Brain infarction from all causes accounts for about 75–80% of causes of acute stroke. Few patients who reach medical attention with brain infarction are left untreated, a point which makes estimates of "natural history" something of a misnomer. This point aside, many population-based studies have shown the risk of brain infarction rises steeply as the age exceeds 65. Expressed as percentages instead of the usual rate per 100,000 for those below age 50, rates are well below 1%, rising to 1% by age 65 and to 3% by age 80. These rates do not imply the cause, severity or fatality rates of the stroke. For patients with ischemic stroke, systemic risk factors may play a more important effect on mortality risk than does the stroke itself. The importance of systemic risk factors is especially well documented in the case of extracranial carotid vascular disease, where it has proved difficult to predict the type of stroke and its arterial distribution. In many of therapeutic trials involving stroke patients, the beneficial effects on reducing recurrent myocardial infarction and vascular death have overshadowed the modest effects of a given therapy in preventing recurrent stroke.

Only lately has data begun to accumulate on the frequency of brain infarction by inferred mechanism, such as large artery atherostenosis and thrombosis with perfusion failure, embolism from cardiogenic cause, occlusive disease of small, penetrating arteries causing syndromes known as lacunes, and other forms of brain infarction whose cause escapes elucidation. One worrisome finding has been that many cases of brain infarction remain unexplained despite detailed work-up which includes timely CT, angiogram and evaluation of cardiac risk factors. The largest such prospective study, the NINDS Stroke Data Bank, found fully 30% of strokes (40% of infarcts) of unknown cause which has been more recently relabeled as cryptogenic type.

In the acute phase of brain infarction, neurological worsening is a frequent occurrence. A high hematocrit (above 45) has been demonstrated to have a relation to worsening but the therapeutic importance of blood sugar seems to have been somewhat exaggerated. There is no doubt that the formation of intracellular brain lactate during brain ischemia and infarction is an important source of the intracellular acidosis which contributes to cell liquefaction. The therapeutic issue is the level of blood or brain sugar which are sufficient to cause important levels of intracellular lactate formation. Unfortunately, blood sugar levels normal for ambulatory humans seem more than sufficient to create enough intracellular brain lactate to contribute to cell necrosis in brain infarction, which may explain the difficulty showing beneficial effects of attempts at lowering blood sugar levels in treatment for acute brain infarction.

It appears, instead, that this intracellular acidosis will prove all but impossible to prevent or treat. The frequency of worsening is decidedly non-uniform across the various subtypes of stroke, least often encountered in strokes that seem to be of embolic mechanism and most often among those that appear due to thrombosis, whether affecting a large or small artery. This higher frequency of worsening in thrombosis has been thought by some to represent the evolving effects of perfusion failure.

Two types of worsening can be documented in brain infarction. In the first, the clinical syndrome adds new features not initially present, such as aphasia, sensory loss, visual loss, or weakness involving other body parts not initially involved. This clinical change presumably correlates with spreading lesion topography, in, for example, enlarging hemorrhage or possibly in perfusion failure with more widespread ischemia to the brain surface. In the second type of worsening, the syndrome retains its original clinical features but all of the elements worsen to the same degree, with no new parts affected. This form of intensification without change in syndrome is less easily explained, but suggests the conversion of brain...
tissue from ischemia to infarction, a process which could also be due to perfusion failure or due to some predestined effects on tissues already dying. Few studies have been specifically directed toward trying to differentiate the possible separate mechanisms that could account for the different types of worsening, and in few the clinical trials has the data been collected to determine the frequency of which type of worsening occurs.

