

**Objectives:**

1. Differentiate between ischemia and hypoxia and their effects on the CNS
2. Describe what is meant by "stroke" and "transient ischemic attack (TIA)" and discuss the interrelationships between hemorrhage, thrombosis, embolism and infarction in the brain parenchyma.
3. Discuss thrombosis, embolism and infarction in the CNS.
4. Discuss intracranial hemorrhage.
5. Describe the etiology, pathogenesis, morphology, distribution of lesions, clinical manifestations and sequelae of intracranial berry (saccular) aneurysms.
6. Discuss arteriovenous malformations.

## I. Introductory Concepts

Disorders resulting from impairment in brain circulation are the greatest single cause of neurological disability in the adult population and the third leading cause of death. "Strokes", which may be classified as ischemic or hemorrhagic, are the most common of the cerebrovascular lesions. The three major pathogenesis categories of thrombosis, embolism and hemorrhage are important because management of patients differs for each group.

Cerebrovascular disease is less prevalent in children, since atherosclerosis, hypertension and diabetes mellitus, major determinants of such disease in adults, are rare in children. A number of conditions in which stroke occurs are inherited in a classical mendelian pattern; usually stroke is only part of the phenotype. The cause of most common strokes is multifactorial and involves both genetic variants and environmental factors.

Due to its very high metabolic demands, the brain depends on a constant supply of glucose and oxygen from the circulation, and on the removal of metabolic waste, primarily in the form of carbon dioxide. Homeostatic mechanisms provide for the maintenance of adequate cerebral blood flow in the event of systemic changes in perfusion pressure, although pathological changes in the vasculature may impair these mechanisms.

## II. Normal Vascular Anatomy

### A. Arterial Supply and Anastomoses

The brain receives its blood supply from paired vertebral and internal carotid arteries as well as from anastomotic channels derived from extracranial vessels. You should be familiar with the pattern of arterial supply in the brain.

#### Anastomotic Channels

- Circle of Willis (via anterior communicating and posterior communicating arteries) – most important
- Channels between external and internal carotid arteries, especially via the ophthalmic artery.
- Leptomeningeal anastomoses between peripheral branches of the anterior, middle and posterior cerebral arteries

### B. Venous Drainage

The veins of the brain drain into the dural venous sinuses and through them to the internal jugular veins. Since the surface veins of the brain have abundant anastomoses of large caliber, localized venous obstructions may produce few effects. Because the veins

of the CNS are valveless, blood may flow in or out of the skull through these connections, providing a potential route for infection.

### C. Factors Affecting CNS Blood Flow

Normally, autoregulation in the brain keeps cerebral blood flow constant over a wide range of perfusion pressures. The mechanism by which arterioles dilate when perfusion pressure falls and constrict when perfusion pressure rises is poorly understood, but several factors are known to regulate these phenomena. The most potent effect is exerted by carbon dioxide, i.e., increased carbon dioxide causes increased cerebral blood flow.

### D. Factors Operating to Ensure Normal Substrate Requirements

- Increased extraction of glucose and oxygen from the perfusing blood
- Autoregulation of blood flow in response to changes in perfusion pressure
- Anastomoses
- Increased percentage of systemic blood flow to the CNS

## III. Ischemic Disorders

### A. Introduction

Ischemia, the failure of cerebral blood flow to a region, results in infarction (complete necrosis). The most common cerebrovascular lesions are ischemic in nature – about 85% of "strokes" are due to thrombosis or occlusive vascular disease. The vasculature that leads from the heart to the brain is the most common location of occlusive disease. The site of infarction and resulting clinical signs depend on many factors in addition to the site of occlusion, including

- extent of collateral circulation,
- presence of anomalies,
- magnitude and suddenness of occlusion, and
- duration of ischemia.

For example, when occlusion of the internal carotid artery occurs, the infarction is most commonly in the distribution of the middle cerebral artery because the area supplied by the anterior cerebral artery receives blood via the anterior communicating artery.

**Transient Ischemic Attacks** (TIAs) can serve as a warning of possible impending stroke. These are transient with **no** permanent deficits or pathology.

