

# Cerebrovascular Disease

## 1.0 Risk Factors and Primary Prevention of Ischemic Stroke

1.1 *Age*. Age is the most powerful risk factor for stroke generally but is least related to subarachnoid hemorrhage and most related to ischemic stroke.

1.2 *Prior Stroke*. Previous stroke generally is also a strong predictor of stroke. As will be seen all patients with prior stroke should be treated with modifiable risk factor reduction and, unless there is a contraindication, one of the several medications or surgery that is known to prevent recurrence.

1.3 *Hypertension*. An understanding of the major risk factors is important because it aids in the identification of the patient who is most likely to develop cerebral infarction and in some cases suggests ways to reduce the risk of the first stroke (primary prevention). A powerful treatable risk factor of hypertension. Both diastolic and systolic hypertension are related to stroke. The Framingham study showed that even mild hypertension (and recently left ventricular mass) is associated with a relative risk of about 1.5. Treatment of hypertension reduces stroke risk.

### Hypertension

- deleterious effects on vessels and the heart
- secondary renal disease
- acute precipitation of hemorrhage
- possibly both stroke and HBP are associated with a 3rd factor

The Systolic Hypertension in the Elderly study (JAMA 1991; 265(24):3255-3264) showed a 36% reduction in stroke with antihypertensive treatment compared to placebo in elderly patients with isolated systolic pressures > 160 mm Hg. Numerous studies have shown the benefit in stroke reduction with blood pressure control. Patients with hypertension are at risk for both large artery and "penetrating" or small artery (100-500 micron diameter) disease (see Lacunar Infarction and Intracerebral Hemorrhage topics below).

1.4 *Cigarette Smoking*. It has become clear that smoking carries at least a 1.5-2.0 relative risk for stroke and that the risk can be greatly reduced by cessation. It certainly predisposes to carotid artery disease but may also add to an unfavorable viscosity situation and contribute to stroke risk in that way as well. Indirectly it affects coronary health and may also add to risk in this way.

1.5 *Blood Lipids*. In general the relationship between high total and LDL cholesterol and low HDL and risk, as has been demonstrated in coronary artery disease has been difficult to establish in stroke. Several studies however, have shown an increased risk of

thrombotic stroke with low HDL. Overall the relationship to stroke risk is relatively weak, possibly because cerebral infarction has important etiologies beyond atherosclerosis which is related to abnormal lipids. This explanation is supported by studies that show a strong relationship of lipid abnormalities to carotid or intracranial atherosclerosis. Recently, lipoprotein a or so called lp(a) has been associated with stroke risk but confirmation in larger studies has not been convincing.

In Asian studies low serum cholesterol has been associated with increased risk of intracranial hemorrhage. This observation has been met with skepticism but received support from at least one large study in Caucasian males (MRFIT study). The reason for such an association is unclear.

There is recent evidence that the newer agents that reduce cholesterol decrease stroke as well as cardiovascular events. This is true for simvastatin (Lancet 1994; 344: 1383-1389) and pravastatin (Circulation 1995; 92: 2419-25). Relative risk reduction is on the order of 30-50%.

Although a few questions remain it is becoming clear that lipids abnormalities predispose to adverse cerebrovascular as well as cardiovascular events. Accordingly the lipid related treatment of stroke patients should be carried out according to published guidelines designed for prevention of heart disease.

1.6 *Diabetes Mellitus*. In the Framingham study diabetes was related to stroke incidence but stood out as an independent risk factor only for older women. Other studies however indicate that stroke and diabetes are often found in the same patients. It is likely that the impact may be obscured because these also have other risk factors, such as hypertension and heart disease and the independent contribution of glucose intolerance per se is difficult to isolate. Diabetics are at risk for both small and large vessel cerebrovascular disease.

1.7 *Alcohol*. The Framingham study established a "J" shaped risk curve for alcohol and myocardial infarction in which low-moderate use (1-2 drinks per day) was associated with reduced risk and heavy use with increased risk. The situation with stroke may be similar but as yet this matter is under debate. What is clear is that heavy use increases stroke risk for intracranial bleeding. It may also predispose to ischemic brain disease at least in men. Confounding factors in this issue relate to the high rate of cigarette smoking in heavy drinkers and the combined deleterious effects of alcohol on blood viscosity and cardiac rhythm.

Alcohol abuse is not a risk factor for coronary artery disease or myocardial infarction and may, in fact, have a protective effect. It appears that the opposite is true in stroke risk. A number of studies seem to conclude that alcohol abuse is a risk factor for occlusive and hemorrhagic stroke. The Framingham study showed that cerebral infarction increased in incidence in men and women who drank, particularly in men age 50-62. The risk increased when the alcohol consumption was above 14 oz. of alcohol per month. A study done in Japan showed an increased risk for both hemorrhagic and occlusive stroke among

those who drank alcohol on a daily basis. The Honolulu Heart Study showed that drinking correlated with higher blood pressure and also a higher mortality from stroke.

The mechanism for increased stroke in heavy alcohol use is unclear. Alcohol may interact with hypertension, a well known risk factor for stroke. Both acute and chronic alcohol consumption are associated with hypertension. Alcohol, if anything, probably has a beneficial effect on lipids. Some have tried to invoke the platelet, with both increased and decreased platelet function related to drinking and alcohol withdrawal. However, these studies are inconclusive. (See: "Stroke and Substance Abuse" by John C. Brust in Stroke, Pathophysiology, Diagnosis and Management, Edited by Barnett, Stein, Mohr and Yatsu, 1992, pp 875-894 and also see Kannel, "Alcohol and Cardiovascular Risk" Circulation 52, Supp. 2200, 1975.)

1.8 Estrogen. A significant increase in the risk of stroke appears to accompany use of oral contraceptives concentrated mostly in older users (>35 years), those who smoke and/or have other risk factors and users of the high estrogen content pills. Although usually associated with "thromboembolism" the risk is highest for subarachnoid hemorrhage especially for older users who smoke.

Data on the cerebrovascular risk attending the use of postmenopausal estrogen supplementation has been conflicting. While the Framingham study reported a relative risk of 2.0 for stroke in women reporting the use of these drugs two other large studies failed to confirm this finding. In fact, both the Nurses Health Study (NEJM 1991;325:756-762) and the NHANES (Arch Int Med 1993;153:73-79) cohort reported a decrease in risk with use of postmenopausal hormones. On balance there is little justification for removing these medications to reduce stroke risk if they are otherwise needed. In fact, there is a secondary stroke prevention trial (WEST) now in progress which is trying to determine if estrogen supplementation prevents recurrent stroke in older women.

1.9 *Other*. Other factors under investigation include race and heredity, patent foramen ovale, atrial septal aneurysm, spontaneous echo contrast ("SMOKE", a finding on transesophageal echo), aortic arch plaques, snoring, lipoprotein fractions, presumed hypercoagulable states including intermediate level of protein C and S and the heterozygote state of homocystinuria or other causes of modest elevation of homocysteine in the blood.

( See: Wolf, Belanger, D'Agostina, "Management of Risk Factors", Neurologic Clinics, 1992;10(1):177-192), Sacco R. "Current Epidemiology of Stroke, in Current Review of Cerebrovascular Disease, Fisher and Bogousslavsky eds, an 1993, pp3-14)

Heart disease (see below) predisposes to cerebral infarction in several ways primarily including embolization from valvular and great vessel disease, dysrhythmias and disorders of the cardiac wall. In addition impaired cardiac function adds to stroke risk independently of other cardiac abnormalities or other stroke risk factors such as

hypertension. Other specific conditions, such as carotid stenosis and cardiac disease, will be discussed under more specific headings. Subclinical brain disease may also indicate higher risk for clinical stroke. Infarcts or infarct like lesions were first associated with stroke in a population based series of stroke patients in the Framingham Heart Study. MRI defined infarcts were similarly associated with prevalent stroke in a population based study from the Cardiovascular Health Study (Stroke 1994; 25: 318-327). Not surprisingly, white matter abnormalities on MRI also were correlated with prevalent stroke but despite the fact that it is biologically plausible the risk of clinical stroke associated with these lesions has not been demonstrated and proof that intervention is needed has not been published.

1.10 *Transient Ischemic Attack*. These neurologic events represent powerful risk factors for stroke if they are associated with certain predisposing. The following general comments about TIA's will be made but it should be noted that most mechanisms of cerebral ischemia including large or small vessel disease and embolism can present with TIA. It bears on the duration of ischemia not the directly on the cause. A transient ischemic attack is a complex of neurologic symptoms, which undergo rapid reversal, which are best explained by interruption of blood supply to the brain. Differential diagnosis includes conditions such as focal seizure, complicated migraine, tumor, subdural hematoma and rarely metabolic derangements. Transient focal symptoms may accompany subarachnoid or intraparenchymal bleeds.

Most TIA's are brief, 5 - 60 minutes. Sometimes, symptoms are transient but CT shows a brain infarction. Although minor (or asymptomatic) stroke is technically different than TIA, both groups should be investigated in a similar fashion and treated the same. In general, the occurrence of TIA's signal a much increased risk of stroke--over 10 times background during the first year and 7 fold during the subsequent 5 years. However, as with atrial fibrillation, there are important differences in prognosis with these general statistics. At the high end of the risk spectrum is the patient with hemispheric TIA's ipsilateral to a carotid stenosis > 70%; on the other end would be the young patient with no vascular risk factors. Overall, the risk rises with the age of the patient, male sex, higher number and more recent TIA's. coincident peripheral vascular disease or left ventricular hypertrophy, brain vs retinal symptoms, presence and degree of carotid stenosis and associated infarction (see Wilterdink and Easton, Arch Neurol, 1992).

Early management remains controversial. On our service acute TIA patients are generally brought into the hospital emergently, given aspirin, and considered for heparin treatment (if CT shows no bleeding). They are then usually admitted so that the cause of the TIA can be investigated. This always includes an evaluation for a cardiac source embolus and an assessment of the cerebral vessels using Duplex ultrasound for the cervical carotid and transcranial Doppler (TCD) for intracranial large arteries. If evidence for one of these conditions is not found, heparin is stopped and the patient placed on long term aspirin or another antiplatelet agent. Not everyone takes this approach using anticoagulants. However, there is agreement among most that evaluation needs to be prompt and include basic blood work, an EKG, cranial CT scanning and carotid imaging at the very least. Additional testing depends on the clinical scenario but may include cranial MRI,

transesophageal echocardiography and tests for antiphospholipid antibodies or coagulopathy. There is no agreement on the ultra early management of TIA patients. Most Studies with antiplatelet agents do not include many patients entered within the first 48 hours but antiplatelet therapy is usually recommended. There is recent data from two trials (International Stroke Trial and the Chinese Aspirin Stroke Study) using aspirin early on for urgent treatment of ischemic stroke (a related but separate issue) and this information is described below under stroke treatment. Carotid surgery is recommended for appropriate TIA patients and it should be performed as soon as possible after presentation(see below). Medical therapy for TIA is discussed under secondary stroke prevention.

- Most are less than 24 hours (usually .5-1 hour)
- If symptoms last > 6 hours, an infarction is likely
- The risk for subsequent stroke is usually quoted at about 40%, with half of these occurring within 3 months of the TIA, 2/3 within 6 mos
- Evaluation should be prompt and include, at a minimum, basic blood work, an EKG, cranial CT and carotid study.
- Medical treatment should be with aspirin, ticlopidine or rarely anticoagulants; carotid enterectomy is beneficial for ipsilateral carotid lesions of  $\geq 70\%$  luminal diameter reduction unless the patient has severe medical illness.
- A peculiar transient phenomenon associated with carotid artery disease and hemodynamic ischemia (upright posture)
- Symptoms consist of seconds to minutes of arm, sometimes leg shaking or repetitive movements not associated with facial twitching or changes in sensorium
- EEG may be helpful in diagnosis; anticonvulsants not helpful in treatment. (Ann Neurol: 18(2) Aug. '85)

Should all TIA patients be hospitalized? The following guidelines were published by the American Academy of Neurology. I think it is prudent to hospitalize most patients with TIA within the past 7-10 days at least unless one can obtain a fairly complete one day outpatient work up looking for carotid disease, a fib or coagulopathy.

TIA/ Who Should be Hospitalized?

- Recent TIA (< 48 hours)
- Prolonged TIA (that is, a stroke)
- Frequent or Crescendo TIA
- Suspected high grade carotid disease
- Posterior circulation TIA

American Academy of Neurology Task Force for Utilization for Stroke; Neurology August 1994: 1531-32.

## 2.0 Common Stroke Types: Diagnosis and Management

*Classification.* Recent stroke registries define stroke entities using clinical and laboratory data. The result is a classification scheme with approximately the same distribution between ischemic and hemorrhagic stroke (80% vs 20%) as older (pre-CT) studies, but subdivides ischemic stroke differently. (See: Classification of Ischemic Strokes by J.P. Mohr and R.L. Sacco, in Stroke: Pathophysiology, Diagnosis and Management, Churchill-Livingst.1992,p.271-284).

Thrombosis (large artery occlusive disease) 15%

Embolism 25%

Lacunar 10%

Infarct cause unknown (cryptogenic) 25%

Hemorrhage -SAH 12%

Hemorrhage -ICH 13%

*Stroke Subtyping.* The determination of stroke subtypes is an important diagnostic exercise. The most basic level of this effort is the distinction between cerebral hemorrhage and cerebral ischemia. Clinical schemes can only go part of the way toward this important distinction and a good quality CT scan is needed to separate the two. Within the broad category of stroke due to cerebral ischemia considerable effort has been expended over the last two decades to develop systems that categorize ischemic stroke into meaningful subgroups. The motivation for this comes primarily from the belief that the most meaningful and accurate prognosis and treatment information will be subtype specific. This thinking is put into practice daily by selection of secondary prevention treatments based on presumed subtype and etiology. However, the efficacy of antiplatelet agents, the mainstay for secondary prevention, has not been determined as a function of ischemic stroke subtype. A new generation of studies, such as the warfarin aspirin recurrent stroke study (WARSS) and the Warfarin Aspirin Study of Intracranial Disease (WASID), now being conducted or planned, will address the issue of selection of treatments from the viewpoint of ischemic stroke subtypes.