Recent clinical trials have indicated therapy given early enough may be helpful in mitigating the effects of acute ischemic stroke. In the just-completed Nimodipine trial, beneficial effects were seen for patients treated within 12 hours of the stroke, but none for those delayed beyond that time. The comfortable concept of “completed stroke” is now outmoded, if it is taken to imply that the occurrence of a stroke means the infarct process was over and the risk of recurrence is at a minimum. Major and disabling stroke recurs with a depressingly high frequency, approximating 10% per year in many studies. The patients with major arterial occlusive disease studied during the Extracranial-Intracranial Bypass trial suffered fatal and major strokes at rates of 8% in the first follow-up year alone. Although the annual rate gradually fell, the total reached 16% at the end of five years.

Evidence accumulated within the last few years indicates that stroke recurrence is not determined by the traditionally recognized factors of cardiogenic embolism. In the New York cohort of the Stroke data Bank, other risk factors played as important a role as did cardiogenic cerebral embolism, among them diabetes, prior stroke and stroke with hemispheric infarction. These findings make it clear that all causes of brain infarction are at substantial risk for recurrence, not just those with obvious cardiac risk factors. Stroke recurrence is a serious problem not just over the years but even within the first 30 days. Recurrence rates have been found to average 3% for all types of brain infarction combined. Recurrent stroke usually adds to the neurological deficit and lengthens the hospital stay considerably. Fortunately, recurrence with severe or catastrophic clinical consequences is rather uncommon: only 7 of 578 patients admitted to the Stroke Unit at the NY Neurological Institute with TIA or cerebral infarction over a three year period suffered a catastrophic recurrence. Although this frequency was low, we were bemused to find all of these seven catastrophic events occurred in the setting of heparin withdrawal preparatory to a planned procedure. This suggests a causal relationship between heparin withdrawal and cerebral infarction, a subject which will doubtless receive more investigation.

Embolism

Embolic and perfusion failure are the two major forms of stroke with embolism the most frequent. Although the cardiac source is the most recognized, embolism may also arise from carotid sources and major occlusions may also occur without an identified source. In embolism, the main issues determining the size of the brain infarct are the particle size of the embolus and the availability of collateral for the endangered territory. Particles large enough to cause infarction in major areas of the brain are rather small. None of the middle cerebral artery branches are more than 1.5 mm in size and even the stem of the major cerebral artery is little more than 2–4 mm. Because the particles are arrested at bifurcations, embolic occlusion tends to affect the region of the sylvian fissure. Judging from the clinical effects, this region is necessary for many clinically important brain functions, making most embolic infarcts clinically very obvious. The clinical effects may be less striking if the particle is very small and passes out into the more distal brain convexity branches or affects those few regions of the brain whose injury does not produce weakness.

In non-anesthetized animal models of brain embolism, tissue suddenly deprived of blood flow undergoes prompt acidosis and tissue liquefaction, a process long known as pathoclysis. Events occur rapidly in ischemia: within 15–20 seconds of the fall of rCBF to critical levels, intracellular pH falls, and lactic acid levels rise due to cessation of aerobic metabolism. These changes are reflected in the occurrence of clinical deficits, loss of power in the EEG, and fall in cerebral evoked potentials when of a fall of regional blood flow (rCBF) to 20 ml per 100 gm per min.

Any therapy to prevent this type of disaster must be administered rapidly enough to be ahead of the timetable of infarction, a process measured in minutes or hours at most. Therapeutic benefits are difficult
to bring about because the same occlusion which prevents normal blood flow prevents any blood-borne therapy from reaching the same site. If the occluding particle can be broken up quickly enough, the tissue could be saved or suffer only scattered foci of infarction. There is a high frequency of intracranial occlusive disease found on angiograms done within the first few hours of a brain infarct, but the frequency is much lower if studies are done after the second day. These angiographic findings mean that natural recanalization of intracranial occlusion is a common occurrence, and has been documented as early as minutes after the occlusion. Attempts to speed this process with tPA have met with surface branches but thus far have been disappointing in the major arterial trunks of the circle of Willis and the carotid.

