Clinical Medicine

Risk Factors in Stroke

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In the United States, stroke accounts for 160,000 annual deaths; only 16% of the 1.8 million stroke survivors are fully independent. The incidence of stroke increases with age. Hemorrhagic strokes outnumber ischemic strokes before age 15. Japanese men in this country have a lower stroke mortality than their age peers in Japan. Excessive stroke mortality for US nonwhites may not be entirely due to the greater prevalence of hypertension among blacks. Hypertension emerges as the single most powerful and reversible risk factor in stroke and for survival after stroke. Impaired cardiac function is the second most important precursor of stroke. The recurrence of stroke in survivors is high. The frequency of completed stroke is high in persons with transient ischemic attacks, but not in those with asymptomatic carotid bruits. Other reversible risk factors are smoking, the use of oral contraceptives, alcoholic excess, a low level of physical activity, blood hyperviscosity and drug abuse.

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From 13% to 20% of the cardiac output goes to the brain,[1] an organ that represents only 2% of total body weight.[2] Cerebral blood flows normally at a rate of 40 to 45 ml per 100 grams of brain per minute. Considerable reduction in flow can occur before a deficit becomes clinically significant. The ischemic tolerance of neural tissue is proportional to the severity and duration of flow reduction.[3] At zero flow (cardiac arrest), this tolerance is about four minutes.[4] A blood flow of 18 ml per 100 grams per minute at an arterial carbon dioxide pressure of 40 torr can temporarily sustain a normal electroencephalogram.[3] Electroencephalographic changes and presumably ischemic symptoms develop at blood flow rates below 17 ml per 100 grams per minute.[3] A further decrease in flow to less than 10 ml per 100 grams per minute results in permanent brain tissue infarction.[5]

The current definition of stroke stipulates that the focal diagnostic neurologic deficits such as hemiparesis, aphasia or homonymous hemianopia be of abrupt or rapid onset; if not fatal, the deficit should last more than 24 hours. The definition also specifies that the vascular origin be limited to either thrombotic or embolic occlusion of a cerebral artery or to spontaneous rupture of a vessel resulting in intracerebral or subarachnoid hemorrhage. The definition excludes changes due to vascular lesions of clearly traumatic, neoplastic or infectious orgin.

Although mortality from stroke has been steadily declining,[6-14] it still accounts for 16% of all deaths in the United States.[15] In addition to the 160,000 annual stroke deaths, more than ten times as many (some 1.8 million persons) survive stroke with varying levels of residual disability.[15] Among the survivors, cerebral infarction reduces the proportion of those who were completely independent from 57% before infarction to 16% after infarction.[13] Aphasia alone is an important residual incapacity in 10%.[16]

General Risk Factors

Developmental Factors

Intracranial hemorrhage. Intracranial hemorrhage that occurs later in life can be due to bleeding "berry" aneurysms.[17] That many aneurysms become symptomatic around age 20 or later suggests that unidentified developmental factors are at play. A statistically valid association links berry aneurysms to coarctation of the aorta and to polycystic kidneys.[18] Subarachnoid hemorrhage was the cause of death in 22% in a study of persons with polycystic kidneys.[19]

Intracranial hemorrhage, whether subarachnoid or intracerebral, may be the first manifestation of atrioventricular malformations that had been silent until early maturity. Bleeding may follow as late as a decade after an initial convulsive seizure suffered during early adolescence.

When developmental defects lead to asymmetric growth, the smaller vessels are more likely to occlude. Of 17 patients with severe asymmetric carotid stenosis, 13 had greater stenosis on the side of the smaller vessels.[19]

Hemorrhagic strokes. Hemorrhagic strokes outnumber ischemic strokes 3:1 in children younger than 15 years, with a

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combined average annual incidence rate of 2.52 per 100,000.[20] After maturity the reverse is true.[21,22] The incidence rate for stroke increases progressively with age[13,23-25] as atherosclerotic plaques and internal thickness of the basilar artery and the anterior cerebral arteries increase. In the anterior cerebral arteries, the onset of the first atherosclerotic plaques lags by about ten years behind similar formations in the basilar artery.[26]

At birth, elastin in the arteries of the circle of Willis and its large branches is concentrated in the internal elastic layer, in contrast to muscular arteries of other organs whose media and adventitia contain abundant elastic fibers in the outer layer.[27] Increasing amounts of elastic tissue can be found in the external layer of the cerebral arteries until age 2. Thereafter, the density of the elastic fibers seems to decrease until, after age 30, few fibers are still visible. This age-related change in proportion of elastin has been attributed to altered biochemical composition indicative of a concomitant dysfunction.[27]

Sex

Coronary heart disease affects predominantly men, but the sex differential is not so pronounced in cases of stroke.[6,10,28-31] In some age groups and in American blacks,[32] there is a slight excess in the incidence of stroke in women.

