The Fallacy of the Lacune Hypothesis

Clark Millikan, MD, and Nancy Futrell, MD

We review the definition, pathogenesis, natural history, and prognosis and describe the first experimental model of lacunes. Defined pathologically or radiologically, lacunes are small cerebral infarcts which become cystic and are caused by occlusion of small arteries. The clinical definition of lacune is confused. The word "lacune" means a small stroke. While the immediate mortality rate from a small stroke is low, many patients are unable to return to work and the long-term prognosis is guarded. Photochemical damage to the carotid artery of rats produces microemboli to the brain, resulting in cavitary lesions resembling lacunes in humans. The "lacune hypothesis" is a fallacy because small cerebral infarcts are not caused solely by a combination of hypertension and small vessel disease, and the various "lacunar syndromes" are simply small strokes which should be investigated as such. (Stroke 1990;21:1251-1257)

The "lacune hypothesis" states that lacunes are caused by a combination of hypertension and characteristic vascular lesions involving single perforating brain arteries. Acceptance of this hypothesis has led some cerebrovascular experts to recommend that no detailed evaluation of a patient is necessary when a diagnosis of "lacunar infarction" is made and that the only treatment needed is control of hypertension. Others have extended the lacune hypothesis to create a new disorder, "lacunar disease."

The "lacune hypothesis" is extremely difficult to support, and the diagnostic-therapeutic nihilism that is logically generated by these notions is dangerous. We review and discuss the 1) definition(s), 2) pathogenesis, 3) natural history and prognosis, and 4) first experimental model of lacunes.

What is a lacune? Three types of definition must be dealt with. These types are 1) the gross and microscopic pathologic descriptions of the lesion; 2) the clinical concepts embodied in such phrases as "lacunar syndrome," "lacunar state," "lacunar infarction," "lacunar stroke," and "lacunar disease;" and 3) the radiologic description of a lacune as seen on computed tomography (CT) or magnetic resonance imaging (MRI).

Many authors give similar definitions for the gross and microscopic pathologic descriptions of lacunes. In 1901, Pierre Marie wrote that a lacune "is a cavity as a result of a healed infarct resulting from obstruction or rupture of a small perforating artery, most commonly in the lenticular nucleus." Fisher referred to lacunes as "small cystic trabeculated scars about 5 mm in diameter (range 3-15 mm)," "ischemic infarcts of restricted size in the deeper parts of the brain," or "the cavities left as the residuum of small infarcts in the deep parts of the brain."

The problem of definition is not so simple when one looks at terms such as "lacunar syndrome," "lacunar stroke," "lacunar dementia," or "lacunar infarction." While Fisher noted at least 21 "lacunar syndromes," Bamford et al. described only four. The most common "lacunar syndrome" is "pure motor hemiplegia," with pure sensory stroke, the dysarthria-clumsy hand syndrome, and ataxic hemiparesis frequently mentioned.

The important idea is that the neurologic deficit (syndrome) depends on the size and site of the lesion and that there can be an infinite number of "lacunar syndromes." The site of the lesion does not precisely determine its pathogenesis as infarction, hemorrhage, infection, or neoplasm. CT has established that small intracerebral hemorrhages and large ischemic infarcts can cause "lacunar syndromes." The cause(s) of "lacunar syndromes" have strayed so far from stroke as to include cysticercosis. Landau recently wrote "the clinical descriptions of lesions identify neither specific etiologies nor locations any more specific than those of well-known anatomic tracts and centers."

A lacune is radiologically defined as a small, low-density, sharply marginated area on a CT scan. The usual sites are within or near the internal capsule, corona radiata, or pons. CT diagnosis of a lacune is often made by a radiologist without knowledge of the patient's clinical state.
Thus, the neuropathologist's and the radiologist's definitions of a lacune are clear. A lacune is a small cerebral infarct that commonly becomes a cavity when macrophages remove the infarcted tissue. The clinician's definition of "lacunar syndromes," "lacunar state," and "lacunar infarction" are so varied that there are major differences of opinion concerning the pathogenesis of these small strokes, the extent of evaluation of such a patient, the treatment, and the prognosis.