As far as acute treatment is concerned, at present only the distinction between hemorrhage and ischemia is important. While it is intuitively appealing to think that large vessel occlusion may respond to a different acute intervention than small vessel or cardioembolic stroke, it remains to be proven. TPA seems just as effective for small as for large vessel stroke subtypes. In addition it is not currently possible to be confident what subtype one is dealing with in the ER. During a recent study of a new treatment the investigators determined how well the 3 month subtype classification compared with the initial impression in the ER. Fully 38% of the patients underwent a change in subtype diagnosis on the basis of either more history or the results of in house testing ( see Madden et al, Neurology 1995; 45:1975-1979). Special testing needed for subtyping slows down the treatment machinery and should be done as part of a protocol.

Subtyping can give useful prognostic and treatment information. Cardioembolic stroke, a category based on the presence of a cardiac source of embolus and absence of other

factors, is often treated with warfarin. In the case of atrial fibrillation, this is based on extensive prospective data.

The concept of Stroke of Unclear Etiology is also useful in that it can drive a more extensive workup looking for rare causes of stroke. Likewise, stroke in the young adult should bring to mind a different set of etiologies and prompt a more extensive work up for unusual causes of stroke. In addition the Stroke Data Bank has demonstrated that subtypes have different early recurrence and in house worsening rates as well as different early mortality rates. Thus subtyping of ischemic stroke is useful provided that the clinician bears in mind its limitations and the fact that these subtypes are not "pure cultures" and more than one mechanism may be present in the same patient.

*2.1 Large Artery Thrombosis.* The mechanism is defined by obstruction due to localized disease processes (most often atherosclerosis but dissection would also be included in this category) with or without superimposed clot formation. Clinical presentations usually suggest relatively large lesions, sensory and motor signs with cortical involvement (exception: pure motor symptoms from a "distal field" lesion). CT/MRI scans show patterns of infarct usually involving an MCA division or the entire MCA territory (so called "territorial" patterns), although borderzone or "distal field" pattern may be seen with lesions proximal to the internal carotid artery (ICA) termination.

Cerebrovascular atherosclerosis may cause distal artery - artery embolism occlusion with relatively localized brain infarcts or may produce symptoms by what is called hemodynamic mechanisms, i.e. creating a low flow situation beyond the lesion in a vascular bed that for whatever reason(s) is not able to compensate with collateral flow. The more intracranial the lesion is the fewer are the opportunities for collateral flow. With an extracranial carotid lesion reversal of flow through the ophthalmic and crossover of blood from the anterior communicator are common ways to "rescue" the brain above the lesion, as in the contribution of blood from the vertebrobasilar circulation via the posterior communicator. Intracranial lesions may be beyond the point where the ophthalmic artery can contribute and may also be in a position to prevent useful contributions from the communicators. There remains what are called "leptomeningeal" collaterals that potentially, to a varying degree in individual patients, connect the named vessels of the circle of Willis.

#### Collateral Circulations Systems

- **extracranial-intracranial ( e.g. reversed ophthalmic art.)**
- **Willisian ( e.g. anterior communicator)**
- **leptomeningeal ( e.g. ACA to MCA on the cortical surface)**

Since the management of **extracranial carotid, intracranial carotid and vertebrobasilar** disease manifestations vary in some respects, they will be dealt with separately.

### 2.1.1 Extracranial Carotid Artery Disease.

**Risk Factors.** Risk factors tend to parallel those of coronary artery and peripheral vessel disease. Cigarette smoking is a particularly strong risk factor for carotid artery atherosclerosis. The incidence increases with advancing age. Hypertension is present in 50-75% and elevated plasma homocysteine has recently been implicated.

**Diagnosis.** Duplex ultrasound or magnetic resonance angiography backed up by conventional angiography is the usual approach to diagnosis. Although some find it useful to know the distal, intracranial arterial status, others argue that angiography may no longer be required simply adds morbidity.

**Risk of Stroke with Stenosis.** Most studies have shown an increase in risk of stroke with the degree of carotid stenosis especially when it gets to around 75% or greater.

**Management of Asymptomatic Carotid Stenosis.** The presence of carotid atherosclerosis even without significant stenosis seems to mark patients at risk. The long term study of Norris and colleagues demonstrated an annual risk of 1.3% in cases with stenosis of <75% by ultrasound and 3.3% in those with >75% stenosis. Whether asymptomatic carotid artery lesions should be subjected to carotid endarterectomy has been the subject of much debate. A large study, the Asymptomatic Carotid Artery Study (ACAS) recently reported on the benefit of prophylactic surgery for lesion of  $\geq 60\%$  diameter reduction by angiography.

A clinical alert based on early analysis from this study was distributed in Sept 1994. " Summary: The investigators of the Asymptomatic Carotid Atherosclerosis Study (ACAS) are reporting the interim results of a randomized controlled clinical trial of carotid endarterectomy in patients who have asymptomatic carotid stenosis of greater than 60% reduction in diameter. In addition to aspirin and aggressive management of modifiable risk factors, one half of the patients were randomly assigned to receive surgery after angiographic confirmation of the lesion. Carotid endarterectomy is beneficial with a statistically significant absolute reduction of 5.8 in the risk of the primary endpoint of stroke within 5 years and a relative risk reduction of 55%. As a consequence of the trial reaching statistical significance in favor of endarterectomy, and on the recommendation of the study's Data Monitoring Committee, physicians participating in the study were immediately notified and advised to reevaluate patients who did not receive surgery. It is important to note that the success of the operation is dependent on medical centers and surgeons who have a documented perioperative morbidity and mortality of less than 3%, careful selection of patients and postoperative management of modifiable risk factors." (National Institute of Neurological Diseases and Stroke Clinical Advisory, September 28, 1994).

A total of 1662 with asymptomatic stenosis of 60% or greater were randomized and data was available on 1659. Although they initially were calling transient ischemic attack stroke or death occurring in the perioperative period were called endpoints but in March 1993 they eliminated TIA's and concentrated on appropriate distribution infarction and

any stroke or death in the perioperative period. After a median follow up of 2.7 years the aggregate risk over 5 years for ipsilateral stroke and any perioperative stroke or death was 5.1% for surgical patients and 11% for medically treated patients. This amounted to a 53% reduction over 5 years. Centers had less than a 3% perioperative morbidity and mortality risk. They did not show a difference between 60-69% and 80-99% but there were few patients with high grade stenosis. No high risk groups were identified but for unclear reasons women had higher surgical morbidity. (JAMA 1995; 273 (18):1421-1428). There is no data to support surgery for lesions less than 60% stenosis. There is also no convincing evidence that patients with asymptomatic carotid stenosis benefit from prophylactic CEA before cardiac or any other surgery.

These results displaced the recent VA randomized trial testing prophylactic CEA for asymptomatic lesions of 50% diameter narrowing failed to confirm the benefits of surgery (Hobson, et al., NEJM 1993;328(4): 221-227).

*The management of asymptomatic stenosis is a rapidly developing area of cerebrovascular disease. Since the ACAS results, more people will likely be referred for surgery but some neurologists may wait elect to refer for surgery at some point beyond 60%, possibly 80% or greater since there is other data which supports an increase in stroke rate when the stenosis reaches about this point.*

Management of Symptomatic Carotid Stenosis. Surgical therapy for prevention of cerebral infarction has been practiced for several decades but only recently has been subjected to careful study. The use of a bypass graft around an occluded carotid in what was called the EC-IC operation (extracranial-intracranial bypass) was tested and rejected as an operation that "works but does not help", meaning that the operation did not reduce subsequent stroke and death incidence. Carotid endarterectomy (CEA) involves opening up the carotid artery and shelling out the atherosclerotic material, usually with primary closure but sometimes using a patch graft. There have been several recent studies testing the benefits of CEA. These studies have supported the use of CEA in symptomatic patients with ipsilateral stenoses of  $\geq 70\%$  luminal diameter by angiography in the most influential of these studies. The reader is referred to American Heart Association Guidelines for a review of current recommendations regarding CEA (Stroke 1995; 26: 188-201).

### **Trial Design**

Randomized, controlled trials involving centers with proven low surgical morbidity and mortality (< 6%).

"ECST" : European Carotid Surgery Trial; (Lancet 1991;337:1235-1243)

"NASCET": North American Symptomatic Carotid Endarterectomy Trial; (NEJM 1991;325:445-453)

**"VA Study": Veterans Affairs Cooperative Study; (JAMA 1991;266:3289- 3294)  
(results not described but trial supported CEA for stenosis > 50%)**

## **Treatments**

Surgery compared to

- ECST: variable aspirin dose with local discretion as to medical management
- NASCET: 1300 mg ASA/day and attempted risk factor reduction (in all patients)

## **Endpoints**

- ECST: primary - ipsilateral stroke; secondary - major stroke or death from any cause
- NASCET: primary - ipsilateral stroke or stroke death; any death within 32 days of randomization; secondary - all nonfatal and fatal stroke and death (any cause)

## **Inclusion Criteria**

- ECST: any age with TIA or non disabling stroke in previous 6 months; any degree stenosis<sup>+</sup> in ipsilateral carotid artery;
- NASCET: < 80 years, TIA or non disabling stroke < 120 days prior to entry; 30-99% stenosis of ipsilateral artery.

+ Based on conventional angiography.

## **Exclusion criteria**

- ECST: unstable neurologically previous ipsilateral CEA; could have treated coronary artery disease;
- NASCET: progressing stroke; severe intracranial disease or odd etiology (e.g. dissection); any previous surgery with 30 days or previous ipsilateral CEA; atrial fib, unstable angina, recent MI (6 months), cardiogenic source for stroke; not expected live 5 years or bad HBP; or severe intracranial occlusive disease.

## **Results**

- ECST - Among 778 patients with severe stenosis (70-99%), the risk of surgical stroke or death, ipsilateral stroke (or any stroke) of 12.3% after 3 years (455 patients) was better than the comparable rate of 21.9% in the (323) medically treated patients (p. < .01 or better). No difference in overall mortality. Surgery not effective for stenosis < 30% (data for 30- 69% stenosis recently reported and no benefit was obvious.
- NASCET - Among 659 patients with stenosis > 70% followed for 2 years (average), the rate of ipsilateral stroke of 9% in 331 operated patients was considerably better than the rate of 26% observed in the 328 treated medically (p

< .001). Perioperative morbidity/mortality was 5.8%. Survival probability was improved by surgery. Efficacy for patients with 30-69% stenosis is not yet clear (randomization continues).

## Conclusions

- Carotid endarterectomy in selected symptomatic patients works - patients live better (ECST and NASCET) and longer (NASCET);
- These results may be generalized to similar patients if surgical morbidity/mortality is low and surgery is performed soon after TIA or stroke;

The NASCET Trial, which was examining high grade (>70% diameter) stenosis of the internal carotid artery in patients with ipsilateral symptoms, was interrupted because a significant "endpoint" had been reached. The monitors of the study became convinced that surgery was significantly better than medical treatment. It must be noted that: These results may not be applicable to centers with a combined surgical morbidity and mortality which greatly exceeds the standards of this study ( $\leq 5\%$ , 2% major morbidity or death) or in patients with significant medical illness.

Coexistent Carotid and Coronary Disease. Finally, the problem of managing coexistent symptomatic carotid and coronary artery disease remains a vexing issue. The AHA guideline paper referred to 57 English language papers relating to this subject but no study is definitive. Their analysis indicated, much as one intuition would suggest, that operating on the carotid first reduced stroke but resulted in more perioperative MI and death; likewise operating on the heart first may have a higher stroke rate. Most neurologist do not recommend prophylactic CEA before CABG for asymptomatic carotid disease. If both beds are symptomatic, we recommend fixing the most urgent one first. If in doubt I recommend heart surgery first and not combined operation on both. It should be noted that the AHA panel could identify no best strategy and no recommendation was made.

## 2.1.2 Intracranial Carotid System Disease

Risk Factors. Diabetes mellitus and race.

Prevalence and Risk of Stroke. Prevalence has been variable depending on the patient population. Most older reports suggested that fewer than 5% of strokes were due to intracranial arterial disease. There was a recent report that indicated that in some settings, and when people are examined with TCD and MRA, the prevalence may be as high as 30%. The stroke incidence associated with intracranial ICA or MCA disease has been reported from the EC-IC study to be 7% per year ( Stroke 1986; 17: 1112-1120). In smaller series the stroke rate has been even higher suggesting that this condition may have a relatively poor prognosis.

Management: WASID study

The best way to prevent recurrent events in someone with symptomatic intracranial large vessel disease has not been subjected to careful study. Recently however a multicenter retrospective study was published which suggested that more people with angiographically proven stenosis > 50% diameter (but not occluded) do better with warfarin than aspirin (Neurology 1995; 45:1488-1493). Of 88 treated with warfarin for median of 15 months the overall rate of major vascular events including stroke and MI/sudden death was 8.4/100 patient years compared to 18/100 patient years for 63 aspirin treated patients.

### 2.1.3 Vertebrobasilar Disease

#### *"Top of the Basilar" Syndrome*

- Visual defects include: disorders of vertical gaze, convergence, "Collier's Sign" (elevation and retraction of the upper lids), skew deviation, pupillary abnormalities
- Somnolence, memory deficits, agitated delirium, hallucinations, symptoms of unilateral or bilateral posterior cerebral artery infarction

Large vs Small Vertebrobasilar Artery Disease. You cannot reliably distinguish large from small vessel disease in the posterior circulation clinically, at least in the acute setting. Any patient whose symptoms suggest VB disease should be considered likely to have large artery disease until further investigation proves otherwise.

Risk Factors. These are pretty much the same as for anterior circulation disease.

Emergency Management. In addition to the measures used for anterior circulation disease, there is a literature on urgent thrombolysis using catheter injected urokinase or TPA for cases of acute (<8 hours) basilar thrombosis. It is unclear whether this would be done in addition to intravenous tpa treatment.

Noninvasive Detection. Transcranial Doppler and Magnetic Resonance Angiography can both detect large artery disease but imperfectly. Some of us think that we need concordance between these two to be sure, at least in some cases, of the prevalence and severity of disease in the basilar.