If the process of recanalization fails to develop, the ischemic zone has a chance to receive collateral flow retrograde via the borderzone vessels shared between the major cerebral territories. The extent of this available collateral determines the brain infarct size, which may vary from little or no reduction in predicted size to a minimal infarct, reflecting the effects of centripetal collateral spreading all the way back to the site of arterial occlusion. There is only limited knowledge of the what governs the immediate size of these collaterals and no therapy has yet been developed which is known to dilate them maximally in the acute phase when they are most needed. To be of help in preventing infarction, the collateral must occur promptly. Its late development serves merely to make it easy for macrophages to digest the necrotic tissue. There has been little evidence that embolic infarcts have much of an ischemic penumbra: cell counts in the boundary between the infarcted and healthy tissue show the infarct is remarkably sharply demarcated, indicating that the collateral is either completely adequate or useless.

Hemorrhagic infarction is a common occurrence in brain embolism. Recanalization of the vessel, once thought the mechanism of hemorrhagic infarction, is not required. Retrograde collateral, if complete enough, can cause the same effect. Anticoagulant therapy is not necessary to cause this effect and its use rarely causes hemorrhagic conversion of infarction unless the infarct is already huge.

**Thrombosis with perfusion failure**

This process, while well recognised, is less common than embolism, but should be far more susceptible to the moderating effects of therapy. Perfusion failure occurs most commonly in carotid and basilar disease and in small, deep infarcts known as lacunes. Tissue perfusion pressure falls as stenosis reduces the cross-sectional area of the principal feeding artery. The effects of perfusion failure fall on the most distal territories before those more proximal, an effect analogized to the low pressure at the shower head in the upper stories of a dormitory building during bathing hours. When first espoused nearly 40 years ago the process was compared to an agricultural irrigation system in which the far fields become dry before the fields nearest to the water supply. In the brain, these “far fields” are near the ends of the arterial branches, where they anastomose in the borderzones shared by the major cerebral surface arteries. Predilection of infarcts in these far fields which terminated in borderzones gave rise earlier to the erroneous theories that the infarcts were limited to the borderzones, a process called watershed infarction.

Pathologically, the tissue affected by perfusion failure is often dry in appearance. Histologically, the preservation of the shrunken cell forms have given rise to the term, morphostatic necrobiosis. Typically, small foci of infarction of varying ages are found scattered over the distal territories supplied by the stenotic vessel. The lack of much liquefaction in the infarct often produces a CT scan showing no contrast enhancement. When the cause of perfusion failure is due to carotid or vertebral stenosis, collateral may have time to develop from unaffected vessels via the circle of Willis, and therapeutic agents may be able to reach the ischemic zones anterograde through the still-patent lumen. The infarcts occur high over the brain surface, well above the Sylvian fissure. The clinical syndromes produced are less striking than those in the Sylvian region of the same size. Some of the syndromes produced are rather mild, featuring little more than numbness or weakness of the hand or fingers, while others have disturbed behavior diagnosed a dementia. A few of the distinctive syndromes have been highly correlated with atherosclerotic stroke, especially the pseudo-ulnar and pseudo-median patterns of weakness, and TIAs of the limb-shaking variety.
The clinical syndromes in these cases typically develop more slowly, at times evolving over several days. Such delays make perfusion failure seem susceptible to dramatic rescue by therapy with calcium channel antagonists or immediate endarterectomy. In some instances, greatly reduced brain metabolism has been documented, reversible to normal after bypass or endarterectomy in some\(^3^{30}\). In other studies the degree of extracranial stenosis has been found not to predict the status of brain perfusion\(^3^{39}\).