The "lacune hypothesis" limits the cause of these small infarcts to a combination of hypertension and small-vessel disease. We propose six basic causes of a lacune (Table 1). Some, such as hypertension, are associated conditions that predispose to an arterial occluding event. Two or more causes may occur in a single patient, that is, hypertension, a cardiac or intra-arterial source of emboli, occlusive disease of the small vessels, polycythemia, or a sudden decrease in cardiac output may coexist. These are the same causes as for any kind of ischemic stroke.

### Pathogenesis (Cause) of Lacune(s)

#### Hypertension

In 1965, Fisher reported 1,042 brains removed and examined at autopsy and found 376 "ischemic infarcts of restricted size in the deeper parts of the brain" in 114 of them. The most frequent location (75, 66%) was the lenticular nucleus. Little attention has been directed to the "associated lesions" found in these 114 brains (Table 2). There was significant intracranial atherosclerosis in 84% of the brains, and 71 brains (62%) contained either cerebral hemorrhages or superficial infarcts in addition to the lacunes. The concomitant occurrence of these strokes is consistent with a basic diagnosis of atherosclerotic cerebral-cardiovascular disease. Of the 114 patients with lacunes, 111 had been hypertensive. This led Fisher to conclude that "the relationship of lacunes to hypertension and cerebral atherosclerosis has now been confirmed" and that "lacunes were not related to internal carotid artery disease, cerebral embolism or diabetes." This high frequency of hypertension associated with lacunes has not been confirmed by others. Table 3 lists the incidence of hypertension in patients with lacunes reported in the literature. Except for Fisher, other authors report that ≤75% of patients with lacunes have hypertension, and in three studies (References 38 and 40 and J.C. Adair, G. Call, and C.H. Millikan, unpublished observations) ≤50% of the patients had hypertension. Except for Fisher, the highest incidence of hypertension was 75% reported in the Harvard Cooperative Stroke Registry.

Table 4 shows the incidence of hypertension in patients admitted with large cerebral infarcts. In one study, 42 of 84% of patients were hypertensive at admission, but without antihypertensive therapy only 34% were hypertensive 10 days after the stroke. In general, approximately 60% of patients with cerebral infarcts have hypertension, and the percentage of patients with hypertension is approximately the same

### Table 1. "Causes" of Small Strokes (Lacunes)

<table>
<thead>
<tr>
<th><strong>Causes</strong></th>
<th><strong>Hypertension</strong></th>
<th><strong>Emboli</strong></th>
<th><strong>Small-vessel occlusive disease</strong></th>
<th><strong>Hypertension</strong></th>
<th><strong>Microaneurysms</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Hypertension</td>
<td>Cardiac</td>
<td>Atherosclerosis with or without ulceration</td>
<td>Hypercoagulable state</td>
<td>Microaneurysms</td>
</tr>
<tr>
<td></td>
<td></td>
<td>source</td>
<td>Fibromuscular disease</td>
<td>Oral contraceptives</td>
<td>Microaneurysms</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Intra-arterial source</td>
<td>Dissecting aneurysm</td>
<td>Small intracerebral hemorrhage</td>
<td>Microaneurysms</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Thrombosis</td>
<td>Hypercoagulable state</td>
<td>Microaneurysms</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Sudden decrease in blood pressure</td>
<td>Oral contraceptives</td>
<td>Microaneurysms</td>
</tr>
</tbody>
</table>

#### Table 2. Lesions Associated With Lacunes in 114 Brains

<table>
<thead>
<tr>
<th>Lesion</th>
<th>No.</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cerebral hemorrhage</td>
<td>41</td>
<td>36</td>
</tr>
<tr>
<td>Superficial infarct</td>
<td>30</td>
<td>26</td>
</tr>
<tr>
<td>Atherosclerosis of cerebral vessels</td>
<td>73</td>
<td>64</td>
</tr>
<tr>
<td>Severe</td>
<td>23</td>
<td>20</td>
</tr>
<tr>
<td>Moderate</td>
<td>17</td>
<td>15</td>
</tr>
<tr>
<td>Mild</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