## 2.2 Medical Management of Stroke

### 2.2.1 Treatment of Acute Ischemic Stroke

The standards for the treatment of acute stroke and for TIA have recently been reviewed by expert groups impaneled by the American Heart Association (Adams, H, Brott, T, Crowell, R, et al: Guidelines for the Management of patients with acute ischemic stroke.

Circulation 1994;90(3): 1588-1601.) and the National Stroke Association (McDowell, F, Brott, T, Goldstein, M, et al: The first six hours. Stroke clinical updates 1993; IV(1): 3-11 (available through the National Stroke Association) and Guidelines for Management of Transient Ischemic Attacks, Stroke; 1994; 24: 1320-1335. These reports, on which my recommendations are largely based, make it clear that the nonemergent attitude and response to stroke are no longer acceptable and do not represent the standard of care which our patients deserve today. The AHA guidelines are now revised to reflect recent advances in treatment (Adams, H, Brott, T, Furlan, T et al: Guideline for Thrombolytic Therapy for Acute Stroke: A Supplement to the Guidelines for the Management of Patients with Acute Ischemic Stroke. Stroke 1996; 27: 1711-1718).

The FDA has recently (June 96) approved the use of TPA for the treatment of acute ischemic stroke. The recommendation is based largely on the NIH study reported in the NEJM, (NIH and Stroke TPA Study Group, Dec 14, 1995) and include these restrictions:

- treatment in less than 3 hours after onset
- no coagulopathy
- no hemorrhage on CT (may be more restrictive and require no sign of early cerebral infarction)

Symptomatic hemorrhage can be expected in at least 6% of patients and may be fatal. Even after considering the hemorrhage risk however, patients treated with TPA had about a 30% greater chance of having no or minimal disability at 3 months compared to standard care. (See revised AHA recommendations)

Patients need to be educated as to the signs of stroke, especially: the abrupt onset of hemiparesis, sudden change in mentation or level of consciousness, severe headache, especially with vomiting, and disorders of vision and other senses. Remarkably, most stroke patients, even those clearly at high risk because of prior stroke or TIA, deny receiving any stroke education before admission. Stroke education reduces delays in presentation for evaluation and treatment. In addition, the patient/family must be instructed to call 911 services and not attempt to reach the patient's personal physician until emergency evaluation is underway. Using 911 (or comparable emergency services) avoids unnecessary delay in the initiation of treatment. (Brott, T: Urgent evaluation and management of stroke. In: Adams, H, ed. Handbook of Cerebrovascular Diseases; New York: Marcel Dekker, Inc., 1993: 385-399).

Stroke is treated with different acuity priorities in different communities. Emergency Medical Personnel need to be clear on rapid recognition, response and treatment of stroke with an emphasis on rapid transport to the hospital. (Brott 1993) Guidelines outlining general measures for emergency personnel have been published (Emergency cardiac care committee and subcommittee: American Heart Association: Special resuscitation situations. Stroke. JAMA 1992; 268: 2242-2244). Treatment of some types of stroke may someday be initiated during transfer. The team in the field should be encouraged provide notification that a stroke patient is en route and to minimize any delay.

Emergency or primary care physicians treating the patient in the emergency setting should complete an initial evaluation within 5-10 minutes. A decision should be made quickly regarding CT scan, which is almost always indicated, in situations where CT personnel are not on site. Acute ischemic stroke most often presents with focal neurological findings without coma. Important differential diagnoses include intracranial hemorrhage which may not produce focal findings and which may present with loss of consciousness; metabolic derangements are rarely associated with focal findings. Patients presenting without history in coma present a greater diagnostic differential which includes brain stem stroke, drugs and metabolic problems and trauma requiring appropriate diagnostic and therapeutic responses.

The initial emergency evaluation includes the history and physical examination, an electrocardiogram, chest x-ray, complete blood count, platelet count, prothrombin and partial thromboplastin times, serum electrolyte and glucose determinations. Erythrocyte sedimentation rate, VDRL, arterial blood gas determinations, drug and alcohol screens are appropriate in some patients. A noncontrast cranial CT scan should be performed on an urgent basis. In patients with a transient ischemic attack (TIA) or cerebral infarction, blood pressure is not treated acutely unless the systolic is at or above 220 or the mean blood pressure > 130, respectively or if TPA is being considered or has been given in which case more aggressive BP control is needed. Patients with heart failure or aortic dissection may require treatment to control blood pressure. Blood glucose concentrations should be maintained between 70 and 170 mg/dL. Supplemental oxygen is recommended only for patients with hypoxia.

Unless the patient has received TPA, I recommend administering aspirin as an acute treatment in the ER. It is likely to do no harm and there is some evidence that it may help. Of course, many patients are already on this drug when they arrive. But if not, one or two given even before the CT is reasonable unless there is the chance of using TPA or an experimental treatment.

Recently, the ultra early use of aspirin has gotten a boost. Two large studies were recently reported which looked at the use of aspirin in the setting of acute (presumed) ischemic stroke. The two were planned with the a priori analysis looking at both groups together. The International Stroke Trial (IST) was a large randomized open trial of up to 14 days of antithrombotic therapy started within 48 hours after stroke. Half of the patients were allocated to receive either 5000 or 12500 IU of heparin SQ twice daily and half were assigned to no heparin. In a factorial design, half of these patients were assigned to receive 300 mg per day of aspirin and the other half to no aspirin. They looked at deaths at 14 days and dependency at 6 months as the primary outcome measures. A total of 19,435 patients were randomized in 36 countries.

The results indicated a small benefit for aspirin. Among aspirin treated patients there was no significant difference in early deaths (9 vs 9.3%); at 6 months there was a trend toward fewer dead or dependent patients; after adjustment for baseline prognosis this was significant (2p= .03). Aspirin allocated patient has fewer recurrent strokes within 14 days (2.8 vs 3.9 % with no increase in hemorrhage (.9 vs .8%). There was a small but

significant reduction in death or nonfatal recurrent stroke ( 11.3 vs 12.4%). Aspirin without heparin had no increase in bleeding. Regarding heparin there were no significant differences in either death or dependency (62%). Patients given heparin had significantly fewer recurrent ischemia stroke within 14 days(2.9 vs 3.8%) but this was countered by a similar sized increase in hemorrhagic strokes ( 1.2 vs .4%) so the total difference in death or non fatal recurrent stroke was not different (11.7 vs 12%). Compared with 5000 IU, 12500 IU BID was associated with significantly more fatal or transfused extracranial bleeds, more hemorrhagic strokes, and more deaths or non fatal strokes within 14 days (12.6 vs 10.8%). The study organizers interpreted this as a small but significant benefit for aspirin and evidence that heparin was not helpful and that if used, the smaller dose is preferred (Lancet 1997; 349:1569-1581).

The Chinese Aspirin Stroke Study (CAST) was a large randomized placebo controlled trial of aspirin treatment (160 mg/day) started within 48 hr after stroke continued for up to 4 weeks. The primary endpoints were death during the treatment period and death or dependence at discharge. In this study 21106 patients with acute ischemic stroke were enrolled in China at a mean of 25 hr after onset of symptoms. They had 87% of patients with an entry CT scan. There was a significant 14% reduction in mortality 3.3 vs 3.9 % (  $2p=.04$ ). There were significantly fewer recurrent strokes (1.6 vs 2.1%) in the aspirin allocated patients but a few more hemorrhagic strokes (1.1 vs .9%). There was a slight but significant reduction in the combined endpoint of death or nonfatal stroke at 4 weeks (5.3 vs 5.9%) ( $2p=.03$ ) for a absolute difference of 6-8 per thousand patients (Lancet 1997;349: 1641-1649).

When the two trials are combined, the authors claim that aspirin is associated with a small but define net benefit, with about 9 fewer deaths or non fatal stroke per 1000 in first few weeks ( $2p=.001$ ) and with 13 fewer dead or dependent per 1000 patients after some weeks or months (  $2p= .01$ ). While these studies may lack the rigor of our own trials say, for instance, the requirement that all patients have a CT before entry, they do indicate that ASA seems not to be harmful and may be marginally helpful.

#### Recommended initial management of cerebral infarction.

- Obtain emergency computerized tomographic scan of the head.
- Treat blood pressure if systolic 220 mm Hg or mean 130 mm Hg, or if heart failure or aortic dissection.
- Treat hypoglycemia or hyperglycemia (170 mg/dL).
- Monitor cardiac function.
- Treat with two adult aspirin acutely unless patient is already on aspirin or cannot swallow.

My recommendation on heparin remains to consider it in patients who are evolving, or patients with minimal to moderate deficits with suspected large arterial disease or cardiac sources of embolism. I recommend using anticoagulation if cardiac lesions, coagulopathy or large artery intracranial including basilar artery stenosis are suspected only until

workup is complete and only if there is acceptable bleeding risk and after no blood on cranial CT. Delay anticoagulation until review of second CT at 48-72 hours in cases with large strokes with edema and mass effect. Anticoagulation should be started or continued in cases with hemorrhagic conversion on CT only if there is a very high recurrent embolism risk. Checking a platelet count 24-48 hours after starting heparin is also a good practice.

- Monitor patients for increased intracranial pressure or seizures after large cortical infarction.
- Aggressively prevent aspiration, malnutrition, pneumonia, deep vein thrombosis, pulmonary embolism, decubitus ulcers, contracture, and joint problems.
- Begin mobilization early, unless bed rest is indicated.
- Initiate early intervention for secondary prevention.
- Educate patient/others on disease and cardiac comorbidity

The decisions and options are similar for the patient with stroke as for the TIA patient provided the patient is not moribund or has very limited potential for survival. Specific issues pertaining to other types of stroke will be briefly discussed below which will be followed by a consideration of common problems occurring after stroke, especially cerebral infarction.

The biggest issue that continues to arise is the use of heparin acutely in patients with stroke or TIA (Korczyn, A: Heparin in the treatment of acute stroke. In: Barnett, H, Hachinski, V, eds. Neurologic clinics: Cerebral ischemia: treatment and prevention. W. B. Saunders Company, 1992; 10(1): 209-217). The AHA panel concluded that the available data did not allow any recommendation and that "the use of heparin remains a matter of physician preference". The argument for its use is that it may help prevent early recurrent stroke or worsening due to propagation of thrombosis. The data are limited and certainly do not indicate that heparin is effective; neither have studies been performed which show that it is not effective or too dangerous to be considered. *It is important to note that there is very little data on ultra early secondary prevention treatment with either anticoagulation or aspirin. Most trials using aspirin recruited patients 7 or more days out from their last event and cannot provide data on the effects of treatment in the first few days when we know the least about the patient and our concerns are high.*

There was recently more bad news for the advocates of using heparin. The TOAST trial, which was testing the use of heparinoid in acute ischemic stroke within 24 hours, reported that this therapy was not helpful when compared to placebo. The full results of the trial have not been published.

Despite this recent data on heparin, if the patient is not in a research protocol, I recommend treating the patient with TIA or minor stroke early with aspirin and after the CT scan using heparin for all but intracranial hemorrhage, major stroke, pure motor hemiparesis without fluctuation, or patients with obtundation and mass effect or a

contraindication. I discontinue the heparin unless the workup produces evidence for a coagulopathy, cardiac source or intracranial high grade stenosis. The rationale is to presume a high recurrence risk situation for the 48 or so hours it usually takes to sort the patient's risk factors and use both types of agents early but decide on long term prevention treatment as soon as possible.

### 2.2.2 Experimental Treatment of Stroke

**Thrombolytic Agents.** Data from the animal experimentation involving cerebral ischemia suggest a limited "therapeutic window" of minutes to several hours duration depending on the conditions and the models used. While the limits of the window have not been firmly established, these experiments have proven that delay lessens the chance of recovery regardless of the treatment employed. Current recommendations are that the clinical evaluation and initial management of cerebral infarction be completed as soon as possible but at least by six hours from the time of onset. Six hours may be too long for most situations and it should be viewed as an outside limit rather than a target.

Many medical centers are participating in treatment trials of acute ischemic stroke. Two major avenues of therapy now being tested involve either attempted restoration of blood flow, usually with thrombolytic agents or protection of ischemic brain with so called "brain saver" or cytoprotective agents. (Biller, J: Medical management of acute cerebral ischemia. In: Barnett, H, Hachinski, V, eds. Neurologic Clinics: Cerebral ischemia: treatment and prevention; W. B. Saunders Company, 1992; 10(1): 63-85). Support of these protocols be referral of patients and participation is crucial if answers to treatment questions are to be found. Agents now being tested include ultra early use of thrombolytics (more than 3 but less than 5 hours from onset of symptoms), brain saver drugs including NMDA receptor antagonists and low molecular weight heparin like agents (heparinoids). There is currently perhaps the greatest excitement over t-PA, a thrombolytic agent. This "clotbuster" drug is intended to restore blood flow to brain. So far only early pilot studies have been reported and have shown that intraarterial injection of tpa is associated with higher recanalization rates than intravenous administration. Safety remains an issue; rates of parenchymatous hemorrhage have ranged from 4-11%. The risk of hemorrhage goes up the later the treatment is administered.

#### Recent Experimental Treatment Approaches

- Hemodilution (does not work)
- Calcium antagonists (probably do not work)
- Heparinoids (not effective)
- NMDA receptor antagonists (toxic but still being tested)
- free radical scavengers (do not work)
- t-pa ( being tested for use > 3 hours from onset)
- anti-ICAM (recently shown no to work and is even harmful)

**Cytoprotective Agents.** A complimentary approach to restoring blood flow is to slow down the deleterious effects of ischemia using a "brain saving" drug. A recent large study

using nimodipine, a calcium antagonist, did not show improvement over control. Currently, drugs are being tested which either block the effects of excitatory neurotransmitters (aspartate, glutamate) or work in ways that are not yet fully understood (lubeluzole, citicholine). A low molecular weight heparin like agent was tested but was found ineffective and an immunological approach with an antibody to intracellular adhesion molecule (enlimomab) was found to be harmful, not helpful.