Race

Mortality in Japanese and US nonwhites of all ages from vascular lesions of the nervous systems exceeds that of US whites at all ages.[32] Studies of emigrant Japanese suggest that the observed excess reflects environmental rather than genetic factors. American-Japanese men tend to have a lower stroke mortality than their peers in Japan.[33-35] Native Japanese men are significantly more likely to have intraparenchymal arteriosclerosis and cerebral infarction than Hawaiian Japanese.[36] Because the Japanese migration to Hawaii and California occurred mainly between 1880 and 1924, it is of interest that stroke mortality in American-Japanese had dropped nearly to the levels for whites by 1960, whereas their mortality from coronary heart disease remained intermediate.[35]

Nonwhite mortality from cerebrovascular diseases in the United States for persons aged 35 to 74 years has been about twice that of whites.[11,37] The greater prevalence of hypertension among blacks remains a mystery, as the higher rates could be attributed to incorrect death certification in states underserved by physicians,[38] or to underenumeration of the black population by census takers.[39]

Familial Clustering

Parental deaths from stroke,[40] cardiovascular-renal disease[41] or any cause[42] are overrepresented among stroke victims. Hypertension and cerebrovascular disease are significantly more frequent in monozygotic than in dizygotic twins of the same sex.[43]

Secular Trends

The past four revisions of the *International Classification of Diseases* introduced an element of uncertainty in the interpretation of long-term trends of stroke mortality.[6-8,28,44] Studies limited to data collected after the 1968 (most recent) revision concur in a downward mortality trend,[8,10] a pattern that emerges also from separate analyses of the four chronologic periods corresponding to the fifth through the eighth revisions.[11] The decline in stroke mortality that accelerated around the late 1960s[9,11,12] or the early 1970s[45] may even have been underestimated. Epidemiologic evidence indicates that the decline in mortality reflects a real decrease in stroke incidence.[16,45] The reduction in mortality for major cardiovascular diseases since 1965 far exceeds what could reasonably be explained by the decline in the changing autopsy rate since then.[46]

The reasons for the decline are unclear,[47] as it started long before effective antihypertensive therapy became widely available. An attractive hypothesis has correlated these changes in mortality with the declining use of salt.[48] If so, the changes in dietary habits made possible by the introduction of refrigeration and deep freezing may have proved one of the most important contributions to preventing stroke.[49]

Specific Risk Factors

Hypertension

Fixed and systolic hypertension. Hypertension emerges from prospective studies in Framingham (Massachusetts),[50,51] Chicago,[52] Honolulu,[53] Rochester (Minnesota),[54] Finland[55] and Japan[23] as the most common precursor of atherothrombotic brain infarction. The risk increases with elevated systolic and diastolic values,[37] the relationship being almost linear independently of age and sex.[51]

Elevated systolic pressure was highly predictive of subsequent stroke, even when not associated with diastolic elevations. Blood pressure values above 140/90 mm of mercury were recorded in all but 10 of the 105 stroke victims identified during the initial 18 years of the Framingham study. The normotensive persons who had contributed the ten cases of stroke had only one fourth of the stroke risk of their hypertensive counterparts.[51] Hypertension is a powerful predictor of atherosclerotic brain infarction when other factors such as gout, diabetes mellitus and obesity are excluded.[30] Systolic blood pressure values discriminated between susceptible and nonsusceptible persons and systolic and diastolic values used together.[30] In a retrospective study of the stroke mortality of former university students,[41] decedents had registered higher mean systolic and diastolic blood pressures when in college, and significantly more persons who had died of stroke (45%) than controls (31%) had had systolic blood pressure levels above 130 mm of mercury.[41] Japanese data have shown a correlation of systolic and diastolic hypertension and mean arterial pressure with the risk of stroke and that increasing values increase the risk for cerebral hemorrhage and cerebral infarction.[23] In cases of hypertension, the risk for atherothrombotic stroke is essentially the same as for hemorrhagic stroke.[33]