From Reference 9.
Emboli vessel(s) may cause a severe neurologic deficit. Penetrating branches of the middle cerebral artery, occlusion of which may cause severe hemiparesis, is ordinarily no way to prove that an embolus from an intra-arterial source has occluded a cerebral vessel. Occasionally at autopsy, the material blocking a cerebral vessel contains cholesterol, which is reasonably convincing evidence that an ulcerated atheromatous arterial lesion was the source of the embolus. Debris from the surface of an atherosclerotic plaque and from plaque ulcers may break off and become emboli. In one study, atheromatous intracranial emboli were found in all of 16 patients examined at post mortem. The lumen of 71 vessels containing atheromatous emboli was measured; the minimum was 17 and the maximum was 585 \( \mu \text{m} \), and 31 were in the range 51–100 \( \mu \text{m} \). Little attention has been paid to the small size of these occluded arteries or even to the somewhat larger embolus generated by mural thrombi in the carotid arteries. In 1967 it was demonstrated that macroscopic and microscopic fissures or breaks in the endothelium of cerebral arteries can be associated with thrombus formation. These tiny bits of thrombus have the potential to become emboli, as has been reported in the coronary circulation. In various models it has been proved that emboli can be carried wherever the blood travels and that whether an embolus occludes a vessel depends on the relative sizes of the vessel and the embolus as well as on the stability of the embolus.

Emboli

Some cerebrovascular experts do not acknowledge that very small emboli may cause serious strokes; for example, Fisher presented reasons why emboli could not cause even transient focal cerebral ischemia. We believe that small emboli are a significant cause of stroke. Occlusion of a small vessel may cause a severe neurologic deficit. Penetrating branches of the middle cerebral artery, occlusion of which may cause severe hemiparesis, have an internal diameter of \(<1 \text{ mm} \), whereas that of the central retinal artery is \(<0.25 \text{ mm} \). There are many kinds of small emboli, including those made of platelets, erythrocytes and fibrin, cholesterol, calcium, air, atheromatous material, or their combinations.

A small embolus may be carried anywhere the blood goes. Many reports identify cholesterol or other emboli in the retinal vessels (50–150 \( \mu \text{m} \) in diameter) and other small vessels in various portions of the brain.

A small embolus may block a vessel then fragment or lyse, ultimately leaving the vessel open. We have observed this many times in the retina. Arteriographic studies a few minutes to days apart have demonstrated the disappearance of an occlusion in cerebral vessels, whereas coronary angiography has revealed thrombi not detected by coronary angiography. In cranial windows of experimental animals, emboli lodged in vessels have disappeared while being observed. Autopsy documentation of emboli in patients with small strokes is not possible because the neurologic deficits are nonlethal.

Table 4. Incidence of Hypertension in Patients With Large Infarcts Reported in Literature

<table>
<thead>
<tr>
<th>Author(s)</th>
<th>( n )</th>
<th>No.</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Milikan and Moersch</td>
<td>144</td>
<td>105</td>
<td>73</td>
</tr>
<tr>
<td>Milikan</td>
<td>225</td>
<td>164</td>
<td>73</td>
</tr>
<tr>
<td>Randrup and Riishede</td>
<td>167</td>
<td>97</td>
<td>58</td>
</tr>
<tr>
<td>Aho</td>
<td>286</td>
<td>147</td>
<td>51</td>
</tr>
<tr>
<td>Wallace and Levy</td>
<td>334</td>
<td>281</td>
<td>84</td>
</tr>
<tr>
<td>At admission</td>
<td>334</td>
<td>112</td>
<td>34</td>
</tr>
<tr>
<td>10 days later</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Solzi et al</td>
<td>1,369</td>
<td>798</td>
<td>58</td>
</tr>
<tr>
<td>Bladin and Berkovic</td>
<td>11</td>
<td>6</td>
<td>55</td>
</tr>
</tbody>
</table>

Cardiac source. Although the role of the heart in the pathogenesis of stroke was emphasized 30 years ago, it is now being recognized that the heart is a frequent source of emboli to the brain. Of course, there is ordinarily no way to prove that an occlusion is embolic, let alone to establish the heart as a source of the embolus. Calcium emboli, indicating a cardiac source, have been observed in retinal arterioles \(<150 \mu \text{m} \) in diameter. Small cardiac lesions generating such tiny emboli cannot be detected by echocardiography. This has contributed to the difficulty of establishing the role of cardiogenic emboli as a major cause of stroke, especially small strokes.