Standard care includes treating coincident medical problems such as myocardial infarction and electrolyte abnormalities, airway support, supplemental oxygen only in hypoxic patients, and usually no treatment of hypertension unless BP is markedly elevated (>130 mean or 200 systolic). Management of cerebral edema is important for large cortical infarctions, especially in young persons, and is accomplished by the usual ICU based methods including graded application of hyperventilation, restriction of fluid, especially hyposmolar fluids, fever and pain control, osmotherapy, reduction in CBF by anesthetic agents and/or intraventricular drainage.

### 2.2.3 Secondary Prevention with Aspirin, ticlopidine or warfarin

Medical therapy for secondary prevention (after TIA or non disabling cerebral infarction) relies primarily on aspirin. There have been several large studies which have shown, depending on the endpoints selected, a modest (20-25%) reduction in stroke risk although in some cases other endpoints must be combined with cerebral infarction to show convincing benefit.

- Aspirin (900-1200 mg/day) produces an aggregate 22% reduction in non fatal stroke (meta-analysis).
- The single study comparing low and high doses aspirin (the UK-TIA Study Group-JNNP 1991;54:1044-1054) suggested no difference in efficacy between 300 and 1200 mg/day.

The optimal dose of aspirin is debated. High dose (1000-1200 mg/day) should probably be called "standard dose" since most older studies used this level of aspirin. Recently, three large trials have confirmed the benefit of different, lower aspirin doses but the experts still debate the recommended dose. It is clear however, that lower doses are less gastrotoxic and many recommend a single 325 aspirin/day. Dipyridamole has been tested several times and adds nothing to aspirin. In the single trial in which it was compared to placebo it showed no benefit.

#### Ticlopidine

- Inhibits platelet aggregation induced by adenosine diphosphate
- Does not inhibit cyclooxygenase

- Now indicated for aspirin intolerant or aspirin failure TIA and stroke patients to prevent stroke

Ticlopidine hydrochloride has recently been approved for stroke prevention. It has an antiplatelet action that is distinct from that of aspirin. Its use was confirmed in two large studies:

### **Ticlopidine Aspirin Stroke Study**

Compared 500 mg Ticlopidine with 1300 mg Aspirin in 3069 patients with recent TIA or non disabling stroke;

Results: 12% reduction in nonfatal stroke or death and 21% risk reduction in stroke; side effects included: diarrhea 20%, skin rash 14% and severe but reversible neutropenia (<1%)(NEJM 321:501-507, 1989)

### **Canadian American Ticlopidine Study**

Compared 500 mg ticlopidine with placebo in 1072 patients with recent ischemic stroke; endpoints were stroke, myocardial infarction or vascular death;

Results: Ticlopidine associated with a relative risk reduction of 30%; side effects: skin rash, diarrhea and neutropenia (severe in about 1%)(Lancet 1988;ii:1211-1220).

*It is important to follow the recommendations to check a CBC every two weeks for the first 3 months since neutropenia does occur and can be significant.*

### Options for Therapy

- Aspirin (at least one adult per day)
- Ticlid 250 mg bid
- Warfarin (INR 2.0-2.5)
- Dipyridole 50 mg TID (use only if cannot take asa or ticlopidine)
- Carotid enterectomy
- Risk Factor Management and Education for Patient and Family (everybody should get this)

### 2.2.4 Prevention of Medical and Neurological Complications

**Blood Pressure.** As mentioned above do not lower the blood pressure acutely. Treat only if blood pressure is very elevated (> 130 mm Hg mean or 220 systolic) or if another crisis, such as heart failure or aortic dissection exists.

**Fluids.** Intravenous fluids are usually needed during the first 2 days. Hypotonic fluids should be avoided because they may worsen intracranial pressure if it is elevated. Most

adults require 75-100 cc/hr of fluids until the oral intake can be established. Avoid putting the IV in a paralyzed arm.

**Activity/Mobility.** There are only three indications for bed rest in this setting: severe angina, deep vein thrombosis (before anticoagulation) and postural ischemia, which may be seen with large artery carotid or basilar disease. These situations can usually be detected so bed rest, if it is used, should ordinarily not exceed 24 hours. Frequent turning, passive range of motion and use of at least an egg crate type mattress are recommended from the outset. Mobilization into a chair or ambulation should be done as soon as possible.

**Diet, Feeding and Swallowing.** The need for nutritional support needs to be balanced with the concern for aspiration which may produce a pneumonia which complicates up to 10% of stroke cases. A decision about oral intake is often not difficult but in all cases should be made within 48 hours of admission, providing that IV fluid support is adequate for the first 2 days. Patients who should be considered high risk for aspiration problems have one or more of these features:

- bilateral or large unilateral hemispheric lesions
- brainstem stroke
- coughing and choking during sipping of water
- prolonged time required for feeding
- obtunded or stuporous condition
- dysphonic voice

Gag reflex is not a helpful sign. The best way to detect swallowing difficulties is with a "modified barium swallow" (MBS) test with video recording. However, it is unclear how many patients benefit from getting this test. I recommend close bedside observation followed by a test with 3 oz of water with a one minute observation afterwards for coughing or a post swallow "wet hoarse" speech. If suspicion persists a MBS is indicated. Speech therapy may help with swallowing training as does sitting the patient in a chair (not upright in a hospital bed) and slight head flexion. If tube feeding is required it should be continued for 2-3 weeks before a decision for a PEG is made unless it is obvious that one will be needed (as in severe brain stem stroke).

**Prevention of Medical Complications.** Pneumonia accounts for about 30% of the mortality from stroke. Aspiration has been discussed above. Most pneumonia after stroke, however, are not caused by aspiration so it may occur in any stroke patient who is immobile despite tube feeding. Aggressive treatment is recommended for most cases.

Cardiac disease accounts for a significant number of the deaths associated with stroke but whether this represents a kind of obligate comorbidity or a cause-effect relationship is unclear. (Love, B, Biller, J., Grover-Mckay, M., Rezai, K: Prevalence of coronary artery disease in patients with cerebrovascular disease. Stroke 1991;22:126.) Large ischemic strokes and subarachnoid hemorrhage can produce transient ECG changes such a

repolarization phase abnormalities including peaked T waves, inverted T waves and prolonged QT intervals. Massive stroke can be associated with a peculiar kind of myocardial injury called "contraction band necrosis" which is distinct from myocardial infarction but which may cause significant dysrhythmia. Extended ECG monitoring is not recommended for all stroke patients but is included in some stroke units. For those with abnormal ECG or a history of significant heart disease it is a good idea. Large ischemic stroke and subarachnoid hemorrhage patients should be in an intensive care unit.

Prophylactic heparin or low molecular weight heparins or heparinoids are strongly recommended for patients with immobility. Intermittent compression devices are an alternative for those who cannot take heparin but stockings have not been shown effective.

Urinary tract problems including incontinence are common after stroke. Initially all stroke patients except those with very minor symptoms should get indwelling catheter until their propensity for urinary retention has been assessed. The Foley catheter should be removed after 2-3 days at the most and the patient monitored for bladder distention. Before removal a urine analysis C and S is recommended; colonization without signs and symptoms of infection does not require treatment but the data on the urine will be useful if infection is suspected in the early days after stroke. Catheter clamping is not recommended. If urinary retention is an issue intermittent cath with recording of the amount of urine and increasing the interval between catheterizations is a method of determining the risk of retention. If after Foley removal the patient is voiding spontaneously the next step is to measure the post stroke residuals which if over 100 cc would prompt a search for a cause for retention such as anticholinergic, fecal impaction, prostate enlargement and/or the use of medications to stimulate bladder contraction. If after removal the patient is not voiding a program of intermittent cath should be undertaken (frequency every 6-8 hours) and volumes monitored to keep them less than 400-500 cc.

The management of neurogenic bladder after stroke is complex and involves the use of measurements of post void residuals and intermittent catheterization as well as medications. The basic problem is to determine if the patient is having more problem with storage or discharge of urine and use appropriate measures and medications to manage the issues as well as possible. The reader is referred to two issues of Stroke-clinical updates, Volume IV (issues 3 and 4) which are available from the National Stroke Association (303 771-1700) for a detailed discussion of management of the stroke patient with urologic problems.

Frequent turning at least every two hours is usually sufficient to prevent skin breakdown.

Prevention of Neurological Complications. Brain edema complicates large MCA distribution strokes and does not become maximal for 3-5 days. Young patient without significant atrophy are at particular risk for severe problems for increase ICP. No routine measures are recommended for mild to moderate edema with less than 2mm midline shift other than basic measures such as treating fever and pain (which increase ICP) and

avoiding hypotonic fluids or hyponatremia which causes the normal brain to swell and may aggravate ICP problems (Williams, M, Hanley, D: Intracranial pressure monitoring and cerebral resuscitation. In: Grotta, J, eds. Management of the acutely III neurological patient; New York: Churchill Livingstone, Inc., 1993: 49-74). If more therapy is needed, the patient needs specialized neuro ICU care for hyperventilation, osmotherapy reduction in cerebral blood flow and possibly surgery for either ventricular drainage or removal of infarcted brain.

Seizures are uncommon after stroke. Treat seizures using established medications such as phenytoin but prophylactic medication is not indicated. I usually keep the patient on medications even after one seizure for the rest of their life although recurrence rate varies widely in the literature and stopping the medication after a seizure free period could be considered.

Serial lumbar punctures are an option only for the hydrocephalus that often complicates subarachnoid hemorrhage. LP may be dangerous in large focal lesions. Surgical consultation should be obtained when CT shows increasing ventricular size. *It is important to note that acute hydrocephalus may cause a rapid deterioration of some patients and CT monitoring of some lesion, particularly those that impinge on the area of the 3rd ventricle may be needed.*

Conversion of a so called "bland" infarct into one with CT evidence of hemorrhage occurs at least 10-30% of the time usually by the third week after infarct but is rarely accompanied by neurological worsening. There is no reason to monitor heparinized patients with serial CT unless there is a clinical change. Neurological worsening is associated with clot formation on CT with mass effect rather than so called "gyral" hemorrhage pattern which if limited probably poses little risk even if anticoagulation is used. Patients who develop hemorrhagic conversion to any degree should be taken off heparin unless a strong case is made for their high recurrence risk outweighing what is probably a real but unclear additional risk of clinical deterioration if heparin is maintained (Hart RG, Easton JD: Hemorrhagic infarcts. Stroke 1986;17:586-589).

### **2.2.5 Chronic Care Issues**

Rehabilitation, who should get it? Families often want and expect extensive rehab for all family members with stroke but the resources should be used judiciously when there is a reasonable expectation of benefit. Virtually all stroke patients except those who are moribund should receive passive range of motion activities; those who are awake should also receive an assessment of early mobility issues especially ability to transfer (which in the early phase is more crucial than ambulation) and therapy directed to maximize this activity. The most important factors to be considered when contemplating a formal rehab program are:

- medical stability
- nature and extent of functional disabilities
- ability to learn

- physical activity endurance

The referral criteria listed in the Agency for Health Care Policy and Research regarding Post Stroke Rehab: Assessment, Referral and Patient Management are reasonable and are quoted from their publication 95-0663, May 1995. A copy can be obtained free of charge by FAX by calling their number from a phone with a receiver to 301 594-2800 24 hours/day.(This actually works.)

1. Patients are potential candidates for formal rehab they have one or more significant disabilities, are at least moderately stable medically, are able to learn, have enough physical endurance to sit supported for one hour and are able to participate to at least some extent in active rehab treatments.
2. Patients are candidates for an interdisciplinary rehab program if they meet the above criteria and also have significant disabilities in at least two of the following areas: mobility, basic ADL, bowel and bladder control, cognition, emotional functioning, pain management, swallowing or communication.
3. Patients with only a single area of disability are candidates for individual rehab but do not require a multidisciplinary program.
4. Patients too impaired to participate in rehab should receive appropriate supportive services and their families should receive thorough education regarding their care.

Some patients may not be candidates for rehab at first but can benefit after they have made sufficient recovery. Patients who are referred for intensive interdisciplinary rehab need to be able to tolerate at least 3 hours of physically demanding rehab activity every day.

Depression/other psychiatric disorders. The prevalence of depression in stroke has been estimated at 10-30% in the acute phase but increases to 20-40% at one year. *I have come to believe it is greatly underdiagnosed and represents a lost opportunity to improve or speed patient recovery.* In addition to the usual DSM features of depression in the post stroke setting a diagnosis of depression should be considered:

- if the patient appears persistently depressed
- there is evidence of diminished interest in activities and a loss or slowing of rehabilitation progress

Treatment has been shown in randomized double blind placebo controlled studies to improve depression scores and perhaps speed rehabilitation. Treatment with nortriptyline at doses of up to 100 mg per day ( q haws) building up the dose over 4 weeks. Trazadone has also been used. Probably any agent that works generally can be tried if these do not work or cannot be tolerated. Less common problems that may be encountered after stroke

are: mania, pathological emotionalism, anxiety and multiinfarct dementia.(Morris, P, Robinson, R: The psychiatric consequence of strokes, including poststroke depression; In: Adams, H, ed. Handbook of cerebrovascular diseases; New York: Marcel Dekker, Inc., 1993: 637-654.)

Pain. The two pain syndromes of note are the **thalamic pain syndrome** which results from stroke in the ventral posterior portion of the thalamus and the so called **shoulder hand syndrome**. The former syndrome appears subacutely after stroke and involves dysesthetic type pain in the opposite extremities and often truncal areas which are usually to some extent hypesthetic. Symptoms may be triggered by emotional upset. Tricyclic antidepressants are often helpful and should be continued for at least 8-12 weeks but may be needed longer. The other syndrome is thought to be a type of reflex sympathetic dystrophy that occurs in patients with paretic arms but in my experience it is now quite rare. It is said to respond to sympathetic block. Good positioning and rehab probably prevents this condition.

Spasticity. Although spasticity is common in the months after significant hemiplegia it is unusual for the patient to be given medication for this condition. The medications work best on spinal cord related spasticity. The first line medications including baclofen and diazepam have central side effects which make them unattractive for elderly patients. The most effective is the muscle targeted agent dantrolene which has a risk of hepatotoxicity. Overall local measures such as passive ranging on a regular basis and treatment of any cause of pain are the most practical and have the fewest side effects. Botulinum toxin has been used but there is no systematic experience. Despite its high cost I have tried it for lower extremity ankle inversion with little evident success but there may be a role yet identified. I am not aware of intrathecal baclofen, which is used for severe spinal spasticity, being used for brain stroke spasticity.

