of spontaneous hemorrhage [33] and supports the decision not to use a revascularization technique.

Fibrinolytic Therapy

The superiority of local intraarterial vs systemic fibrinolytic therapy is due to its greater efficacy in obtaining thrombolysis with decreased risk of systemic hemorrhagic complications [34]. In this series, streptokinase was used in all but one case by injecting 25,000-unit boluses as close to the clot as possible. When intracerebral arteries were occluded, fibrinolysis was generally performed with an intracerebral catheter. In most cases, complete thrombolysis was not obtained immediately. A maximum dose of 150,000 units was used in this series and treatment did not last more than 60 min. Angiograms obtained during the following days usually showed marked improvement in the number of revascularized intracerebral arteries.

The largest study of local intraarterial fibrinolysis in the carotid territory was reported by Zeumer et al. [9, 10]. Of 13 cases, revascularization occurred in 10, clinical improvements in three, and death in one. In three cases, hemorrhage was demonstrated on CT performed after treatment, without worsening of the clinical state. It should be emphasized that the two cerebral hemorrhages in our series (cases 11 and 12) occurred in perforating arteries arising proximal to a still-occluded middle cerebral artery. These occlusions were presumably at least partially atherosclerotic. In case 12, the lenticulostriate arteries that bled were freshly revascularized. We presume that a major factor in the prevention of these hemorrhagic complications would be strict control of arterial pressure, as already reported for the prevention of hemorrhagic complications after emergency carotid surgery [35].

Urokinase, favored by Zeumer et al., is less antigenic, more readily available, but more expensive than streptokinase. The new fibrinolytic human tissue–type plasminogen activator drug (Actilyse) [36] may provide advantages related to its short half-life (5–8 min) and selectiveness on bound fibrin. In our opinion, this short half-life is a major advantage, particu-

larly in the treatment of group 3 patients, because it lowers the risk of hemorrhage when revascularization is not obtained before the sixth hour. Considering this, urokinase (14 min) should also be preferred, at least in group 3 patients, to streptokinase (16–80 min) because its half-life is shorter.

Hemorrhagic transformation of an embolic intracerebral infarction is rather common and already has been demonstrated on repeat CT examinations. The incidence ranges from 22% [37] to 43% [38] of cases. Considering that most patients are anticoagulated once CT shows no intracerebral blood, we believe that some of the patients are at risk for severe cerebral hemorrhage [39], the frequency of which fortunately is limited by the low doses usually prescribed. Fibrinolytics injected directly into occluded cerebral vessels have mostly local effects. Patient selection based on the location of the occlusion and time of occurrence should yield better results in larger series. In our opinion, it is also not advisable to use anticoagulants that increase the risk of secondary hemorrhagic complications after fibrinolysis, unless a heart condition is responsible for recurrent emboli.

It was reported recently that CT does not provide enough definition to demonstrate the secondary hemorrhage that is seen on MR after hemoglobin is transformed into methemoglobin [40]. This has been found only in deeply located infarctions, which implies revascularization of occluded lenticulostriate arteries supplying this territory. If it is considered dangerous to perform fibrinolysis more than 4 or 5 hr after these arteries are occluded, this MR finding does not preclude early fibrinolytic therapy, but it certainly demonstrates the risk in prescribing anticoagulants. Perhaps high-field MR will allow direct demonstration of intracerebral blood before transformation into methemoglobin and permit new progress in the understanding of this disease [41].

Finally, in two cases (cases 3 and 5), CT after fibrinolysis (17 days in case 3, 90 min in case 5) showed marked attenuation of the initial hypodensity. In both cases, CT several months later again showed a hypodensity. A recent MR study clearly demonstrated that "disappearing infarcts" correspond to the revascularization of an ischemic territory with minor hemorrhage and attenuate the hypodensity on CT [42].