TIAs are brief episodes, usually involving numbness, weakness, or blindness, which are common warnings of an imminent thrombotic stroke. Symptoms and signs usually last

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less than an hour; in 90% of cases, symptoms last less than 10 minutes. Multiple TIAs usually indicate critical narrowing of the lumen of the involved artery by an atherosclerotic plaque with superimposed thrombus. Permanent occlusion (stroke) is preceded by TIAs in about 50% of cases.

#### B. Global cerebral ischemia:

Occasionally cerebrovascular lesions result from generalized reduction of cerebral perfusion. For example, if a failing myocardium inadequately perfuses a vascular system already interrupted by moderate amounts of occlusive disease, infarctions of the brain may result. These may be either "watershed" infarcts at the junctions of major arterial supplies or infarcts localized to distributions of specific arterial branches.

In addition, generalized reduction of blood flow is associated with hypoxic encephalopathy, with widespread damage. Anoxic poisons (carbon monoxide, cyanide, carbon disulfide), hypoglycemia and ischemia produce similar pathology in the nervous system. **Hypoxic encephalopathy** is characterized by necrosis of **pyramidal neurons** in selectively vulnerable deep layers of cerebral cortex (laminar necrosis), **Purkinje cells of cerebellum**, **hippocampal pyramidal cells** and (in some cases) **globus pallidus** neurons.

#### C. Focal Cerebral Ischemia -- Thrombotic (Pale Infarction due to Focal Cerebral Arterial Occlusion)

##### 1. Pathogenesis of vascular occlusion

Atherosclerotic plaque formation and thrombosis is the most common cause of stroke. The most common locations for plaque formation are the origins of the internal carotid arteries, vertebral arteries and middle cerebral arteries. Other etiologies listed below are uncommon

- Variations in coagulability of blood; e.g. post-operative changes, polycythemia
- Reduction of circulation in an impaired system; e.g. sleep, hypotension, immobilization for fracture.
- Vascular occlusion secondary to inflammatory processes, e.g. primary angiitis of the CNS or vasculitis associated with immunosuppression and opportunistic infection
- Cerebral autosomal-dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL; rare hereditary form of stroke caused by mutations in the Notch3 gene)
- Cerebral amyloid angiopathy (CAA)
- Drug abuse
- Dissecting aneurysm of extracranial vessels

Since the majority of cases of thrombosis are related to atherosclerosis, cerebral thrombosis generally occurs in individuals who have one or more risk factors producing accelerated atherosclerosis. The most important factors include hypertension, diabetes mellitus, obesity, abnormal serum lipid levels, and smoking. In young women, the combination of smoking and birth control pills is a significant risk factor.

## 2. Clinical Features

Infarction of the brain in an area supplied by a cerebral artery tends to produce a clearly recognizable clinical syndrome. The onset of symptoms is sudden, and gradual improvement may occur beginning after a few days. Specific symptoms depend on the site of infarction. A brief summary of the syndromes produced by infarction in the territory of major arteries is provided below:

**Middle cerebral artery:** paralysis of the contralateral face, arm and leg; sensory impairment over the contralateral face, arm and leg; homonymous hemianopsia or homonymous quadrantanopsia; paralysis of conjugate gaze to the opposite side; aphasia if the lesion is on the dominant side (usually the left side of brain); unilateral neglect and agnosia for half of external space if the lesion is on the non-dominant side (usually right side).

**Anterior cerebral artery:** paralysis of contralateral foot and leg; sensory loss over toes, foot and leg; impairment of gait and stance.

**Posterior cerebral artery:** homonymous hemianopsia; sensory loss and spontaneous pain (if central territory including thalamus is involved - called thalamic syndrome); third nerve palsy and contralateral hemiplegia (if central territory including midbrain is involved - called Weber's syndrome).