Intra-arterial source. Although this source of cerebral emboli was postulated and evidence of an intracarotid source of retinal cholesterol emboli was presented more than 30 years ago, workers in the neurovascular area have been reluctant to infer that similar emboli are carried to the brain. As with emboli from a cardiac source, it is seldom possible to prove that an embolus from an intra-arterial source has occluded a cerebral vessel. Occasionally at autopsy, the material blocking a cerebral vessel contains cholesterol, which is reasonably convincing evidence that an ulcerated atheromatous arterial lesion was the source of the embolus. Debris from the surface of an atherosclerotic plaque and from plaque ulcers may break off and become emboli. In one study, atheromatous intracranial emboli were found in all of 16 patients examined at post mortem. The lumen of 71 vessels containing atheromatous emboli was measured; the minimum was 17 and the maximum was 585 \( \mu \text{m} \), and 31 were in the range 51–100 \( \mu \text{m} \). Little attention has been paid to the small size of these occluded arteries or even to the somewhat larger embolus generated by mural thrombi in the carotid arteries. In 1967 it was demonstrated that macroscopic and microscopic fissures or breaks in the endothelium of cerebral arteries can be associated with thrombus formation. These tiny bits of thrombus have the potential to become emboli, as has been reported in the coronary circulation. In various models it has been proved that emboli can be carried wherever the blood travels and that whether an embolus occludes a vessel depends on the relative sizes of the vessel and the embolus as well as on the stability of the embolus. Recently, the validity of this concept was demonstrated again. We have postulated that fibromuscular dysplasia and dissecting aneurysms are potential sources of emboli of various sizes. Emboli from an intra-arterial source are common potential causes of occlusion of small cerebral arteries.

Small-Vessel Occlusive Disease

Atherosclerosis and lipohyalinosis (associated with hypertension) have been championed as the mechanisms of the occlusions that cause lacunes. This does not account for the 30–50% of patients with lacunes who are normotensive. In our experience, the neurologic deficit that is the clinical expression of a small stroke often comes on quickly, which means that there was rapid failure of perfusion, through either the primary or the collateral channels. The nature of the arterial occlusion has not been studied within hours or a few days after the clinical event because such strokes are nonlethal. In 1979, Fisher reported the results of studying thousands of
brain sections, searching for the nature of the occlusion causing small capsular infarcts (lacunes). In 10 infarcts the appropriate artery was studied, and an obstructive vascular lesion was found in nine. In two of the nine there was an atheromatous plaque with a superimposed thrombus, in four there was severe stenosis due to atherosclerosis, in one only was there lipohyalinosis, in one the nature of the obstruction remained "uncertain," and in one the penetrating arteries were obstructed at their orifices by an atheroma in the superior division of the middle cerebral artery. Fisher stated that "in two cases the vessels were patent, suggesting embolism."

The middle cerebral and basilar arteries are often affected by atherosclerosis. Atherosclerotic lesions may develop small thrombi that in turn could block the origin of a penetrating artery, causing a small infarct (lacune). Terms such as hyalnosis, hyaline fatty change, angionecrosis, segmental arterial disorganization, fibrinoid necrosis, lipohyalinosis, fibrinoid arteritis, and small-vessel disease are descriptive but are given as a cause for lacunes without any substantive evidence that such changes actually stop the flow of blood and cause infarction. Alternate hypotheses are that hyaline changes in the walls of small blood vessels are the result of ischemia in the vessel produced by its temporary occlusion or that these changes are a result of mechanical trauma to the vessel as an embolus passes through it.

Microatheromas are thought to be a common cause of lacunes by some authors. No systematic study of the lenticulostriate arteries in human autopsy material has been reported. The frequency of atherosclerosis in these vessels by age group is not known. The penetrating branches of the middle cerebral arteries of 14 brains from persons aged 31–65 years were examined, and the authors concluded that the size of lacunar infarcts depends on the size and zone of supply of the occluded penetrating arteries. The phrase "small-vessel occlusive disease" has been used without proof. The term should be "small vessel occlusion," the occlusion caused by an embolus, a thrombus, or disease of the wall of the vessels.