The contribution of hypertension to the risk of stroke is independent of arterial rigidity.[56] Oscillometric finger recordings in the Framingham study of 1,825 consecutive persons graded the depth of the dicrotic notch from absent to pronounced. Because the dicrotic notch is the combined result of rebound elastic recoil after aortic valve closure and such factors as the tone of smaller vessels and peripheral vascular resistance, peripheral vasoconstriction may cause the incisura to disappear. In the absence of peripheral vasoconstriction, aortic valve disease or heart failure, the incisura is largely a

reflection of arterial elasticity and arteriolar tone. Regression analysis of stroke incidence on age, systolic pressure and pulse-wave configuration indicates that the contribution of the pulse-wave is not significant, whereas that of systolic pressure has a high coefficient of correlation. This relationship obtains even though the elastic tissue in the arterial walls diminishes with age and contains more calcium, so that fewer aging persons have a normal pulse-wave tracing.

In persons older than 30 years, isolated systolic hypertension cannot be considered an innocent concomitant of aging inelastic arteries[57] but rather an often-neglected precursor of stroke,[56] hypertensive cardiac failure, coronary heart disease and occlusive peripheral arterial disease.[57] In monkeys, experimentally induced aortic coarctation resulted in systemic hypertension and in multifocal brain lesions at the capillary level. The pathologic changes that could be explained by successive episodes of regional ischemia or hyperperfusion (or both) resembled those seen in the brain of hypertensive humans.[58]

Labile hypertension. In contrast to the gravity of labile diabetes mellitus, labile hypertension is generally viewed either as the relatively benign manifestation of an exaggerated stress response or, at worst, a possible prelude to "fixed" hypertension.[59] Thus there is the tendency to disregard an elevated initial blood pressure reading and to repeat the measurement after the patient is relaxed.

In the Framingham cohort, hypertension was designated by two pressure determinations exceeding 160/95 mm of mercury. Normal tension was defined by values consistently below 140/90 mm of mercury and intermediate readings were considered borderline. It was found that higher pressures were more labile than lower ones, so that persons with fixed hypertension had more labile pressures than those with so-called labile hypertension. Lability also increased with age. For any given average pressure, the risk of cardiovascular events was unaffected by the degree of variability of the pressure. In other words, the higher the average reading, the greater the risk of cardiovascular complications. Rather than disregarding a single hypertensive reading and drawing reassurance from a subsequent normal basal pressure, to identify patients at risk for cardiovascular complications, one should rely on the average of several readings preferably taken on more than one occasion.[60]

Effect on prognosis. In prospective studies in the United States and Canada, survival after stroke was shorter in persons who had hypertension before stroke developed.[61,62]

Effect of treatment. In an Australian study based on regular biannual health screening of a small township, better control of blood pressure was associated with lesser stroke mortality in men aged 50 years and older, but not in women.[63] In a US double-blind study, only 6 cases of stroke occurred among hypertensive persons receiving antihypertensive drugs, whereas 25 cases of stroke occurred in the comparison group receiving a placebo.[64] The study also showed that stroke had occurred in patients whose diastolic pressure had not been reduced below 100 mm of mercury.[64] A study of 10,000 persons with hypertension in 14 cooperating centers confirmed that clinical control of hypertension protects against stroke,[65] especially in patients younger than 70 years. Among patients admitted to hospital for stroke, two thirds were known to have hypertension[66]; although most (91%) were treated with antihypertensive drugs, in the physicians' judgment, one in four had not been taking medications for two or more days. Almost a third of the study group had had diastolic readings above 105 mm of mercury on at least one occasion, with systolic values exceeding 180 mm of mercury at least once in almost half of them.

In Minnesota, a community hypertension control program increased from 40% to 76% the proportion of persons whose hypertension seemed adequately controlled.[67] These impressive results were associated with a declining incidence of and increased survival in cerebral infarction.[13]

Heart Diseases

After hypertension, impaired cardiac function is the most powerful precursor of stroke and atherothrombotic infarction.[68] Embolic stroke can be a complication of cardiac arrhythmia.