Joint problems. These can be minimized by good rehab but are hard to prevent completely. Surgical release of contracture may be needed if the problem is severe. Severe ankle spasticity can lead to problems which may require motor blocks or surgery but otherwise the limitation of motion at the joint is not a major issue. Pain however may result and will require management.

Driving after stroke. Although stroke is not specifically considered in most states in driving regulations, some countries( e.g. United Kingdom) restrict driving for a time after stroke and require assessments to evaluate fitness for operating a car. There are specific stroke related conditions which prohibit driving in some states, such as hemianopia and epilepsy. Severe hemineglect should also be considered. Relative contraindications such as marked memory loss, poor concentration and severe aphasia should be factored in. In the long run we are often caught between wanting to keep our patient involved in society and protecting them and other from harm. It is suggested that:

- the patient **and** family members be questioned together about their perception as to the stroke survivor's driving capability

- if driving is an issue and there is **any** significant impairment the patient should be counseled to inform their insurance carrier and to contact the Dept of Motor Vehicle in their area and discuss what must be done to retain a valid license after stroke.
- the next step is usually to have their driving assessed by one of these commercial driving assessment services which will use actual testing. They will for a fee do the testing and provide the results to the Dept of Motor Vehicles.
- document your advice to the patient and family.

Sexual function after stroke. Perhaps the best general advice for the physician, patient and family except to have a positive attitude toward adjusting rather than assuming that sex is out of the question and to create an environment where patient can ask questions or send them to someone with whom they may be more comfortable discussing these issues. I particularly recommend the AHA FAMILY Guide to STROKE: Treatment, Recovery and Prevention which can be obtained through their local or state affiliate of the AHA or by calling 1 800 AHA-USA1. Both the AHA and the National Stroke Association have patient oriented newsletters and 800 numbers (NSA # 800 787-6537). I recommend hooking up all your stroke survivors and their families to these resources to help them best recover from stroke.

### 2.3 Embolism from the Heart and Aorta

This stroke subtype accounts for up to 20-25% of stroke. For this discussion cardiac source embolism will be emphasized. The most common cardiac causes include: atrial fibrillation; valvular heart disease (including mitral valve prolapse); mural thrombus (post-MI); other (intracardiac tumor, etc). A venous source of embolus may produce arterial embolism by a "paradoxical" route through a patent foramen ovale.

#### Cardiac Causes of Cerebral Embolism

- Valvular disease
- Dysrhythmias
- Disorders of the Cardiac Wall and Aorta

CT/MR patterns: small cortical branch or major vessel occlusion with early hemorrhagic change; Angiography: occluded vessel(s) in isolation without generalized evidence of atherosclerosis

Clinical evaluation often suggests abrupt symptom onset; there is a higher incidence of early onset seizures and hemorrhagic infarction on CT. CT/MRI patterns include a "major vessel occlusion" or a wedge shaped "cortical branch occlusion" picture of infarction. The latter is considered by some to be inferential evidence of an embolic stroke. Angiography rarely shows a branch occlusion unless it is performed within 48 hours of symptom onset. Distal field or "watershed" patterns are possible but less likely.

#### 2.3.1 Valvular Disease

Some of the important causes of embolism from valvular disease are:

- Rheumatic mitral disease - 3% stroke/yr 30-65% will have recurrent stroke;
- Risk increases (4x) if combined with atrial fibrillation
- Mitral incompetence associated with a lower risk for stroke
- Calcific aortic stenosis less clearly related to stroke risk
- Mitral Annulus Calcification (MAC): may be a significant stroke risk in patients over 60 years - also may predispose to (endocarditis)
- Bacterial and non bacterial endocarditis

Mitral Annulus Calcification(MAC)

Prevalence of MAC in the Framingham study was 10.3% for men and 15.8% for women among 1159 subjects who were entered with echo and no stroke history. In 8 years of follow up, multivariate analysis showed that MAC was associated with a relative risk for stroke of 2.10 (1.24 to 3.57) independent of other more traditional risk factors. Risk persisted (RR = 1.78) when considering only ischemic strokes and accounting for age, gender, SBP, diabetes, smoking, A FIB, CHF and coronary artery disease.(NEJM, Benjamin, et al, Vol. 327 (6) August 8, 1992).

- Mitral Valve Prolapse - "association" in young patients is strong;
- MVP: found in 5-10% of background population but also associated with connective tissue diseases (Marfan's, Ehlers-Danlos, pseudoxanthoma elasticum); MVP is a significant "cause" of stroke in young persons - but risk of stroke in general is low (1/6000)
- Marantic Endocarditis: DIC, AIDS, mucin secreting tumors such as adenocarcinoma of lung, pancreas, colon; hypercoagulable states
- Bacterial endocarditis: seen with abnormal substrate and IV exposure

15% have cerebral embolism, 5% mycotic aneurysms (MCA, distal, multiple); anticoagulation usually not recommended for mycotic aneurysms; surgery only if they expand despite antibiotic Rx;

Strep viridans, Group D and Staph aureus are the usual agents;

- Risk for stroke greater with mechanical than prosthetic valves; and higher for mitral (3-4%/yr) than aortic (1.2-2.2%/yr); mechanical valve patients are anticoagulated; +/- added aspirin

### 2.3.2 Dysrhythmias

**Atrial fibrillation(AF)**. Prevention of stroke in AF represents the most well established use of anticoagulation in neurology. AF increases the risk of stroke five fold.

Nonvalvular atrial fibrillation is common being observed in 2-5% of persons over 64

years of age. Although the presence of AF identifies patients at risk for stroke, whether prophylactic long term anticoagulation is warranted in the absence of embolism remains in debate. It is clear that aspirin provides overall greater benefit in some patients because it poses less risk.

Once an embolic stroke has occurred, early recurrence has been estimated to be as high as 15% in the first 2 weeks and anticoagulation is the standard of care. Anticoagulation may reduce this recurrence rate significantly and the only issue is when to start anticoagulation. Chronic anticoagulation has been advocated for suitable candidates following submaximal AF associated stroke but concern for early hemorrhagic conversion has led some to withhold anticoagulation for 48 hours until a repeat CT can be performed. If the CT shows a large infarct with mass effect or hemorrhage anticoagulation is deferred. However, some disagree with this approach and argue that anticoagulation can be safely administered in the face of hemorrhagic conversion of an infarct. The literature contains examples of both good and bad outcomes with anticoagulation in this setting but no conclusive data. My recommendation is to be withhold heparin if the CT shows hemorrhage unless you document a particularly high recurrence risk and indicate that you think heparin is worth the risk.

**Atrial Fibrillation** - 5X increase in stroke risk Recurrent stroke risk 15% within the first 2 weeks after cerebral embolism; risk is not confined to the period just after AF onset;

**Chronic Sinoatrial Disorder** - definitions and estimates of stroke risk vary but its stroke risk may be 10% or more (note: sinoatrial disorders found in Friedreich's ataxia, myotonic and limb girdle dystrophy);

PVC's, ventricular tachycardia - no increased risk has been established.

#### A-Fib Recent Clinical Trials

- AFASAK(Lancet 1989 I: 175-179)
- BAATAF(NEJM 1990;323(22):1505-1511)
- SPAF I (Circulation 1991, 84:527-539)
- SPINAF(NEJM 1992;327:1406-12)
- SPAF II(Lancet, 1994 vol 343: 687-691)
- SPAF III (Lancet, 1996; 348: 633-638)

The AFASAK study compared anticoagulation with Warfarin to 75 mg. per day aspirin or placebo in over 1200 patients with atrial fibrillation in a randomized, controlled trial. They were followed for 2 years and the endpoints of stroke, TIA and other thromboembolic events (viscera and extremities) were compared. Endpoint occurrence was significantly lower in the Warfarin group compared to either aspirin or placebo. Of 335 patients who received warfarin, therapy was discontinued in 23 due to side effects, all non-fatal; two of these had malignant and 7 had inflammatory conditions discovered after bleeding while on warfarin. These results provide the strongest evidence to date that

prophylactic anticoagulation in atrial fibrillation can safely reduce thromboembolic complications and should be strongly considered in such patients.

The Boston Area Study, BAATAF compared warfarin vs. other therapy (40% on aspirin, 60% placebo). They found a significant benefit from warfarin. The Stroke Prevention in Atrial Fibrillation (SPAF) was in the process of examining the relative benefits of Warfarin vs. aspirin (325 mg/day) vs. placebo when the study was stopped because those in the placebo arm were having more strokes. The study continued (as SPAF II) to settle the question of whether warfarin was significantly better than aspirin for stroke prophylaxis in AF.

The SPINAF was a randomized, placebo controlled trial using warfarin in 571 men with chronic non rheumatic AF. It also found a significant benefit for warfarin over placebo. The SPAF II Study did not really settle the issue. The study compared aspirin and warfarin in two parallel randomized trials involving 715 patients aged 75 years or less and 385 patients over age 75 years. In the younger group warfarin decreased the absolute rate of primary events (ischemic strokes and systemic embolism) by .7%/yr (1.3% vs 1.9%). Among older patients warfarin decreased the absolute rate of primary events by 1.2%/yr (3.6% vs 4.8%). However the overall rate of any stroke with residual deficit, a measure which included cerebral hemorrhages, was 4.6% with warfarin vs 4.3% with aspirin indicating that hemorrhages more than consumed the marginal benefit found for ischemic stroke. In SPAF III, the investigators compared adjusted dose warfarin (the way it is usually given) to fixed, low dose warfarin plus aspirin for primary prevention of stroke in patients with a fib. Although the use of low dose warfarin, given at a dose just sufficient to barely move the INR, but not enough to require checking INR regularly, in combination with aspirin seemed like a good idea it did not work. It was necessary to get the INR to at least 1.5-1.9 before achieving any significant stroke reduction (Lancet, 1996; 348: 633-638) so that this idea has now been abandoned.

In summary, patients with AF but without a history of stroke should be on at least aspirin 325 mg a day, and warfarin provides better protection unless the patient is at high risk for hemorrhage. The differences in stroke risk within AF based on certain other risk factors. On the one hand a patient with "lone AF" has a low risk, less than 5%/yr and, pending better data, should be on aspirin. The patient with hypertension, a poorly functioning left ventricle and a previous thromboembolism has a much higher risk (>10%/yr) and should be on warfarin.

*Recommendations from the American College of Physicians (Guidelines for Medical Treatment for Stroke Prevention. Ann Intern Med 1994;121:54-55): " Warfarin is the drug recommended for patients who are candidates for anticoagulation. However, patients younger than 60 years without specific clinical or echographic risk factors have a low risk for stroke and do not need treatment with warfarin. To achieve an acceptable benefit to risk ratio, it is crucial to carefully monitor the intensity of anticoagulation based on INR, aiming for a ratio approximately between 2 and 3."*

Atrial Fibrillation and Stroke

- Average 5% per year stroke risk which is 6X above baseline;
- 2/3 of strokes believed to be embolic from the heart;
- Recent studies show 4 - 7%/yr overall stroke risk and a spectrum of risk based on clinical characteristics;
- SPAF: 568 control patients, risk varied from 2.5 to 17.6% depending on the number of risk factors;
- From SPAF:- Recent CHF, HBP, Previous thromboembolism
- Risk factors are additive.
- From SPAF: Echo Data
  - LV dysfunction; left atrial size

### 2.3.3 Disorders of the Cardiac Wall and Aorta

In this category are included mural thrombi, ventricular aneurysms, cardiomyopathies resulting in a dilated chamber and patent foramen ovale allowing paradoxical embolization. The most important of these is mural thrombus after myocardial infarction.

- Myocardial Infarction (MI): stroke occurs usually within 4 weeks after MI- highest risk is with large, transmural anterior and anterolateral MI;
- high-incidence of thrombi either by echo (18-30%) or path (35-60%) but much lower clinical incidence of embolism;
- incidence of in hospital stroke with MI is about 1%
- anticoagulation is indicated in the presence of left ventricle thrombus after MI
- left ventricle aneurysms do not justify anticoagulation
- aspirin reduces the risk of stroke after MI
- treatment of MI with TPA and APSAC but not streptokinase is associated with a higher incidence of stroke (1.35%) due to hemorrhage( see Hess et al. Neurologic Clinics 1993;11(2):399-417)
- dilated cardiomyopathy has a 1.4-3.5%/yr risk of stroke

### 2.3.4 Cardiac Indications for Aspirin and Warfarin

Most patients with known cardiac disease including angina and myocardial infarction should be on aspirin to prevent recurrent MI. Warfarin is usually reserved for patients with severe valvular disease or artificial heart valves.

### 2.3.5 Cardiac Comorbidity

It is important to discuss Cardiac Comorbidity. This term refers to the fact that patients with ischemic stroke (and most with TIA) have a high probability of also having coronary artery disease. Studies examining this question have found as high as 50% of TIA and

elderly ischemic stroke patients have evidence of CAD on noninvasive testing which can detect myocardial ischemia.

Stroke patients have a greater chance of dying from an MI in the five years after becoming symptomatic than from a recurrent stroke. It is imperative, then, to look hard for high cholesterol, unstable angina, unrecognized MI, etc. in these patients. The management of asymptomatic CAD is as controversial as that of asymptomatic carotid disease. But at least patients can be identified, counseled as to their risk and as to recognition of angina symptoms, etc. Calcium antagonist might also be used in some patients. Smoking cessation and a cholesterol < 240 are essential.

- Studies of patients with TIA, asymptomatic bruit or stroke demonstrate about a 5%/year risk of cardiac death.

### 2.3.6 TEE/Paradoxical embolism

Transesophageal echo (TEE) is superior to transthoracic in the detection of left atrial and atrial appendage thrombus, patent foramen ovale, atrial septal aneurysm, spontaneous echo contrast ("Smoke"), and myxomatous MV degeneration. The degree to which these entities contribute to the risk of cerebral infarct remains to be established. TEE is usually reserved for younger stroke patients in whom other testing including transthoracic echo has not resulted in a likely candidate mechanism for stroke.