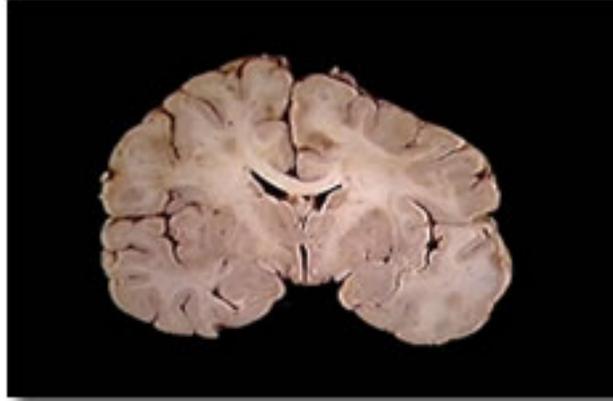
**Posterior inferior cerebellar artery:** pain, numbness, impaired sensation in face ipsilateral to lesion; impaired pain and temperature sensation in body contralateral to lesion; ataxia of limbs; falling to side of lesion; nystagmus, vertigo, Horner's syndrome, dysphagia, hoarseness.

## 3. Gross Pathology

In the first 6-12 hours a lesion is difficult to discern at autopsy. By 48 hours, the tissue becomes pale, soft, and swollen, and the gray-white matter junction becomes indistinct. From 2-10 days the lesion becomes gelatinous and friable. From 10 days to 3 weeks, the tissue liquefies, eventually leaving a fluid-filled cavity.

Edema reaches a maximum in 4-5 days. Edema acts as a space-occupying lesion and may cause adjacent damage (see image CVD 01)

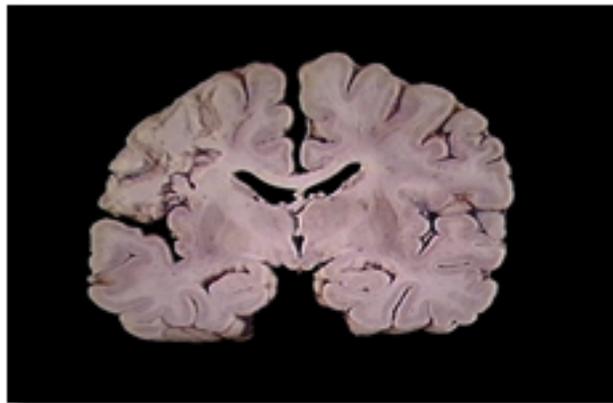
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**CVD 01**

**Coronal section showing infarct with edema in the temporal lobe at the bottom right of image.**

Cell loss, myelin breakdown, phagocytosis and glial scar production result in shrinkage and distortion of structure; cysts may form in large infarcts and compensatory ventricular enlargement may occur (see image CVD 02).

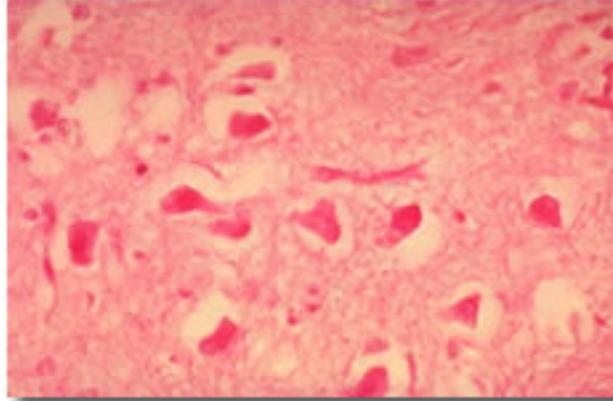


**CVD 02**

**An old infarct is shown on the left side of the image.  
This is fairly small and did not yet lead to severe shrinkage.**

#### 4. Microscopic Pathology – note time course of events

After about 12 hours: neuronal nuclear pyknosis and cytoplasmic eosinophilia (referred to as eosinophilic, ischemic or red neurons) (see image CVD 03)



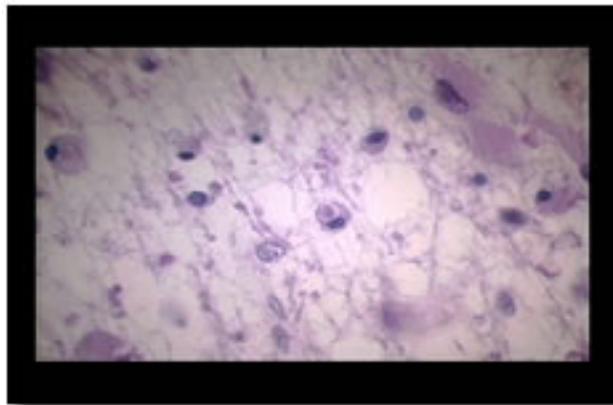
**CVD 03**

**Many eosinophilic neurons are prominent in this H&E-stained section.**

After 1-2 days: polymorphonuclear leukocyte infiltrate; capillary prominence; endothelial swelling; vacuolation of white matter

After 3-5 days: macrophages appear

After 7-21 days: astrocytes proliferate (gliosis) and may become gemistocytic; glial fibers increase; cysts are traversed by blood vessels and surrounded by firm glial tissue (see image CVD 04).