Atrial arrhythmias. Atrial arrhythmias will predispose to left atrial thrombus formation and cerebral embolization. Atrial fibrillation increases the risk of stroke sixfold; in the presence of rheumatic mitral disease, the risk increases 17-fold.[69] The annual incidence of cerebral embolization in the presence of sick sinus syndrome is 7.2%.[70] Atrial arrhythmias were identified during long-term electrocardiographic monitoring in 44% of patients with nonhemorrhagic stroke, twice the percentage in the reference population.[70]

Mitral valve prolapse. This valvular abnormality affects 5% of the general population.[71] It has been associated with the development of focal neurologic signs in young normotensive persons who had no overt coagulation defect and who were not using oral contraceptives.[71,72] Angiograms have suggested an embolic pathogenetic mechanism,[73] possibly mediated via platelet coagulant hyperactivity[74,75] or shortened survival time[76] or by newly recognized links between coagulation and cardiovascular disorders.[72]

Mitral valve prolapse was the only identifiable precursor in 5% to 30% of young adults with otherwise unexplained cerebral infarction,[77-80] but the actual risk of stroke in young adults with asymptomatic mitral valve prolapse seems rather low, possibly of the order of 1 in 6,000 per year.[78] During an observation period of some 3,800 person-years contributed by 760 patients with mitral valve prolapse, only one suffered a stroke,[81] suggesting an annual rate of 1.5 in 6,000. No prophylactic treatment seems warranted in asymptomatic persons with this valvular dysfunction.[78] Among persons with mitral valve prolapse, the prevalence of stroke is four times that observed in the general population.[82]

Hypertensive and atherosclerotic heart disease. The risk for atherothrombotic cerebral infarction is greatest among hypertensive persons with electrocardiographic[23,53] or radiologic evidence of cardiac involvement,[30] reflecting suboptimal cardiac output and reduced cerebral perfusion at the level of severely narrowed vessels.[30] A previous history of myocardial infarction almost trebles the risk of stroke (relative risk = 2.9).[25]

Effect on prognosis. Besides being risk factors, prestroke hypertension, coronary heart disease and congestive heart failure reduce the five-year survival rate for cases of brain infarction from 85% to 35% in men and from 70% to 56% in women.[66] The higher the systolic blood pressure before stroke, the higher the mortality.[62]

Previous Stroke

The Framingham study showed that the recurrence rate among stroke survivors is substantial.[61] Most recurrences are of the type of the previous stroke. Most strokes are atherothrombotic, reflecting the poor survival after the hemorrhagic ones. Men have a higher (42%) five-year cumulative recurrence rate than women (24%). The observed sex difference could reflect better control of hypertension and its complication in women.[61]

Transient Ischemic Attacks

The age-adjusted annual incidence rate for transient ischemic attack (TIA) is 31 in 100,000 in Rochester, Minnesota, where age-specific rates increase with advancing age and show a prominent jump after age 65.[83] In southern California, elderly persons with a history of transient focal or nonfocal cerebral ischemic symptoms carry an increased risk for the development of a completed stroke whether nonfocal symptoms such as spells of dizziness, syncope, vertigo or loss of balance were manifestations of vertebrobasilar ischemia or were caused by impaired cardiac function.[84] Both focal and nonfocal ischemic symptoms were significant and independent predictors of stroke.[84] The cumulative rates of completed stroke were 2.3% among those with focal and nonfocal symptoms, twice the value observed among an asymptomatic comparison group.[84] Patients who have had a TIA are at increased risk for stroke. During the first year after the initial attack, one group had 33 strokes versus the expected 2.[83] A lower relative risk for TIA-related stroke was reported among Hawaiian-Japanese in whom 2 strokes occurred instead of the 0.7 expected.[85]

The observed conditional probability of surviving free of stroke after the first TIA was 62% after five years and 50% after ten years, whereas 90% of the general population would have remained free of stroke for ten years.[83] Regardless of the anatomic source of TIAs, twice as many of the subsequent deaths were due to cardiac causes as to stroke.[86] Because of the accelerated total mortality associated with TIAs, only 25% rather than the expected 50% of a study cohort was still alive ten years after the initial TIA. A similarly accelerated mortality for cardiovascular illness and stroke was shared by a biracial population in Georgia who had symptomatic TIAs.[87] When nonfatal stroke and death were combined as an endpoint, there was no significant difference between the survival curves for vertebrobasilar insufficiency and carotid insufficiency in either men or women.[84]