**TREATMENT**

**Agents that protect brain metabolism**

Calcium antagonists: Uncontrolled calcium entry into ischemic cells is thought to cause potentially viable cells to die. Infarct size has been limited by using nimodipine and nicardipine in a cat models even when treatment was given after experimental middle cerebral artery occlusion. A series of clinical trials with Nimodipine have shown no benefits save in the American trail, where 1040 patients were randomized within 48 hours of stroke onset to placebo, Nimodipine 60 mg, 120 mg or 240 mg daily. Intention-to-treat analysis found a statistically significant benefit for nimodipine at a dose of 60 or 120 mg daily when treatment began within 12 hours, for 120 mg daily when treatment began within 24 hours, and even for 120 mg daily if given within 48 hours if the initial CT scan was negative. The results suggest benefits can be obtained if treatment is given early or if no evidence of brain infarction has (yet) developed. These data suggest a link with the data developed in subarachnoid hemorrhage when Nimodipine was given before the ischemic event.

NMDA antagonists: The concentration of excitatory amino acids increase in ischemia, notably glutamine and gamma-amino-butyric acid concentration and \(\text{n-methy-d-aspartate (NMDA)}\), allowing calcium entry into cells. Agents which block \(\text{n-methy-d-aspartate (NMDA)}\) hold the potential for inhibiting the entry of calcium into cells and could reduce the infarction which would otherwise be expected in certain setting of acute cerebral ischemia. NMDA antagonists occur as mixed excitatory amino acid antagonists, competitive antagonists, and non-competitive antagonists. Among the last type are Phencyclidine (PCP), dextromethorphan and MK-801. Thus far no human testing has been done with NMDA antagonists in acute ischemia although some small trials are being organized. MK-801 has recently been withdrawn from clinical testing.

**Agents that alter coagulation**

Tissue Plasminogen Activator (tPA): In the hopes of creating a more safe means of clot lysis, recent efforts have been undertaken using tissue Plasminogen Activator. Two trials have been underway for the past two years. One, sponsored by Burroughs-Wellcome, has now accumulated over 62 cases and another is sponsored by the NINCDS. The two trials differ somewhat in that the one sponsored by Burroughs-Wellcome requires angiography, intravenous infusion for an hour followed by re-angiogram to determine if the occlusions have disappeared. In that trial sponsored by the NINCDS, so long as the stroke is associated with no hemorrhage on CT scan, the agent can be given intravenously. In both trials there is an emphasis on rapid institution of therapy. Thus far in the Burroughs-Wellcome trial in 93 patients treated, recanalization has occurred in branch occlusions but not reliably in occlusion of larger vessels near the circle of Willis. Safety issues remain, as hemorrhagic infarction is a regular feature of treated cases with recanalization. Studies underway with streptokinase and urokinase in France have suggested a similar outcome may be achieved with these agents.

**Platelet antiagregant therapy**

Aspirin has undergone numerous clinical trials for the prevention of stroke and death after TIA or stroke. The most recent trial, the European Stroke Prevention Study, demonstrated a beneficial effect of aspirin. The ESPS showed roughly the same frequency of endpoints of stroke recurrence or death in the aspirin-treated groups (8-10% annually) as have earlier studies\(^4^{0}\). The differences between doses of ASA in the prevention of stroke seem trivial; the major effects appear to be in the TIA and cardiac events. The scientific basis of the choice of any ASA dose 325 mg was reviewed in the *Antiplatelet Trialist’s Collaboration Report*. They cited three trials (UK-TIA, Cardiff-I, VA) using doses of 300-325 daily and
compared the outcome for major vascular events, including stroke, to the 15 using 900–1500 daily. The
authors concluded "...the studies of 300–325 mg/day appeared to have yielded results that were at least as
good as those yielded by 900–1500 mg/day". This conclusion was also made by the WHO group: "The
optimum dose of aspirin is not known, and conflicting opinion persists. Benefit has been reported with
doses ranging from 1,200 mg/day in several large trials and with a dose of 300 mg in one large trial in which
combined endpoints were analyzed...Patients who cannot tolerate the higher amount of aspirin should be
advised to use less, down to one tablet (300–325 mg) a day".