**CVD 04**

**A gemistocyte is shown in the top right corner; several macrophages are present in this cyst.**

D. Ischemia -- Embolic (Infarction, pale or hemorrhagic, due to Embolism)

1. Pathogenesis

Emboli are circulating bodies which lodge in vessels, generally involving the smaller vessels. The commonest cause of cerebral embolism is a thrombotic embolus in the middle cerebral artery. After an embolus occludes a vessel, the tissue undergoes infarction and the distal portion of the vessel becomes necrotic. If the occlusive material breaks up or moves into the necrotic area of the vessel, blood flows through the weakened wall and into the area that has been infarcted. The result is a hemorrhagic infarction. Hemorrhagic infarction often occurs with emboli, but pale infarctions may also result when the embolus does not break up or move.

## 2. Incidence

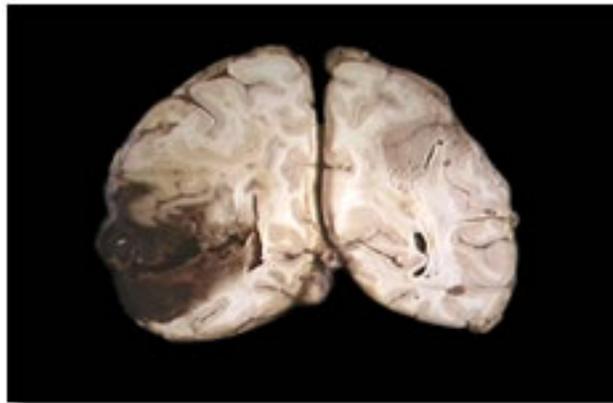
Cardiac mural thrombi are among the most common sources, and myocardial infarct, valvular disease, and atrial fibrillation are important predisposing factors.

## 3. Clinical Course

Clinical symptoms consist of sudden onset of focal impairment, within seconds to minutes. Most patients survive and marked clinical improvement often occurs.

## 4. Pathological Changes

Emboli most often produce small **hemorrhagic infarcts** in the cerebral cortex. The area involved is generally smaller than for thrombotic occlusion. Hemorrhagic infarction is characterized macroscopically by multiple, sometimes confluent, petechial hemorrhages. The superficial location may lead to associated subarachnoid hemorrhage. Fat and nitrogen emboli lodge in capillaries and cause petechial hemorrhages (see image CVD 05).



**CVD 05**

**This coronal section illustrates the appearance of a hemorrhagic infarct. Note the preservation of tissue architecture in the presence of blood.**

## 5. Types of Emboli

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The most common type is thromboemboli . These arise most frequently from the heart, but may also arise from atheromatous plaques on carotid and vertebral-basilar arteries. Fat emboli may occur following lung injury or surgery. Nitrogen bubbles may form with rapid decompression in deep sea divers.

#### E. Venous or Dural Sinus Thrombosis (Hemorrhagic Infarction)

This is the least common pattern of cerebral infarction. Hemorrhagic infarction occurs when blood stasis in large veins or venous sinuses leads to infarction, then, increased pressure disrupts capillaries causing blood to enter the infarcted areas. Abrupt occlusion of several cerebral veins or dural sinuses is necessary to produce a large hemorrhagic infarct. Slowly progressive venous or dural sinus occlusion rarely results in tissue necrosis. Predisposing factors include dehydration in children, spread of infection from adjacent foci (nasal sinus or middle ear) and disorders that cause hypercoagulability of blood.