**Hemodynamic Cause of Stroke**

This term refers to the concept that a sudden decrease in blood pressure in a patient with a severe arterial stenosis can significantly decrease blood flow distal to the stenosis and thereby cause a focal neurologic deficit. In our experience this is an uncommon cause of transient ischemic attacks (TIAs) and therefore, inferentially, of small cerebral infarcts. In earlier studies of this theory, patients who had experienced TIAs or who had carotid artery stenosis or occlusion were investigated. In a report of 35 patients who had their blood pressure reduced with hexamethonium and tilting in an attempt to reproduce their TIAs, in only one patient did evidence of focal ischemia appear. The response of these patients was the usual one caused by diffuse cerebral ischemia—syncope or near-syncope. It is unlikely that a hemodynamic mechanism is important in causing lacunes.

**Abnormalities of Blood**

Polycythemia, thrombocytosis, diabetes mellitus, and hypercoagulable states do not appear to be significant causes of lacunes. Obviously, most patients with lacunes do not have abnormalities of the blood.

**Prognosis and Natural History of Lacunes**

The clinical, radiologic, and pathologic definitions of a lacune contain a common denominator: the lesion is small (<1.5 cm in diameter). It is not surprising that the case–fatality rate for these small strokes is close to 0. Recovery rates from "lacunar stroke" are not given by many authors who emphasize that lacunes are benign and that recovery from them is excellent. Other authors do not agree. In one report, a third of patients with a lacune were not capable of independent living 1 month or 1 year after their stroke, and in another study patients with "pure motor hemiparesis" did not recover sooner than survivors of other cerebral infarcts; the degree of motor deficit was the same in the two groups a year after the stroke. This has been our experience.

The long-term prognosis of patients having a first small stroke has received little attention. Bamford et al reported the natural history of lacunar infarction in 108 patients who had a "lacunar syndrome." Of these 108 cases six were excluded, and of the remaining only one died during the first month; 10 died during the first year. The cause of death was complications of immobility in four, cardiac in three, and unrelated to the stroke in the other three patients. Twelve patients had another stroke during that year, for a recurrence rate of 11.8%. In another study, patients with CT evidence of one lacune were followed for 36 months. Seven patients had another small stroke, three developed a "cerebral hemispheric stroke," two had myocardial infarction, and one died suddenly of an unknown cause. The coexistence of large cerebral infarcts, cerebral hemorrhages, and lacunes is evidence that the latter do not occur in isolation and that "lacunar disease" is not a benign process. These findings coincide with ours; a small stroke is a highly significant risk factor for a subsequent stroke, with a >10% recurrence rate during the first year.

**Model of Lacunes**

There has been no animal model of lacunes, and the role of hypertension in their pathogenesis has not been experimentally tested. Stroke has been studied in stroke-prone spontaneously hypertensive rats (SHRSP), but lacunes in these animals have not been reported.

Even though emboli can go anywhere the blood goes, there has been resistance to the concept that
emboli enter penetrating branches of the main cerebral arteries (anterior, middle, and posterior cerebral arteries) because of the 90° angle at their origins. Bremer et al.\textsuperscript{72} produced a model of embolic stroke by injecting silicone spheres 1–1.5 mm in diameter into the carotid artery of primates and found that the route followed by the embolic particle at arterial bifurcations depended on the diameter of the embolic particle, the angle of the arterial branching, and the caliber of the arteries at the bifurcation. Since they were larger than the deep penetrating vessels in the primates, these emboli could not enter the penetrating branches. Swank and Hain\textsuperscript{71} injected paraffin emboli into the carotid arteries of dogs and observed that small emboli produced lesions mainly in the white matter, with larger emboli producing lesions in both the gray and the white matter.