Conclusions

Local intraarterial fibrinolysis appears to be an attractive technique of cerebral revascularization. It should be used more frequently in carotid occlusions with hemodynamic intermittent clinical signs (group 1) and in distal cortical arterial occlusions (group 2). In the second group, immediate complete revascularization is not obtained in most cases, but the drug seems to help delayed dilution of the clot, improve collateral flow, and decrease stagnation distal to the occlusion. At this time, it seems risky to perform fibrinolysis on lenticulostriate arteries occluded for more than 4 or 5 hr (group 3). Rapid transportation of stroke patients is recommended so that CT and complete arteriography may be performed before deciding whether to use fibrinolytics.

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REFERENCES

1. Kurtzke JF. Epidemiology of cerebrovascular disease. In: McDowell FH, Caplan LD, eds. *Cerebrovascular survey report 1985.* Bethesda, MD: National Institutes of Health, **1985:**1–34
2. Adams RD, Vander Eecken HM. Vascular diseases of the brain. *Annu Rev Med* **1953**;4:213–252
3. Kurland LT, Choi NW, Sayre GP. Current status of the epidemiology of cerebro-vascular diseases. In: Fields WS, Spencer WA, eds. *Stroke rehabilitation: basic concepts and research trends.* St. Louis: Green, **1967**: 3–22
4. Silver FL, Norris JW, Lewis AL, et al. Early mortality following stroke: a prospective review. *Stroke* **1984**;15:492–496
5. Ruskin AP. Understanding stroke and its rehabilitation. *Stroke* **1983**;14: 438–442
6. Solis OJ, Roberson GR, Taveras JM, et al. Cerebral angiography in acute cerebral infarction. *Rev Interam Radiol* **1977**;2:19–25
7. Mohr JP, Caplan LR, Melski JW, et al. The Harward Cooperative stroke registry. *Neurology* **1978**;28:754–762
8. Fletcher AP, Alkjaersig N, Lewis M, et al. A pilot study in urokinase therapy in cerebral infarction. *Stroke* **1976**;7:135–142
9. Zeumer H, Hundgen R, Ferberta A, Rigelstein EB. Local intraarterial fibrinolytic therapy in inaccessible internal carotid occlusion. *Neuroradiology* **1984**;26:315–317
10. Zeumer H. Vascular recanalizing techniques in interventional neuroradiology. *J Neurol* **1985**;231:287–294
11. Miyakawa T. The cerebral vessels and thrombosis. *Rinsho Ketsueki* **1984;**25:1018–1026
12. Del Zoppo GJ, Copeland BR, Waltz TA, Zyroff J, Harkler LA. Thrombolytic therapy in a baboon model of acute stroke. *Thromb Haemost* **1985**; 54:221–232
13. Del Zoppo GJ, Zeumer H, Harker LA. Thrombolytic therapy in stroke: possibilities and hazards. *Stroke* **1986**;17:595–607
14. Courtheoux P, Theron J, Derlon JM, Alachkar F, Casasco A. In situ fibrinolysis in supraaortic main vessels. A preliminary study. *J Neuroradiol* **1986**;13:111–124
15. Baron JC, Comard D, Bousser MG, Soussaline F, Castaigne P. Noninvasive tomographic study of cerebral blood flow and oxygene metabolism in vivo. *Eur Neurol* **1981**;20:273–284
16. Baron JC. Phénomènes physiopathologiques au cours de l'ischémie focale aigue du cerveau. *Rev de Médecine* **1983**;38:1853–1863
17. Baron JC, Bousser MG, Rey A, Guillard A, Coma D, Castaigne P. Reversal of focal "misery-perfusion syndrome" by extra-intracranial bypass in hemodynamic cerebral ischemia. *Stroke* **1981**;12:454–459
18. McIntyre KE, Goldstone J. Carotid surgery for crescendo TIA and stroke in evolution. In: Bergan JJ, Yao JST, eds. *Cerebrovascular insufficiency.* New York: Grune & Stratton, **1983:**213–226
19. Jones TH, Morawetz RB, Crowell RM, Marcoux FW. Thresholds of local cerebral ischemia in awake monkeys. *J Neurosurg* **1981**;54:773–782
20. Astrup J, Siesjö BK, Symon L. Thresholds in cerebral ischemia. The ischemic penumbra. *Stroke* **1981**;12:723–725
21. Olsen TS, Larsen B, Herning M, Bech Skriver E, Lassen NA. Blood flow and vascular reactivity in collaterally perfused brain tissue. Evidence of an ischemic penumbra in patients with acute stroke. *Stroke* **1983**;14: 332–341
22. Symon L, Branston NH, Chikovani O. Ischemic brain edema following middle cerebral artery occlusion in baboon: relationship between regional cerebral water content and blood flow at 1 to 2 hours. *Stroke* **1979**;10: 184–191
23. Petito CK. Early and late mechanism of increased vascular permeability following experimental cerebral infarction. *J Neuropathol Exp Neurol* **1979**;38:222–234
24. Ng Lky, Nimmannitya J. Massive cerebral infarction with severe brain