### IV. Spontaneous Intracerebral Hemorrhage

#### A. General Comments

Intracerebral (intraparenchymal) hemorrhage accounts for about 15% of "strokes". It is much less common than infarction but more lethal - hemorrhage is the most common cause of death among cerebrovascular disorders and about 35-40% of patients survive the first year. Hypertension is the most important risk factor for spontaneous intracerebral hemorrhage. Other etiologies include AV malformation, ruptured aneurysm, amyloid angiopathy, leukemia and associated blood dyscrasias. Hemorrhage most often results from spontaneous rupture of small vessels damaged by chronic hypertension or amyloid angiopathy. In this module, only hypertensive hemorrhage will be discussed.

#### B. Pathogenesis of Hypertensive Hemorrhage

Hypertension is associated with **arteriolosclerosis** - a disorder of small arteries and arterioles (arteriolosclerosis is one type of arteriosclerosis; atherosclerosis of large arteries is also a type of arteriosclerosis). Hypertension-associated pathological changes in small vessels include thickening of the vessel walls with increased cellularity, hyalinization of the media, and the formation of small (micro-) aneurysms known as Charcot-Bouchard aneurysms. Autoregulation is impaired and vascular permeability increases. Rupture of blood vessels results in hemorrhage into the substance of the brain, but the cause of rupture is not clear. There is spontaneous rupture of small penetrating vessels damaged by chronic hypertension.

#### C. Incidence of Hypertensive Hemorrhage

The age at onset is usually greater than 50. In most cases, occurrence is associated with chronic hypertension. The incidence increases with increasing age.

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#### D. Most Common Sites

In the majority of cases hypertensive hemorrhage occurs in the area of the basal ganglia or thalamus. The pons and cerebellum are less common sites. All of these regions are supplied by penetrating arteries.

#### E. Clinical Course and Prognosis

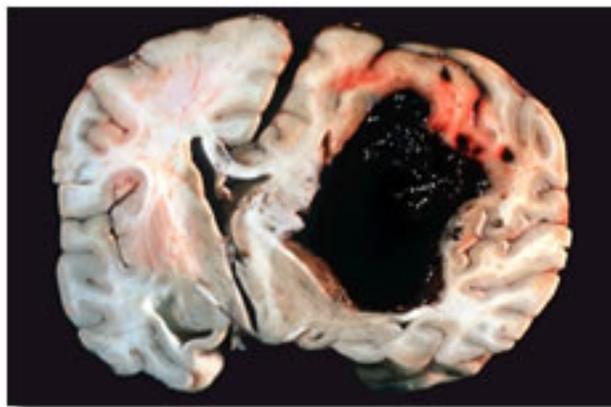
In the majority of cases there is acute onset of headache and rapid development of stupor followed by coma. Signs and symptoms depend on the location of the hematoma. CT scan readily reveals the presence of an intracerebral hematoma. Hemorrhage is not instantly fatal - death occurs in 6-36 hours in 50-70% of patients. Patients who recover may have good return of neurological functioning.

#### F. CSF Changes

CSF may be bloody because the hemorrhage may rupture directly into the subarachnoid space or intraventricular blood may enter the lumbar subarachnoid space via fourth ventricular outlet foramina.

#### G. Pathological Changes

The hemorrhage produces a large cavity filled with clot. This is a highly destructive, space-occupying lesion. Uncal herniation may occur with brainstem compression and secondary (Duret) brainstem hemorrhages. In cases of less severe hemorrhage, resolution may be associated with marked clinical improvement. The hemorrhage may expand over time, either because of continued bleeding or mechanical disruption of surviving vessels. Both vascular and cytotoxic edema may contribute to the clinical picture (see image CVD 06).



**CVD 06**

**A massive hemorrhage is seen. The cause of death was herniation leading to Duret hemorrhages in the brainstem. Note the cingulate gyrus herniation above the corpus callosum and the midline shift.**

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## V. Subarachnoid Hemorrhage and Intracranial Aneurysms

Aneurysms are abnormal localized dilatations in arteries. ***The most common non-traumatic cause of clinically significant subarachnoid hemorrhage is rupture of a berry aneurysm.***

A. Characteristics of berry aneurysms (saccular or congenital aneurysms; most common type)

1. Prevalence: Aneurysms occur in about 1-5% of the population (most of these are asymptomatic).
2. Structure: The walls are composed of adventitia and intima only; the muscular and elastic coats are absent.
3. Most common sites: In adults, aneurysms most commonly occur at bifurcations of vessels at the base of the brain, especially in the anterior circulation
4. Sequelae: Rupture is the most common sequel, with subarachnoid hemorrhage occurring most often. In addition, aneurysm enlargement may exert local pressure on adjacent structures.