Patent Foramen Ovale - may be a potential source of emboli but it is seen in 17% of otherwise normal folk and the risk for stroke is not clear. The prevalence of PFO has been reported to be much higher in "cryptogenic" stroke than in cases with other more common risk factors suggesting that it may be an important underrecognized cause of stroke. While PFO is easily detected with echo or Transcranial Doppler techniques the diagnosis of a paradoxical embolism (due to PFO) is difficult and is usually proposed in the patient without a clear cause of stroke who has other evidence of venous clots usually in the legs. (See: Cardiac Brain Embolism: Incidence, Varieties, Treatment, Streifler, Furlan and Barnett, in Stroke: Pathophysiology, Diagnosis and Management, Barnett, Mohr, Stein and Yatsu, eds, Churchill-Livingstone, 1992, pp.967-994)

### Aortic Arch Atheroma

- ulcerated plaques were present in 26% of 239 patients with cerebrovascular disease at autopsy compared to 5% of 261 with other neurologic disease
- adjusting for other causes aortic arch ulcerated plaques seemed to exert an independent risk especially in patients with no other obvious cause for stroke
- another reason to get a TEE

(Amerenco et al., NEJM 326(4): 221-5, 1992)

## 2.4 Lacunar Stroke

### 2.4.1 Risk Factors/ Pathogenesis

Attention to this type of stroke as a separate entity is due to the work of C.M. Fisher. The designation "lacune" refers to small, subcortical infarctions, usually less than .5 cm produced by occlusion of either one or several penetrating lenticulostriate arteries (from the MCA) or thalamoperforant arteries (from the basilar termination or PCA). The pathology of arteries so affected is described as "lipohyalinosis" or "fibrinoid necrosis" of penetrating vessels although microatheroma may also play a role.

Hypertension, and to a much lower extent, diabetes mellitus are the key risk factors. No clear cut racial predominance has been demonstrated. CT is positive in about 40-50% of cases. Better sensitivity is seen with MRI. A number of clinical "lacunar syndromes" have been described:

- pure motor hemiparesis (face, arm, leg): internal capsule (posterior) corona radiata, other areas;
- pure sensory stroke (arm, leg, face and trunk): thalamus (ventral posterior);
- ataxic hemiparesis (leg weakness, arm and leg ataxia): pons;
- dysarthria-clumsy hand syndrome (upper limb dystaxia, dysarthria, weakness, may also have facial weakness, and dysphagia): internal capsule (anterior), pons;
- movement disorders (hemichorea; hemiballism, dystonia): caudate, subthalamus;
- sensorimotor (rare, sensory may be of the hemibody pattern): border of the internal capsule and thalamus.

### 2.4.2 Management

Lacunar stroke is best prevented by good blood pressure and serum glucose control. Many physicians treat patients with lacunar stroke with aspirin or ticlopidine for prevention of recurrent stroke although the efficacy of treatments have not been separately evaluated for this type of stroke compared to other mechanisms. It is clear that patients with lacunar stroke have a lower risk of death, recurrent stroke, carotid stenosis and cardiac source of embolism (CSE). An important operational issue is whether this risk of carotid disease and CSE is so low that looking for it is a waste of time. In reviewing this question I found data from several series that indicates a much lower risk of carotid stenosis, 3-17% vs 37-65% for other subtypes combined, but the prevalence rate is still over 10%. The likelihood, in my opinion is still high enough that a work up with ultrasound is reasonable in most patients with a lacunar type presentation. Likewise, 3 studies looking at the prevalence of CSE in lacunar vs other subtypes showed lower rates, 10-15% vs 20-35%. Again, although lower the prevalence may not be negligible and consideration for at least a transthoracic echo should be given for most patients with lacunar stroke. Another very interesting issue is whether patients with lacunes are destined to have only more lacunes or other stroke subtypes. This was looked at in the Dutch TIA/Stroke trial and at the Mayo clinic (Sacco et al, 1991). Both reports indicate that a minority of recurrent strokes, 28 and 17%, are lacunes and the rest are other

subtypes. So it appears that patients presenting with lacunes have or will develop other potential stroke etiologies in many cases and a respect for this fact should guide workup and management.

## 2.5 Intracerebral Hemorrhage (ICH)

This entity refers to direct bleeding into the brain substance. The biggest risk factors are hypertension (90%) and oral anticoagulants (9%). Diabetes and cholesterol are not strong risk factors. Bleeding has been attributed to rupture of small vessels weakened by years of hypertension.

### Intracranial Hemorrhage/ICH

- Putamen (50%), lobar, thalamic, cerebellar, pontine (10-15% each)
- Small vessel pathology; coagulopathy; drugs
- Indications for angiography based on clinical setting and CT
- Management: reverse coagulopathy, treat mass effect

Do not abruptly lower blood pressure if mass effect is present

### WHEN THE CT SHOWS BOTH SUBARACHNOID AND INTRAPARENCHYMAL HEMORRHAGE:

\*\*It is safer to assume that a ruptured aneurysm caused intracerebral extension with minimal subarachnoid blood than it is to ascribe the subarachnoid blood to a "hypertensive" hemorrhage.\*\*

#### 2.5.1 Risk Factors

Hypertension is the primary risk factor (along with age) for ICH. ICH due to hypertension is characterized by the lack of a tendency to rebleed. The clinical picture is distinguished from cerebral infarction by a higher incidence of headache, nausea and vomiting and lethargy. Diagnosis is readily made by CT.

#### 2.5.2 Clinical Presentation/ Prognosis

Patients present with acute or subacute onset of focal symptoms often with the history of a headache. The headache typically is not as sudden as that of subarachnoid hemorrhage and may be more focal.

#### Prognostic Factors

- a) Clinical condition on admission
- b) Size, depth and location of hematoma
- c) Pineal calcification displacement on CT
- d) Ventricular extension of blood

## e) Hydrocephalus

### 2.5.3 Location

Anatomic locations in a rough order of frequency are: putamen, lobar, thalamic, cerebellar, pontine, other.

### 2.5.4 Management

Management involves identification of cause, especially if a treatable coagulopathy is involved and treatment of the patient for the mass effect created by the lesion. Except as noted surgery is usually not performed but use of ventriculostomies to control ICP may be helpful in salvageable cases with extensive mass effect. The prognosis is related to the size and location of the clot. In general, surgery for putaminal hematomas has been considered only for nondominant hemisphere lesions of such a size as to threaten survival. Proponents of evacuation of putaminal bleeds have so far failed to show that the surgery results in more high level survivors. In contrast, removal of lobar clots is accomplished more easily but is often unnecessary as the increased intracranial pressure can be managed non surgically. However, in some cases removal of temporal or frontal hematomas, especially when they are in the non dominant hemisphere, is advocated to increase survivorship without adding measurably to the morbidity.

### 2.5.5 Special Etiologies and Situations

Causes other than hypertension that need to be considered: small AVM's, drug abuse (more often lobar than putaminal), cerebral amyloid angiopathy ("congophilic angiopathy", usually affecting older patients, tending to be lobar in posterior parietal or occipital regions), tumors, anticoagulant and thrombolytic drugs and coagulopathies, severe pain or cold exposure and the hyperperfusion state after carotid enterectomy. Angiography is used in cases involving drug abuse, absence of hypertension or when CT appearance of the bleed is atypical suggesting aneurysm or arteriovenous malformation.

Amyloid or congophilic angiopathy, is clinically characterized by recurrent lobar (mostly parietal and occipital) hemorrhages in the elderly (sometimes in the absence of HBP). There are familial forms occurring in Iceland and the Netherlands. The process involves amyloid deposition in small, leptomeningeal arteries producing thickening of the vessel media. Clinically, the hemorrhages are often symptomatic but unrecognized small infarctions have been noted at autopsy. (See the NEJM Case Record of Vol. 318 (10), March 10, 1988 for a discussion by C.S. Kase and J.P. Vonsattel.)

#### Amyloid Angiopathy

- Sporadic and familial forms
- Relationship to Alzheimer's

- Pathological Spectrum
  - Lobar hematoma
  - Infarction
  - White matter disease
  - Senile plaques/tangles
  
- Clinical spectrum
  - Hemorrhage (ICH, SAH, SD, IVH)
  - Infarcts
  - Dementia (40%)

Two special ICH situations merit specific discussion:

Cerebellar Hematoma represents a neurological/neurosurgical emergency in which the outcome greatly depends on the initial recognition and management. Symptoms include sudden occipital headache with nausea and sometimes ataxia. Cranial nerve, motor findings and abnormal reflexes may be absent. The hematoma may be relatively well tolerated until edema produces sudden deterioration from brain stem compression at which time surgery may be too late. Diagnosis is made by CT and patients are managed in the ICU with surgery being the usual recommendation for lesions over 3.0 cm in diameter. Outcome of surgery performed before the "crash" is usually good.

Intraventricular Hemorrhage (IVH) is a subset of intracranial bleeds which can be caused by extension of putaminal, thalamic or caudate bleeds into the ventricular system associated with hypertension or other predisposing factors or extension of bleeding from a ruptured aneurysm often arising from the anterior communicator. While often said to be a grave prognostic sign the prognostic significance of IVH in fact depends on the extent and nature of the parent lesion. For instance, when a putaminal bleed extends into the ventricles it is usually a large bleed with a poor prognosis anyway. A thalamic bleed which extends into the third ventricle also often tracks into the midbrain causing initial coma. Conversely, a caudate hemorrhage from the caudate, which lies close to the lateral ventricle, is not associated with a poor prognosis unless there is also a third ventricle clot. A clot in the third ventricle from any source can be associated with delayed deterioration and death due to acute onset of hydrocephalus. This complication can be prevented by diligent observation and CT of the patient at risk and use of ventricular drains. In some cases thrombolytic agents have been given intrathecally to speed the dissolution of the clot.

## **2.6 Subarachnoid Hemorrhage (SAH)**

The American Heart Association has recently published guidelines for the management of SAH (Stroke 1994;25(11):2315-2328).

## Intracranial Hemorrhage:SAH

- Symptoms: severe headache, syncope, seizure, vomiting
- Aneurysm locations - Circle of Willis
- Prevention of rebleeding/early surgery
- Prevention and treatment of delayed arterial vasospasm using nimodipine 60 mg p.o. q 4 hours and
- Hypervolemic, Hypertensive Hemodilution (triple "H" therapy)

Accounting for about 10% of strokes, SAH results from extravasation of blood into the subarachnoid space. Most often it is caused by a ruptured saccular aneurysm; other causes include AVM, head injury, sinus thrombosis, and bleeding disorders. The clinical presentation is marked by non focal symptoms including photophobia, early headache with nausea and vomiting, sometimes brief deterioration of consciousness, and/or seizures. Aneurysms are present in 6% of population, but the annual rupture rate is only 10-12 per 100,000. Clinical course and prognosis are discouraging. Only 30% do well, surviving without major disability. Of the survivors who are not surgically treated, the rebleed rate is usually quoted at 3% per year. As many as 25% of victims in U.S. and Canada are misdiagnosed initially and do not receive definitive therapy due to late referral. Diagnosis is by CT scan which shows subarachnoid blood, localized hematoma (when in the temporal lobe or sylvian fissure suspect MCA aneurysm) or by lumbar puncture. The CT may show the aneurysms themselves when they are greater than 10 mm in size. The likelihood (and distribution) of subsequent delayed vasospasm can be estimated from the location of the SA blood on the initial CT. A negative CT does not rule out SAH.

Angiography is definitive in most cases. If multiple aneurysms are encountered, the size and configuration of aneurysm as well as clinical and CT data are used to infer the one that ruptured. Negative angiography occurs in 13-22% of SAH. However, the prognosis is generally considered to be better in these patients compared to angio positive cases. Although the bleeding source is unknown, leakage from lenticulostriate and thalamoperforant vessels has been postulated in those cases in which aneurysm is not detected.

## Intracranial Hemorrhage/SAH

- Usually caused by the rupture of an aneurysm arising from the Circle of Willis (if trauma excluded)
- A variant is the "perimesencephalic hemorrhage"
- described by Van Gijn and colleagues (Neurol,35:493-497,1985)
- Perimesencephalic Hemorrhage- Accounts for up to 10% of SAH but 50% of SAH with negative angiography

- The slow onset of HA, predominance of blood in the perimesencephalic cisterns and the excellent prognosis
- suggests venous or capillary source of bleeding.
- Diagnosis: based on CT and a single negative angiography

The following are general statements about treatment of SAH: 1) patients admitted in good condition do better regardless of the timing of surgery; 2) while early surgery lowers rebleeding risk (highest during the first week after SAH, occurring in about 20% of non-operated cases), it is associated in some series with a higher incidence of delayed vasospasm. Most vasospasm is reversible and outcome may not be adversely affected. Many neurosurgeons now recommend delayed surgery in patients entering the referral center in Grades III or IV (Hunt and Hess classification); 3) the use of antifibrinolytics (e.g. Amicar) continues to be debated; a recent review of the experience of an international cooperative study (J. Neurosurg. 1984;61:225-230) suggested that the decreased incidence of rebleeding with antifibrinolytics is offset by a higher incidence of delayed complications leaving morbidity and mortality unaffected. 4) medical therapy to prevent or reverse delayed ischemic deficits from vasospasm has been advocated using nimodipine and/or plasma expansion and hypertensive therapy (after clipping). Current trials are testing nicardipine, another calcium antagonist, and tirilazad, a free radical scavenger.

Two randomized controlled trials have shown that nimodipine (60 mg po q 4 hours for 21 days) improved outcome in both good (Allen, et al., NEJM 308:619-624, 1983) and poor (Petrucci, et al., J. Neurosurg. 68(4), 505-517, 1988) grade SAH patients. It should be noted that in neither study was angiographic degree of vasospasm affected. The beneficial effect is apparently mediated by some action other than reduction of large vessel vasospasm. (See: Stroke, A Clinical Approach, by L.R. Caplan and R.W. Stein, Butterworth's 1986).