Ticlopidine is a platelet antiaggregant whose mode of action is not identical to that of aspirin. It
underwent two extensive clinical trials comparing the agent against aspirin and placebo for prevention of
stroke after TIA and minor stroke and against placebo for secondary (recurrence) prevention of ischemic
stroke (Canadian American Ticlopidine Study-CATS). The results of the CATS study showed a reduction
in stroke events compared with placebo using a one-tailed test. Some disadvantages of ticlopidine include
expense, the incidence of side effects including diarrhea and bone marrow suppression, and the increases in
lipid levels of about 10%. The effect of the drug is not revolutionary when compared with that of aspirin.
Most physicians would consider its use in events of aspirin failures or allergy to aspirin, assuming
warfarin did not become more widely used meanwhile. Ticlopidine also increases serum lipids by about
10%, a point which has been brought up repeatedly at recent meetings in criticizing the use of the drug. In a
meeting with the FDA 14-Dec-90, ticlopidine was not given unlimited approval. It was recommended it be
approved for patients allergic to aspirin, those having a TIA or minor (not major stroke) and to be used only
for one year.

Platelet antiaggregants apart from ticlopidine have thus far not shown any benefits in preventing
recurrent ischemic stroke. These include dipyridamole, sulfinpyrazone, and sulodexidyl.

Warfarin
Most studies in secondary stroke prevention were done prior to the widespread use of CT and in the
time when therapeutic prothrombin time values were set at higher levels (with correspondingly higher
complication rates) than are encountered at present. The low recurrence rates in studies of cardiogenic
embolism on warfarin therapy raise the possibility warfarin might reduce recurrence rates further than
does aspirin in other settings. Yet the scanty data do not settle whether the risk reductions differ. Warfarin
use has regularly been debated. In some countries, notably Britain, a clinical trial in the testable setting of
non-valvular atrial fibrillation was deemed impractical because of the claims that there would be few
eligible patients and pre-treatment CT scans would be too costly to justify the study, an opinion which has
not been shared in other countries where trials of therapy for atrial fibrillation are either underway or
recently completed. Warfarin in primary prevention has been study with increasing frequency recently. In
the Danish Study, 1007 patients with atrial fibrillation were entered in a three arm trial comparing
warfarin, aspirin at a dose of 75 mg daily, and placebo. The warfarin arm was open but the other two arms
were blinded. The study demonstrated a statistically significant lower frequency of stroke in the warfarin
treated group. There was no difference in the rate of stroke events in the aspirin and placebo arm. The
definitions for events in this trial were: TIA: focal symptoms lasting less than 24 hours; Minor stroke: focal
symptoms lasting more than 24 hours but less than 7 days; Non-disabling stroke: focal symptoms but
almost normal after 1 month; Disabling stroke: focal symptoms persisting after 1 month; fatal stroke
within a month. The trial stopped at 10 month follow-up. The side effects of warfarin therapy included no
examples of stroke or fatality. Warfarin was used with a prothrombin time at \(\times 1.6–2.0\) control. The results
of this study argue that warfarin can be used safely and that aspirin may not approach warfarin in
effectiveness. However, the study was directed at primary prevention, not secondary, and used “minidose”
warfarin, whose effects compared with “normal dose” aspirin remain unknown. The trial results support
the contention in this proposal that a trial of aspirin versus warfarin can be undertaken with reasonable
safety but the results for secondary prevention are not settled by the results of this primary prevention
study. The Warfarin Re-Infarction Study (WARIS) was a double-blind randomized study conducted in Oslo,
Norway, to study the effect of warfarin therapy in patients aged less than 75 for at least 2 years after acute
myocardial infarction. Of the 1214 randomized patients, 123 (20%) died in the placebo group and 94 (15%) in the warfarin group, a risk reduction of 24%. There was a 43% risk reduction for recurrent myocardial infarction. The incidence of cerebrovascular events was lower in the warfarin group with a 61% risk reduction. The Boston Area Trail of Asymptomatic Atrial Fibrillation showed an almost 10 fold benefit for warfarin compared with other agents including placebo. The SPAAF study showed an effect for aspirin but awaits completion for warfarin.