The risk for ischemic stroke associated with TIAs is most increased in the presence of heart disease[54] and stenosis of large arteries. Stenosis is important mostly as a source of emboli because the arterial lumen of the internal carotid must be reduced by 80% to 90% before there is a significant effect on flow.[88] Both embolic and hemodynamic factors are important in the pathogenesis of TIAs; microemboli are more frequent in the carotids, and hemodynamic factors are of special importance in the vertebrobasilar system.[89]

Asymptomatic Carotid Bruits

As verified by Doppler findings, the hallmark of internal carotid artery stenosis is a high-pitched bruit best heard at the angle of the jaw.[90] In a review of seven prospective studies cumulating 703 persons with asymptomatic carotid bruits, it was concluded that the mean annual rate for completed stroke events is low, probably around 2%.[90] The side of the bruit often does not coincide with the side of the stroke, but this could simply mean that when both carotids are atherosclerotic, a bruit is heard over the least diseased artery.

Because of the low annual risk for stroke in these patients, it is recommended that if a corrective operation is to be done, it should be done in institutions where surgical risks are similarly low—that is, not exceeding 2% or 3% at most.[90] The risk of stroke in the region of a significant but asymptomatic carotid-bifurcation plaque was low (3%) in persons who had undergone contralateral endarterectomy for a TIA or a minor stroke.[91] Stroke was just as likely to develop either in the area of a previously operated carotid artery (5%) or in the vertebrobasilar area (4%).[91]

Other Observations

In a number of studies,[25,31,50,92,93] *impaired glucose tolerance* and *clinical diabetes* were identified as significant and consistent contributors to stroke risk, with an adjusted relative risk of 2.2.[25] At any level of blood pressure, the risk for atherothrombotic stroke is increased in persons with impaired glucose tolerance.[21] Apparently, treating diabetes does not seem to alter the risk for stroke.[94] Thus, it has been concluded that there is no known justification to treat hyperglycemia without evident diabetes if the aim is to reduce the likelihood of stroke.[95] In a study of cases of hyperglycemia with or without diabetes mellitus, the neurologic outcome in stroke was considerably worse, and there was a significantly greater number of stroke-related deaths.[96] In a double-blind, randomized clinical trial, the presence of diabetes mellitus erased the prophylactic effect of aspirin in cases of threatened stroke.[97]

The relationship between *blood lipids* and stroke is weak and uncertain,[95] possibly because patients with higher serum lipid values may not survive to the age at which strokes are common. The Framingham study suggested an association of blood lipid levels with the development of precocious atherosclerotic brain infarction only in men younger than 55.[21] Native Japanese, however, who have a higher stroke mortality than US Japanese, had lower cholesterol levels than Japanese-Americans.[98] Serum cholesterol levels were negatively associated with the risk for intracranial hemorrhage among Hawaiians of Japanese extraction.[31]

In 138 patients who had not suffered a completed stroke but who underwent carotid endarterectomy for extracranial vascular disease, the mean elevation of triglyceride levels was significantly higher than in controls, suggesting that elevated triglycerides rather than cholesterol are a risk factor in extracranial atherosclerotic cerebrovascular disease.[99] Hypertriglyceridemia and elevated pre-β-lipoprotein levels were described in 50 patients with ischemic thrombotic stroke.[100] In men, the presence of elevated serum triglyceride levels doubles the risk for cerebral infarction.[55] Hypertriglyceridemia rather than hypercholesterolemia seems to correlate best with thrombotic stroke occurring before age 50.[100-102] In one study, elevated serum cholesterol values were inversely related to the occurrence of intracranial hemorrhage.[53] Serum triglyceride levels tended to be higher in patients suffering infarction in the distribution of a cortical artery. In them, the ratio of high-density lipoprotein to low-density lipoprotein cholesterol was lower than in patients with strokes traceable

to obstruction of a perforating artery,[103] suggesting that these lipoprotein abnormalities may play a part in the pathogenesis of cerebral cortical infarctions.