## SAH

- Rebleeding rate: 15 - 20% in first 2 weeks
- Rebleeding risk after six months has been estimated at 3%/year
- 10% of SAH patients have a family history
- Associated conditions: polycystic kidney disease, coarctation of aorta, Marfan's, Ehlers-Danlos, FMD, pseudoxanthoma, elasticum, Moya Moya, AVM's

## PREVENTION OF ISCHEMIA FROM VASOSPASM

- Period of risk: 5-21 days post SAH
- Patients with SAH are volume depleted and develop hyponatremia due to salt loss
- Patients need plasma expansion with at least 3 l/day and

- Nimodipine 60 mg p.o. every 4 hours for 21 days

### 2.6.1 Risk Factors and Related Conditions

This type of stroke is least related to hypertension although it may play some role. Smoking has also been implicated in some studies as has acute alcohol use. Drugs may cause SAH or ICH. Unruptured aneurysms are the major risk and are present in 1-2% of the population.

### 2.6.2 Clinical Presentation

The presentation of SAH with the acute onset of severe headache without focal symptoms but often with vomiting, syncope or seizure is among the more well known scenarios in clinical medicine. Less severe headaches due to a "warning leak" may be harder to recognize and a high index of suspicion is recommended for atypical and new onset headaches.

### 2.6.3 Aneurysms: etiology, size and location

### 2.6.4 Management of the Morbidities of SAH

Prevention and Treatment of Neurological Complications:

- prevent rebleeding by early clipping of the aneurysm; antifibrinolytics have been tried but do not provide overall benefit;
- prevent ischemic stroke from vasospasm by "HHH" therapy which is *hypervolemia, hemodilution* and if necessary *hypertensive* therapy along with nimodipine
- look for hydrocephalus with repeat CT scans and treat either with repeated lumbar punctures or intraventricular drainage
- consider surgery to remove large intraparenchymal hematomas. Management of the patient with SAH is complex and should only be attempted in a tertiary neurological/neurosurgical ICU setting.

Rebleeding. Rebleeding has been estimated at 4% the first day after the initial bleed, 1-2% per day for the next few weeks then gradually stabilizing at a rate of 3% per year. Prevention of rebleeding is best accomplished with direct surgical repair of the aneurysm.

Vasospasm. "Vasospasm" is perhaps a poor name for this entity because it implies a highly phasic event (like a muscle spasm) when in fact the time course of this process is over days to weeks. This complication starts about 305 days after SAH and may go on for several weeks. The arteries undergo gradual narrowing and when the reduction in lumen is significant the patient may suffer the added insult of an ischemic stroke on top of injury to the brain from SAH. Vasospasm may be lessened or prevented by the use of

aggressive plasma expansion (Hypervolemia), reduction in hematocrit (Hemodilution) and, if necessary and after the aneurysm is identified by angiography and clipped at surgery, the cautious elevation of blood pressure (Hypertension). Standard care now includes the use of 60 mg q 6 hours of nimodipine p.o. for up to 21 days after SAH. Intravascular techniques including injection of papaverine and angioplasty are being tried at larger centers but their role for treatment of VSP has not been clarified as of yet.

Medical Complications. Prevention and treatment of medical complications includes:

- cautiously treat elevated blood pressure
- prevent depletion of plasma volume
- treat hyponatremia....this is not SIADH but it caused by natriuresis...give saline and Florinef
- monitor for and treat cardiac dysrhythmias

### 2.6.5 Surgery and Other Techniques

Surgical therapy continues to be debated but the trend in the US is towards early angiography and surgery (within the first 2-3 days) followed by aggressive management to prevent vasospasm. Although there are a variety of techniques for dealing with aneurysms other than clipping most of these are considered distant second choices and not as effective.

### 2.6.6 Other Causes of SAH

Is the SAH from a ruptured aneurysm? Unless there is evidence of head trauma, a ruptured aneurysm is the presumed cause. About 10-15% of the time the first angiogram does not show an aneurysm. In such cases a repeat angio is often performed in 2-3 weeks and shows a lesion in the minority of cases. Recently a pattern of SAH not associated with aneurysm has been described which is called "perimesencephalic hemorrhage". In this scenario the bleed is restricted to the interpeduncular prepontine and ambient cisterns around the midbrain with very little blood elsewhere. The patients have a good clinical course and a negative angiogram. The reason for identifying such patients, it is argued, is that a single angio suffices and the patients can be reassured of a good long term prognosis. The speculation is that the bleeding comes from venous or capillary sources.(van Gijn and Wijdicks, in Handbook of Cerebrovascular Disease, Marcel Dekker, 1993 pp 467-508 and Adams and Love, in Stroke Pathophysiology, Diagnosis and Management, Barnett,Stein, Mohr and Yatsu eds, Churchill-Livingstone, pp 1029-1054).

### 2.7 Cryptogenic Stroke

- Believed by some to represent primarily unrecognized embolism
- CT or angio have no distinguishing features except the absence of clues to other, better defined mechanism

Despite modern diagnostic tools a distressingly high percentage of ischemic stroke cases (as much as 25%) remain difficult to classify in terms of mechanism.

### 3.0 Less Common Causes of Stroke and other Issues

#### 3.1 Drug Abuse.

Illicit drugs associated with stroke include opiates such as heroin, amphetamines, cocaine and phencyclidine. Mechanisms include acute dramatic increases in blood pressure, associated myocardial infarction, complications with intravenous delivery and perhaps arteritis. Amphetamine abuse can produce a necrotizing angiitis involving medium sized arteries. Hemorrhages occur with oral and IV abuse; infarcts with any route of administration. In some but not all cases it is associated with an angiographic appearance of "arteritis". It is not clear how amphetamines cause angiitis, but direct toxicity, vasospasm and/or hypersensitivity have been proposed as mechanisms. (See: J.F. Rothrock, et al., "Ischemic Stroke Associated with Metamphetamine Inhalation", *Neurology*, 38; 589-592, 1988.)

For cocaine, the risk involves both infarction and hemorrhage and attends any form of the drug in any mode of administration. Seizures are the most common neurologic complication of cocaine or crack abuse. Strokes and transient ischemic attacks have also been reported. To date, ischemic strokes, subarachnoid hemorrhage and intracranial hemorrhage have all been reported as complications of cocaine abuse. Recently a case of anterior spinal artery syndrome associated with cocaine abuse was reported. Generally, the relation of symptoms to cocaine use is either instantaneous or within minutes to a couple of hours. Some of the patients with subarachnoid hemorrhages have had AV malformations or saccular aneurysms noted on angiography. Cocaine abuse, by an interaction with blood pressure, probably promotes rupture of these vascular abnormalities. Some reports refer to vasculitis, however, there is no clear pathological confirmation of vasculitis in any neurovascular complication of cocaine abuse. It is possible that what might be interpreted as vasculitis is actually vasospasm. Some of the patients with ischemic strokes secondary to cocaine abuse have had normal angiography. Cocaine can precipitate myocardial infarctions and ventricular arrhythmias. It is thought the pathophysiology could involve the blockade of norepinephrine and epinephrine from presynaptic uptake. This increase in norepinephrine and epinephrine in the synaptic cleft would potentiate adrenergic transmission and lead to increased blood pressure, perhaps vasoconstriction and even ischemia.

It is prudent to perform an angiogram on any patient who presents with a stroke associated with cocaine abuse to look for a saccular aneurysm or AV malformation. (See: "Neurological Complications of Cocaine Abuse" by Mody et al. in *Neurology*, August 1988 pp. 1189. One could also see Wojack, "Intracranial Hemorrhage and Cocaine Use", in *Stroke*, 1987 Vol. 18, 712-715 and lastly Schwartz, "Subarachnoid Hemorrhage Precipitated by Cocaine Snorting", *Archives of Neurology*, 1984, Vol. 41, pp. 705.)

## 3.2 Arteritis

Temporal arteritis. Also known as "giant cell" arteritis, it is an inflammatory disease involving medium and large arteries systemically, including the extracranial circulation of both the anterior and posterior systems. TA is uncommon in patients less than 60 years of age, and is almost always associated with an elevated ESR. Intimal proliferation and fibrosis result in lumen stenosis and thrombosis, threatening mainly vision by producing anterior ischemic optic neuritis (AION). The retinal circulation can be affected by posterior ciliary vessel involvement and/or central retinal artery occlusion. Prominent symptoms include headache, scalp tenderness, jaw claudication, constitutional symptoms (polymyalgia rheumatica), and neuropsychiatric symptoms, including depression and confusion.

### Cranial Arteritis

- Temporal (giant Cell)
- Isolated CNS angiitis
- Polyarteritis Nodosa
- Wegener's Granulomatosis
- post Zoster

Visual loss is often sudden and usually monocular. Findings include decreased visual acuity, swollen optic disc, altitudinal and inferior field cuts. Ophthalmoplegia (15%) results from III nerve (pupil is spared) or VI involvement. Stroke is uncommon, but may be the presenting symptom. Reports suggest that symptomatic vertebral artery involvement exceeds that of the extracranial carotids. Intracranial vessels (beyond the dura) are usually spared. Steroids are therapeutic and should not be delayed pending temporal artery biopsy.

### Giant Cell (Temporal) Arteritis

- Inflammatory condition affecting aorta and branches;

Stroke is well known but rare

Stroke with thrombosis of vertebral or internal carotid artery

- Intracranial involvement of vessels is rare

### Isolated Granulomatous Angiitis of CNS

Rare: recurrent small strokes with small leptomeningeal vessel involvement, abnormal CSF; not-confined to elderly and does not respond to steroids; few systemic clues or symptoms. Infections. Pial artery (cortical) involvement occurs in bacterial meningitis and may result in infarction. Organisms producing basilar meningitis with involvement of the MCA and penetrating vessels include: TB, cryptococcus and histoplasmosis. "Heubner's arteritis" is a term used to describe the thickening and inflammation of arteries in this setting. Involvement of the branches of the ICA can be seen after Herpes Ophthalmicus. During secondary syphilis, involvement of cerebral arteries may occur and can cause stroke as well as other neurologic manifestations (myelopathy).

Although not clearly an infection, neurosarcoidosis must be considered a potential (but rare) cause of stroke. Involvement is more likely to be concentrated at the venous, however, rather than the arterial level. Other inflammatory disease associated with stroke but with mechanism poorly defined include: ulcerative colitis, Crohns, and Wegener's granulomatosis.

Arteritis related to Autoimmune Disease. Autoimmune diseases ("collagen vascular disease") are associated with stroke; primary inflammation of arteries, however, is rare, even in SLE, and is restricted to small penetrating vessels. Other causes of stroke in these patients may be related to renal disease, coagulopathy, endocarditis. Very rare causes of stroke include polyarteritis nodosa and rheumatoid arthritis. In fact, with SLE, most strokes are probably related to mechanisms, especially cardiac, besides CNS vasculitis. (See: P.M. Moore and T.R. Crupps, "Neurological Complications of Vasculitis" *Ann-Neurol* 14(2), p.155-167, 1983).

Takayasu's Disease. This disease affects the vessel wall brachial vessels originating from the aorta with mononuclear infiltration and progressive narrowing. It primarily affects young women. Neurologic symptoms include headache, dizziness, syncope and, rarely, stroke. Steroids have been used, but the optimal therapy is unclear.

### 3.3 Fibromuscular Dysplasia

This idiopathic condition is characterized by vessel wall and smooth muscle abnormalities in small and medium sized arteries, notably the renal and internal carotid. Other arteries involved include the vertebral and intracranial vessels. An association with intracranial aneurysms has been noted. The pathology is not entirely unique, being characterized by smooth muscle hyperplasia, fibrous tissue proliferation and disorganization of the arterial wall. Notably absent: atherosclerotic changes, inflammatory infiltration, calcification. Clinically, the disease is most common in middle aged females. It may present as a cervical bruit or subjective tinnitus; occasionally cervical and/or facial pain or Horner's syndrome occurs. FMD may cause severe stenosis and occlusion of the ICA or vertebral arteries. Incidence of stroke has been estimated from 0-28%.

### Fibromuscular Dysplasia

- Carotid-renal arteries involved
  - Pathology: three types have been described: adventitial, intimal and medial (most common)
- Females predominate in the common (medial) variety
- .6% of angios done at Mayo showed FMD
- Treatment: ASA/anticoagulation/surgery

The key to the diagnosis is angiography. Features include: irregularly spaced areas of concentric narrowing ("string of beads"), seen in 80-90%; tubular stenosis (4-12%), abnormalities such as dissection or false aneurysm may also occur. These findings are usually seen in the distal ICA rarely extending intracranially and also in the cervical vertebral artery. The optimal treatment for either symptomatic or asymptomatic cases is unclear. Overall prognosis is good, suggesting that surgery should be limited to high grade symptomatic stenotic lesions. Antiplatelet agents have also been advocated to prevent stroke. (See: Caplan and Stein, p. 183-183.)

### 3.4 Arterial Dissection

Arterial dissection has been recognized in the extracranial and/or intracranial carotid and vertebrobasilar arterial systems. Among these, basilar dissection is considered the least common. Dissection should be considered in the setting of abrupt unilateral head or face pain, bruit, TIA, stroke (or no neurological symptoms). In some cases of carotid dissection, a Horner's, or lower cranial nerve palsy may be seen. A history of craniocervical trauma (including sports) is present in 50% of recognized cases. Patterns of head, neck and/or face pain may be quite focal and specific and should arouse suspicion on this basis. The diagnosis is usually entertained in younger patients. Dissection and hemorrhage into subintimal, medial or, less often, adventitial layers has been demonstrated by pathology. There are several distinctive but not entirely specific arteriographic features, including: long "string sign", total occlusion, pouches or false aneurysms. The natural history is unclear; however, TIA's and evolving stroke are not uncommon. Treatment is controversial. Recommended practice includes: 1) immediate anticoagulation with heparin, then warfarin for 3 months, followed by a re-imaging procedure to determine lumen characteristics. Surgery may be considered in cases in which medical therapy fails to prevent recurrent symptoms. (See: R.G. Hart and J.D. Easton, "Dissections of Cervical and Cerebral Arteries", in Neurologic Clinics, Vol. 1(1), 1983.

### 3.5 Coagulopathy

Disorders of the coagulation system predisposing to CNS hemorrhage include classical hemophilia and a host of less common factor deficiencies (IX, von Willebrand, VI, VII, XII, XIII). There has been recent interest in conditions which predispose to thrombosis as potential causes of stroke. Antithrombin III (which inactivates thrombin) deficiency predisposes to venous thrombosis and pulmonary embolism. A few cases of cerebral arterial thrombosis with antithrombin III deficiency have been described. It can be

inherited (as an autosomal dominant) or acquired (as in severe renal disease). Relative Protein S deficiency may predispose to stroke, but data are, as of yet, inconclusive.