Heparin
It has been in use for several decades in the belief such therapy will provide protection while concurrent warfarin therapy builds its effect on the coagulation factors. Little evidence exists, pro or con, on the efficacy of heparin. In open trial of heparin, 150 consecutive patients with acute cerebral infarction or transient ischemic attacks were treated. None of those with transient ischemic attack experienced any complications but four (3%) of those with infarction suffered worsening or a new infarct and six (4.4%) had hemorrhagic complications. An attempt at a randomized trial of heparin in acute stroke has been reported in which a treatment group of was compared with a placebo group. In this trial, the sample size was small for the effects sought but no benefits were found. A randomized placebo-controlled double-blind study is now underway with ORG 1017241, a heparinoid, whose composition is thought to achieve anticoagulant effect with a lower risk of hemorrhage. Patients will treated within 24 hours of onset and with increasing doses of the agent, beginning at 300 u/kg, a dose lower than that which has caused hemorrhage.

Disappointing therapies
Anesthesia, hypothermia and/or barbiturates has been used based on the assumption that these maneuvers will reduce the metabolic activity of the brain and tide it over a period of impaired blood flow. Unfortunately, despite several vigorous effort in both animals and man, no evidence favors use of anesthesia, hypothermia or barbiturates in acute stroke.

Naloxone, a popular antinarcotic agent, has had some beneficial effects in inhibiting spinal cord injury in a rodent model. It was tested in an open trial sponsored by the NINCDS in doses up to 5 gm per patient (2600 mg/M2) over 24 hours but no detectable effect on stroke course or severity was observed, when given in an average time of 14 hours from onset. Although the time from onset before treatment may have been too long, the disappointing results appear to have cooled enthusiasm for more thorough trials.

Vasodilators were thought useful because it has been known for two decades that cerebrovascular reactivity is lost almost immediately and blood flow becomes pressure dependent in the ischemic zone of a cerebral infarct. This long known dependency prompted many efforts to increase flow. The simplest notion was to dilate vessel using agents having systemic and, hopefully, cerebral effects. Despite many trials, no studies have showed any benefit from vasodilators. Hyperventilation, another potential mechanism for altering vascular lumen diameters, has also been ineffective. A small trial of prostacyclin had encouraging results but one organized as a pilot study failed to show enough benefit warrant a large clinical trial.

Steroids have been tried in at least eight trials since 1956, totaling some 460 cases of heterogeneous type, over 400 treated within 24 hours, most of the patients were in the more serious category of stroke. No benefits have been demonstrated in mortality or reduction in stroke progression, even in those subject to cerebral edema. In the last review of such therapy no difference was found among groups given no treatment and those with steroids.

Hyperosmolar agents have been used to prevent stroke progression or recurrence have been somewhat encouraging. Glycerol has had little popularity despite a few trials suggesting benefits from oral or intravenous administration. One reason may be the risk of dangerous elevation of serum glucose with non-ketotic hyperosmolar hyperglycemia. Mannitol has been tested in many animal models and in a few human studies with mixed results.

Hemodilution has been tried several times over the past 15 years, but no trials have shown any major effect on progressing or recurrent stroke despite large enough series to be certain of the effect. A recent two center trials sought to reach a hematocrit of 33% by a combination of venesection and volume replacement using dextran-40 but did not achieve encouraging results42. A Scandinavian trial randomized of 183
patients to hemodilution (venesection and Dextran-40 administration) compared with 190 controls, and found a slightly higher case fatality rates among those who underwent hemodilution. They were unable to find any subset of patients who might have benefited from the therapy.

Pentoxifylline (Trental) was hoped to smooth flow through stenotic vessels. A trial of pentoxifylline in acute non-hemorrhagic stroke in 297 patients started within 12 hours of onset at intravenous doses of 16 mg/kg/day for three days followed by oral doses of 400 mg t.i.d. for 25 days had virtually no benefit.

ENDNOTES