We\textsuperscript{51} have produced a model of microemboli to the brain in rats. Photochemical (laser and dye) damage to the endothelium of the carotid artery leads to platelet aggregation within it, followed by platelet emboli to the brain and the production of multiple cerebral infarcts. We found 18 infarcts in the basal ganglia and thalamus of 12 normotensive rats killed after 6–12 weeks. Eight infarcts contained cavities 0.5–1.0 mm in diameter, surrounded by infarcted tissue with gliosis. Two cavities contained a central blood vessel, and four had areas that appeared to be trabeculated with septae. The shapes of the cavities were variable; some were oval while others were irregular. The location and appearance of these cavities\textsuperscript{74–93} resemble those of lacunes in humans. Thickened blood vessels were seen near the cavities. These rats remained normotensive.

SHRSP have multiple cerebral infarcts,\textsuperscript{92} most (68%) located in the cortex, but 24% and 6% in the basal ganglia and thalamus, respectively. The ratio of superficial to deep infarcts is similar to that in our microembolus model. Thus, the experimental evidence is that small, deep cerebral infarcts caused by embolic arterial occlusion can become lacunes in the absence of hypertension and that hypertension alone does not produce lacunes.

Discussion

The common denominator for the definition of lacune, whether used by a pathologist, clinician, or radiologist, is that it's small. A lacune is clearly defined by the pathologist and radiologist. Confusion has come to clinical practice when the adjective form is used, as in "lacunar disease," "lacunar state," "lacunar syndrome," "lacunar infarction," and "lacunar stroke," often with the implication that these small infarcts are caused by hypertension and small-vessel disease (the "lacune hypothesis").

It is now obvious that the "lacune hypothesis" is a fallacy; these small cerebral infarcts are not caused solely by hypertension and small-vessel disease. The incidence of hypertension in these patients is the same as that in patients with large infarcts and hemorrhages. In Fisher's\textsuperscript{41} most recent study of 10 small infarcts, only one demonstrated lipohyalinosis and in five there was no small-vessel obstruction or such obstruction remained "uncertain."

From clinical experience and the production of small infarcts (lacunes) by embolic arterial occlusion in normotensive rats a number of facts emerge. These include

1. Any stroke syndrome depends on the site and size of the focal ischemia. Because of the infinite complexity of the human brain there are an infinite number of "stroke alias lacune syndromes."

2. Large infarcts and hemorrhages can occur in the same brains as small infarcts (lacunes).

3. A small or large cerebral infarct is caused by failure of the primary and/or collateral blood supplies to a local area of brain.

4. The frequency of small atheromas and other lesions of penetrating arteries (from the circle of Willis, the anterior, middle, or posterior cerebral arteries, or the basilar arteries) is not known and should be studied.

5. A sudden decrease in cardiac output (hemodynamic mechanism) is not a common cause of small strokes but also warrants further investigation.

6. An embolus can be carried anywhere the blood goes; emboli may block the vessel, then fragment or lyse to leave the vessel patent. Based on the temporal profile of the clinical events, small emboli are probably the most common cause of the arterial occlusions that produce small cerebral infarcts. Intraarterial as well as cardiac lesions are common sources of small as well as large emboli.

7. While the immediate fatality rate from a small stroke is low, many patients are unable to return to work. The long-term prognosis is guarded as there is a 10% recurrence rate during the first year after a "lacunar stroke." The diagnostic evaluation of a person with a small stroke should be the same as that for any patient with a recent TIA, a progressing stroke, or a recent stable stroke to construct an appropriate plan of immediate or preventive treatment.

It is not likely that we will ever be able to prove the pathogenesis of a small infarct at the time of the event. From analysis of the entire history, the physical examination, and the laboratory investigation the clinician should develop a hypothesis as to the cause of the stroke in each patient.

We agree with Landau\textsuperscript{29} "that the adjective (lacunar) with its baggage of false clinical implications should be evicted from the bedside, where it has caused only misleading confusion." The phrase "lacunar stroke" is like the expression "free-gratis!" A lacune is a stroke, just a small one. The word lacune has been popularized to imply a mechanism of hypertension and small-vessel disease. We believe the word lacune should be used to mean a small stroke. There are a variety of causes, each of which should be sought in every patient.
Acknowledgments

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