Recent attention has been directed to the presence of "lupus anticoagulants", also called "antiphospholipid" or "anticardiolipin" antibodies (APA or ACA) in patients with otherwise unexplained cerebral infarction. Circulating "lupus anticoagulants", despite the name, predispose to arterial and/or venous thrombosis. Clinically, their presence should be suspected in young ischemic stroke victims; other evidence of autoimmune disease is often present but may be lacking. Most (but not all) have a prolonged PTT. Laboratory confirmation is by: false positive VDRL, coagulation tests for the anticoagulant, or RIA or ELISA tests for anticardiolipin antibody (the most sensitive and specific). A history of spontaneous abortions is often present.

### Antiphospholipid Antibody and Cerebral Ischemia

- General Features
  - young, female preponderance
  - minority with SLE
  - prior thrombosis or stroke
  - spontaneous abortions
- Pathology
  - thrombotic occlusions with no evidence of inflammation
- Laboratory
  - low titer ANA in half
  - thrombocytopenia in one third
  - prolonged aPTT in one half (lupus anticoagulant)
  - mitral valve lesions in some patients
- Associated signs/symptoms
  - migraine
  - amaurosis fugax
  - chorea
  - livedo reticularis

The prevalence of these antibodies in the general population is unknown. Associated conditions besides SLE include other autoimmune diseases, malignancy and infectious diseases. A number of reports now link the antibodies with TIA and stroke. The incidence of these antibodies in patients with TIA and stroke is probably about 6-8%. Cerebral angiography shows large artery stenosis or occlusion in about 50% of CNS symptomatic cases. Treatment of symptomatic patients is currently empirical; both antiplatelet agents and anticoagulation have been advocated. I recommend use of anticoagulation in cases with high titers (> 40) of IgG and with a slightly higher target for the INR of around 4. Lupus anticoagulants, livedo reticularis and stroke have been labeled "Sneddon's syndrome". (See: Hess, D. Stroke Associated with Antiphospholipid Antibodies, Stroke 1992, suppl I: 23-28.)

One of the important aspects of recognizing this is that some workers in this area believe that recurrent stroke in the presence of significant antiphospholipid antibodies is best prevented with anticoagulation at an INR of 3-4, rather the usual 2-3.

### 3.6 Venous Infarction

Cerebral venous thrombosis can involve cerebral draining veins or the large intracranial sinuses. Older studies cited infection as the leading cause. More recent reports implicate oral contraceptives, pregnancy, postpartum period and systemic conditions producing coagulopathy such as malignancy. Etiologic considerations have been divided into factors which cause:

1. Changes in blood constituents;
2. Changes in vessel wall;
3. Changes in blood flow and miscellaneous causes.

Among the conditions associated with venous thrombosis 1): Antithrombin

III deficiency, oral contraceptives, polycythemia, pregnancy, paroxysmal nocturnal hemoglobinuria, adenocarcinoma, nephrotic syndrome (causes acquired antithrombin III deficiency), DIC, and leukemia. Invasive disease of the vessel wall is seen with cancer, sarcoidosis, meningitis, Wegener's granulomatosis, aspergillosis, and mastoiditis. Dehydration, cardiac failure, COPD, and congenital heart disease are potential causes of venous thrombosis by mechanism #3.

Patients with malignancy may have venous thrombosis by leukostasis, invasion of vessel wall, hypercoagulable state, or altered coagulation due to chemotherapy (example: antithrombin III deficiency with asparaginase deficiency). Thrombosis in any patient raises the likelihood of cerebral venous thrombosis. Symptoms may be produced by raised ICP or infarction (often hemorrhagic and not clearly defining an arterial territory). Seizures are not uncommon. Stepwise progression of symptoms has been described.

### Venous Thrombosis

- Usually occurs in a setting of altered coagulation state (unless direct invasion of the vessel by tumor or infection)
- Causes: pregnancy and post partum, estrogen effect, coagulopathy (adenocarcinoma, DIC), dehydration (usually children), hyperviscosity, invasion by infections or neoplastic lesions.

A specific form of venous occlusive disease is cavernous sinus thrombosis (CST). Antecedent sinus or periorbital infection is the rule although facial or cranial trauma may precede CST. Headache, chemosis, proptosis, ophthalmoplegia and, in some cases,

blindness should prompt consideration of CST. Bacterial agents include beta-strep, staph, and H-flu.

The optimal treatment is controversial. Anticoagulants have been used without clear cut adverse effects in most cases. Mortality is high, being estimated at 15-20%. Thrombolytics have been used. (See: Gates and Barnett, "Venous Disease: Cortical Veins and Sinuses", in Stroke: Pathophysiology, Diagnosis and Management, Church Hill-Livingston, 1986.)

### 3.7 Stroke and Pregnancy

There are some special considerations when it comes to stroke in the patient who is pregnant. Some of these are diagnostic and others therapeutic.

- Search for a Cause is Important
  - for Prevention of Recurrence
- Causes include all etiologies of " Young Adults" plus some pregnancy specific ones
- 90% of stroke during pregnancy are arterial;
- 80% of strokes in puerperium are venous
- Treatment decisions are affected by Consideration of the Fetus

#### 3.7.1 Pregnancy Specific Causes of Stroke

##### 1. eclampsia and preeclampsia

- seizures or coma) + hypertension, proteinuria and edema
- preeclampsia seen in 5-7% of pregnancies
- CT in eclampsia shows edema and rarely intracranial hemorrhage
- MRI can show reversible white matter lesions
- hemorrhages due to hypertension;( ?+ DIC)
- cerebral edema due to loss of autoregulation

##### 2. coagulopathy

- relative hypercoagulable state: rise in fibrinogen; decreases in ATIII, prot S and C; hyper platelets
- DIC
- higher ATIII complex levels; lower (88%  $\pm$  27% of normal ATIII); higher plasminogen activator levels; ATIII activity decrease correlated with severity of eclampsia;

### 3. cerebral embolism

- peripartum cardiomyopathy
- air and amniotic fluid embolus
- fat embolus ( esp with SS or SD disease)
- tumor cells from choriocarcinoma

#### 3.7.2 Treatment Considerations.

How should pregnant women with TIA and minor stroke be treated for stroke prevention? This special situation arises infrequently and presents special problems. Basically, the risk of recurrence depends on the cause and often the cause may be inapparent. Transient protein S deficiency has been reported during pregnancy but the significance is hard to determine. There is only one therapeutic option, heparin, that is considered clearly "very likely" to be safe for the fetus (Chest 1989;95;156S-160S). Heparin associated osteoporosis in the mother, however, is a concern and is considered a risk in patients treated with at least 20000 units daily for more than 6 months. Warfarin has risks to the fetus but can be started just after delivery even during breastfeeding. Heparin should be discontinued just prior to delivery and both restarted soon after delivery. After oral anticoagulation is achieved the heparin can be stopped. Alternatively, if the indication for anticoagulation is weak, the patient can be covered for the normally hypercoagulable period after delivery lasting 1-2 weeks with sq heparin and then switched to ASA.

Recommendation: Treat with 15-20,000 units of subq heparin daily during pregnancy stopping briefly near delivery but restarting soon after delivery. Choice of longer term therapy should be based on the underlying risk condition. If protein S deficiency was documented during pregnancy, measurement at least 3 months post partum should be considered to reassess the continuing need for anticoagulation.

### 3.8 Connective Tissue Disorders

- EDS: Ehlers-Danlos
- MfS: Marfan's syndrome
- OI: Osteogenesis imperfecta
- PXE: Pseudoxanthoma elasticum
- NF: Neurofibromatosis
- ADPKD: Autosomal dominant polycystic kidney disease

(Schievink et al., Stroke 1994; 25: 889-903)

### 3.9 CADASIL

This topic could also appear in the section below on young stroke. This condition was first described in 1977 as hereditary multiinfarct dementia ( Acta Neuropathologica 1977; 39:247-254). This is characterized clinically by recurrent subcortical ischemic strokes starting in early adulthood in a familial pattern. Other symptoms include headache and psychiatric symptoms. Small deep infarcts and leukoencephalopathy. The brain examination shows numerous small deep infarcts with myelin loss. The small penetrating arteries of the subcortical areas are diseased by a process not considered related to atherosclerosis or amyloid angiopathy. A gene for this condition has been identified at 19q12. Most cases have been reported in European families but a few have been recognized in the US (Stroke 1994; 25: 704-708).

### 4.0 Stroke in Young Adults

The list here overlaps that of risk factors and stroke etiologies in young adults and to name a few includes:

- antiphospholipid antibodies
- dissection
- drugs (all routes of delivery)
- premature athero
- ttp
- coagulopathies
- sickle cell disease
- heart disease
- lupus and connective tissue disease
- syphilis
- moyamoya
- Susac's syndrome
- FMD
- neurofibromatosis
- pregnancy
- homocysteinemia

### 5.0 Stroke in Children

#### 5.1 Risk Factors

Although stroke is generally rare in childhood, it does occur, especially in association with heart disease and sickle cell anemia. In most cases with childhood stroke a likely cause can be found given sufficient investigation.

### *Stroke in Children*

- Leading causes:
  - Cardiac disease -
    - congenital
    - acquired
  - Hematologic disorders -
    - Sickle Cell Disease
    - Trauma(child abuse or "popsickle stick")
- Other causes:
  - Vasculitis
  - Vasculopathies
  - Structural abnormalities
  - Coagulation defects
  
- "Moyamoya" Disease
  - Term/Definition
  - Clinical spectrum
  
- Age of onset
- Symptoms
- CT/MRI/Angio
- Doppler
- Pathology/Etiology

Work-up should always include:

- History and physical
- CBC with diff, platelets, ESR, chemistries, urinalysis, PT, PTT, drug screen
- Cranial CT scan with contrast or MR
- Heart evaluation, chest x ray

Work-up may include:

- Evaluation of cerebral vessels with either ultrasound or angiography (cerebral, arch, and maybe renal arteries as well)

- Special laboratory tests such as: homocysteine screen, MELAS work-up, hemoglobin analysis, SLE test, anticardiolipin antibodies, AT III, proteins S and C, cryoglobulins, blood cultures, VDRL, HIV, fibrin splits
- Echocardiogram
- Lumbar puncture (if infection is suspected)

## 5.2 Sickle Cell Disease

About 10% of Hb SS patients will develop stroke. The majority of these (75%) result from occlusion of arteries (ischemic stroke or cerebral infarction) and 25% from intracranial hemorrhage. Ischemic stroke is particularly common in young children with Hb SS. It is a major cause of morbidity and mortality. Once thought to be primarily due to microvascular occlusion, it is now clear that symptomatic cerebral infarction is usually associated with abnormalities of large intracranial arteries. Histological studies of these stenotic arterial lesions reveal fibrotic scars. The angiographic and pathologic appearance of these lesions does not suggest inflammation. The cause of these lesions is not clear. Incremental thrombus formation has been suggested, possibly with sickled erythrocytes incorporated into the lesions. Most believe that injury to the endothelium is involved, and abnormal adherence of erythrocytes containing Hb S may play a role. Infarction results from occlusion of major feeding arteries and severe reduction of cerebral blood flow.

Symptoms include focal seizures, hemiparesis, and visual and cognitive deficits. Ischemic stroke in Hb SS is treated with emergent simple or exchange blood transfusion. Most patients then go on to be treated chronically with periodic (every 3 to 4 weeks) simple or exchange blood transfusions maintaining Hb S levels at less than 30% of total hemoglobin. Periodic transfusion is associated with a significant reduction in recurrent stroke and is the basis of secondary stroke prevention in children with Hb SS. There is no currently accepted strategy for primary prevention although identification of patients at risk with transcranial doppler may lead to prophylactic treatment before stroke.

The most frequent sites of involvement are the distal intracranial internal carotid artery (ICA), and proximal portions of the middle cerebral (MCA) and anterior cerebral (ACA) arteries. The vertebrobasilar system is not the target of the occlusive process but supplies collateral flow to the anterior part of the brain. Cerebral angiography was repeated in patients with and without extended transfusion and revealed that abnormal areas stabilized with regular transfusion. Without transfusion, lesions worsened over months or years indicating a slow pace of development and progression. The condition of abnormal large arteries with stenosis precedes the development of symptoms in most cases by months or years.

Intracranial hemorrhage accounts for about 25% of the strokes and has a tendency to occur later in life similar to Moyamoya disease. Hemorrhage into the brain substance ("intraparenchymal") is a recognized late manifestation of the occlusive vasculopathy associated with prior infarction in sickle cell disease. In some cases both hemorrhage and infarction may be related to the same process. Release of blood into the subarachnoid space ("subarachnoid hemorrhage") is usually caused by rupture of a berry aneurysm

but may also be associated with occlusive vasculopathy. A minority of cases with sickle cell disease and intracranial hemorrhage do not have aneurysm or occlusive vasculopathy and the cause of bleeding remains unclear. Aneurysms have been successfully clipped in Hb SS which presumably reduces recurrent bleeding risk. In the absence of aneurysm, the best method to prevent recurrent bleeding is not known. The effect of chronic blood transfusion on the risk of recurrent intracranial hemorrhage is not clear. (See: Powars ER, Wilson B, Imbus C, Pegelow C, Allen J. The natural history of stroke in sickle cell disease. Am J Med 1978;65:461-71 and/or Adams RJ, McKie V, Nichols FT, et al. The use of transcranial ultrasonography to predict stroke in sickle cell disease. NEJM 1992;326(7):605-610 and/or Adams RJ, Nichols FT. Sickle cell anemia, sickle cell trait and thalassemia. In: Vinken PJ, Bruyn GW and Klawans HL, eds. Vascular Diseases III; Handbook of Clinical Neurology. Netherlands: Amsterdam Elsevier, 1989;11(55):503-515 and/or Pavlakis SG. Neurologic complications of sickle cell disease. Adv Pediatr 1989;36:247-276.)