swelling: a clinicopathological study. *Stroke* **1970**;1:158–163
25. Bounds JV, Wieberger DD, Whisnant JP, Okazaki H. Mechanism and timing of deaths from cerebral infarction. *Stroke* **1981**;12:474–477
26. Di Chiro G, Timins EL, Jones AE, Johnston GS, Hammock MK, Swann SJ. Radionuclide scanning and microangiography of evolving and completed brain infarction. A correlative study in monkeys. *Neurology* **1974**;24:418–423
27. Lassen NA. The luxury-perfusion syndrome and its possible relation to acute metabolic acidosis localized within the brain. *Lancet* **1966**;2:1113–1115
28. Siesjo BK. Cell damage in the brain: a speculative synthesis. *J Cereb Blood Flow Metab* **1981**;1:155–185
29. Ames AM, Wright RL, Kowada M, et al. Cerebral ischemia. II. The no-reflow phenomenon. *Am J Pathol* **1968**;52:437–453
30. Kamijyo Y, Garcia JH, Cooper J. Temporary regional cerebral ischemia in the cat. A model of hemorrhagic and subcortical infarction. *J Neuropathol Exp Neurol* **1977**;36:338–350
31. Nenci GG, Gresele P, Taramelli M, Agnelli G, Signorini E. Thrombolytic therapy for thromboembolism of vertebrobasilar artery. *Angiology* **1983**;34:561–571
32. Zeumer H, Hacke W, Ringelstein EB. Local intraarterial thrombolysis in vertebrobasilar thromboembolic disease. *AJNR* **1983**;4:401–404
33. Hayman LA, Evans RA, Bastion FO, Hinck VC. Delayed high dose contrast CT: identifying patients at risk of massive hemorrhagic infarction. *AJR* **1981**;136:1151–1159
34. Dotter CT, Rosch J, Seaman AJ. Selective clot lysis with low dose streptokinase. *Radiology* **1974**;111:31–37
35. Wylie EJ. Discussion of paper by Thompson. *Arch Surg* **1967**;95:791–801
36. Papadopoulos SM, Chandler WF, Salamat M, Topol EJ, Sackellares JC. Recombinant human tissue–type plasminogen activator therapy in acute thromboembolic stroke. *J Neurosurg* **1987**;67:394–398
37. Hakim AM, Ryder-Cooke A, Melanson D. Sequential computerized tomographic appearance of strokes. *Stroke* **1983**;14:6:893–897
38. Hornig CR, Dorndorf W, Agnoli AL. Hemorrhagic cerebral infarction—a prospective study. *Stroke* **1986**;17:179–184
39. Shields RW, Laureno R, Lachman T, Victor M. Anticoagulant related hemorrhage in acute cerebral embolism. *Stroke* **1984**;15:426–437
40. Kricheff II. Arteriosclerotic ischemic cerebrovascular disease. *Radiology* **1987**;162:101–109
41. Gomori J, Grossman RI, Goldberg HI, Zimmerman RA, Bilaniuk LT. Intracranial hematomas: imaging by high field MR. *Radiology* **1985**;157:87–93
42. Deveikis JP, Fox AJ, Pelz DM, Brothers MF, Drake CG. "Disappearing infarcts": signs of apparently reversible ischemic changes on serial CT and MR scans (abstr). *AJNR* **1988**;9:1041–1042