Serum *uric acid* elevation has been mentioned as a contributor to the risk for stroke in one study[100] but not in others.[99] Neither persons with gout nor their first-degree relatives were found to have an increased risk for dying of cerebrovascular diseases.[104]

The slight excess in deaths from cerebrovascular diseases reported in smokers of both sexes[105] was verified for men.[55,106-108] Male college students smoking ten or more cigarettes a day were at twice the risk for eventual fatal stroke than those who smoked less or not at all.[42] Although some studies failed to identify a definite relationship between *cigarette smoking* and stroke,[95,105] a relationship probably exists in view of the presence of a dose effect and the reduction in risk that follows cessation of smoking. This emerged from a study of US World War I veterans. Designating 1.0 as the mortality ratio for cerebrovascular diseases among nonsmokers, the following ratios were calculated: current smokers, 1.40; exsmokers, 1.07; pipe and cigar users, 1.06. Among cigarette smokers, a noticeable gradient was associated with increasing daily consumption: fewer than 10 cigarettes, 1.26; 10 to 20 cigarettes, 1.33; 21 to 39 cigarettes, 1.54; two packs a day or more, 1.88.[108] The relationship was stronger in younger age groups and the increased risk associated with smoking appeared to decrease rapidly after cessation.[108]

A collaborative case-control study undertaken in 12 US university hospitals determined that the use of *oral contraceptives* entailed a relative risk of about 9 for thrombotic stroke and of 2 for hemorrhagic stroke.[109] The combined effect of smoking and the use of oral contraceptives selectively increased the risk for subarachnoid hemorrhage.[110] Hypertension compounds the risk for thrombotic stroke among users of oral contraceptives, the relative risk ranging from 3 times baseline value for normotensive users of an oral contraceptive to 14 times in users with severe hypertension.[111]

Alcohol consumption has been positively associated with cerebrovascular diseases,[31,53] the risk increasing with increasing consumption.[112] Acute ethanol intoxication was an immediate antecedent in almost half of 23 consecutive patients younger than 40 years admitted to a Finnish hospital with acute brain infarction.[113] Another Finnish study concluded that a *low level of physical activity* at work was associated with an increased risk for acute myocardial infarction and cerebral stroke in both sexes, even after controlling for age, diastolic pressure, weight and smoking.[114] This observation concurred with the findings of earlier studies of San Francisco longshoremen[115] and of college students[42] indicating that physical activity at work or during leisure time reduced the risk for stroke. Parallel inferences were drawn from a Dutch community-based study that described a dose effect linking inversely the level of physical activity during leisure time with the adjusted relative risk for strokes.[25] The following relative risks were reported: little physical activity, 1.0; light activity, 0.8; heavy physical activity, 0.4. The difference in relative risk between the aggregate of light and heavy physical activity during leisure time and little activity—that is, mainly sitting, was statistically significant.[115]

The literature seems about evenly distributed as to the role of *obesity* in stroke.[25] If anything, the link is weak,[21] as reflected by a relative risk of 1.5[42] to 1.7.[25]

Suboptimal cerebral blood flow, whatever its cause, is potentially harmful in patients at risk for stroke. Thus, under pathologic circumstances, the rheologic properties of blood may become critical,[116] but neither blood viscosity nor the risk for cerebral infarction changes remarkably until the *hematocrit* exceeds 46%, when both increase sharply.[117] The slower flow associated with a higher hematocrit may limit the efficiency of an alternate blood supply through collateral vessels[116] and, distal to a tight stenosis, shear rates may fall and viscosity increase many times. A progressively slower flow will favor thrombus formation.

Fortunately, factors contributing to *hyperviscosity,* such as dehydration, polycythemia and paraproteinemia, can be corrected or at least modified relatively easily. Unfortunately, the same cannot be said about *sickle cell disease,* the cerebrovascular complications of which seem to occur preferentially in children younger than 15 years[118] and where the victim of an initial stroke is more likely to have recurrent cerebrovascular accidents.[118,119] Cerebral infarction in carriers of the sickle cell trait is a rarity[120] and apt to occur only during potentially hypoxic episodes such as status epilepticus or during general anesthesia.

Especially in young adults and adolescents, *drug abuse* is now a significant cause of intracerebral hemorrhage (amphetamines; pentazocine [Talwin] and tripelennamine [Pyribenzamine]; cocaine and phencyclidine); subarachnoid hemorrhage (amphetamines); embolic stroke (pentazocine and tripelennamine, methylphenidate), and ischemic stroke (heroin; pentazocine and tripelennamine; LSD). Direct toxic injury, embolization of foreign matter and pharmacologically mediated vascular change are considered less important etiopathologic pathways than endocarditis and immunologic mechanisms. The latter could explain the frequent polymorphic vascular response and nodose distribution of vascular lesions seen in drug abusers, as well as the delayed onset of stroke after injection or its occurrence after an unusually long period of abstinence.[121] Retrospective observations suggest that in young adults classic *migraine* may be antecedent of stroke.[122]

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