B. Aneurysm Rupture (rupture of a saccular aneurysm is the most common cause of spontaneous subarachnoid hemorrhage)

1. Incidence: The age group 20-50 is most often affected but a ruptured aneurysm may occur at any age.
2. Clinical course: Rapidly developing severe headache (the "worst headache of my life"), nuchal rigidity (stiff neck), unconsciousness (consciousness may return soon). CAT scan, arteriography, and bloody CSF on lumbar puncture are helpful in diagnosis. After 3 weeks the CSF becomes xanthochromic due to breakdown of hemoglobin.
3. Prognosis: One-third of patients die of initial rupture, one-third die of a subsequent rupture (recurrence is common within 2 weeks).
4. Complications:
  - Localized arterial vasospasm due to blood and its breakdown products in the subarachnoid space
  - Hydrocephalus from subarachnoid hemorrhage and reactive leptomeningitis

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**CVD 07**

**Blood fills the subarachnoid space at the base of the brain.  
The blood is more dense in the center, surrounding the circle of Willis.**

## **VI. Vascular Malformations**

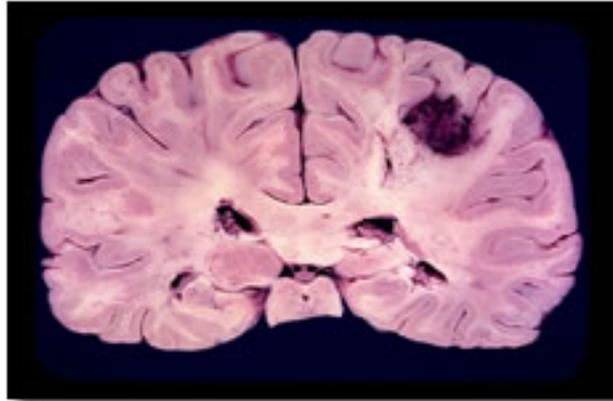
There are four major categories of vascular anomalies: arteriovenous malformations (most common), cavernous angiomas, capillary telangiectasias, and venous angiomas. These lesions are found in about 5% of patients at autopsy. They are generally asymptomatic. Clinical manifestations occur most often in young people. In fact, a vascular malformation would be the most likely cause of intracerebral hemorrhage in a child. The arteriovenous malformation is most often clinically significant.

### **A. Arteriovenous Malformations (AVM) (see image CVD 08)**

#### **1. Characteristics**

- Tangles of abnormal vessels or channels of various sizes with thin walls; vessels are separated by gliotic neural parenchyma
- Developmental (congenital) origin
- Bleeding most common in 10-30 year age group
- Most often located in cerebral hemispheres

#### **2. Clinical Signs: seizures, headache, focal neurological signs.**



**CVD 08**

**An AVM is seen in this coronal section. Microscopically there would be abnormal vessels of various sizes.**

3. Consequences:

- Hemorrhage--subarachnoid or intracerebral
- Ischemic necrosis of tissue surrounding the malformation

B. Arteriovenous Shunt

A large brain AV malformation with a sizable shunt is a common cause of cardiomegaly and congestive heart failure on the first day of life. The shunt operates throughout gestation and causes high output cardiac failure. These shunts generally occur between the vein of Galen and the middle or posterior cerebral artery. Surgical intervention can be successful in closing the shunt.

**VII. Hypertensive Cerebrovascular Disease**

The effects of hypertension on the brain include hypertensive hemorrhage, as discussed previously, lacunar infarcts, and hypertensive encephalopathy. Lacunes or lacunar infarcts (small infarcts) are the result of arteriolar pathology, and occur mainly in the basal ganglia, thalamus and subcortical white matter.

These vascular lesions greatly accentuate the severity of dementia in Alzheimer's disease; thus, reducing risk factors for small, deep brain infarcts enables greater cognitive ability in patients with lesions of Alzheimer's disease.