ANIMAL MODEL OF HUMAN DISEASE

Saccular Cerebral Aneurysms in Rats

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Biologic Features

Saccular cerebral aneurysms are produced in adult rats by ligation of one or both common carotid arteries in animals made hypertensive with deoxycorticosterone and salt treatment and fed a diet containing β-aminopropionitrile. In most rats cerebral aneurysms develop 1 month or more after starting the β-aminopropionitrile feeding.[1,2] Aneurysms develop in the large vessels at the base of the brain where hemodynamic stresses are increased.[3-5] When one carotid artery is ligated in the neck, aneurysms develop in the anterior cerebral–anterior communicating arterial complex and the proximal portion of the posterior cerebral artery on the side of carotid ligation. When both carotid arteries are ligated, aneurysms develop only in the posterior circulation. Without carotid ligation, aneurysms have never appeared. When rats are treated with carotid ligation and made hypertensive experimentally but without feeding β-aminopropionitrile, aneurysms also develop but less frequently.[2,5] Cerebral aneurysms are also induced in rats treated with carotid ligation and made hypertensive by renal infarction with or without β-aminopropionitrile.[6] Hypertension, combined with carotid ligation, plays a distinct role in the production of cerebral aneurysms in rats. Sodium chloride enhances the systolic hypertension and increases the incidence of aneurysms.[6]

Rats may die from rupture of the aneurysm. Sometimes huge aneurysms are found in rats with abnormal behavior or with decreased activity. Aneurysms are also found in rats without symptoms. Macroscopically, induced aneurysms are located on large arteries at the base of the brain. Most aneurysms are saccular in shape, and some obviously arise at the apex of the arterial bifurcation (Figure 1). Microscopically, the intima of the parent artery is thickened near the entrance to the aneurysmal sacs.[7] The internal elastic lamina and the media of the parent artery end abruptly at the opening of the aneurysm (Figure 2). The wall of the aneurysmal sac usually is composed of fibrous connective tissue, although some have cellular walls. In large aneurysms, the cavity of the sac often contains a thrombus. In some aneurysms, blebs or "daughter" aneurysms are found, which protrude from the fundus and are extremely attenuated. Scanning electron microscopic examination of induced aneurysms has revealed disarrangement of endothelial cells and craterlike defects of the intima, with adherence of leukocytes. In large aneurysms, a layer of platelets may cover the inner surface of the aneurysm.

Comparison With Human Disease

Most saccular cerebral aneurysms in man originate at the apex of the arterial bifurcation, usually of large arteries at the base of the brain. At least some aneurysms develop where hemodynamic stresses are increased. Microscopically, the intima is thickened near the entrance to aneurysmal sacs. The internal elastic lamina and the media of the parent ar-

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tery end abruptly at the entrance into the aneurysm. The wall of the aneurysmal sac is composed of fibrous connective tissue, although some have cellular walls. In large aneurysms, the cavity of the sac may contain a thrombus. These features are all seen in experimentally induced cerebral aneurysms in rats.

Catastrophic rupture is the most frequent event in the natural history of cerebral aneurysms in man. Aneurysms that do not rupture may enlarge progressively to reach a large size or may remain stationary in size and undergo thrombosis. All these features also are observed in experimentally induced aneurysms in rats.

Usefulness of the Model

Experimentally induced cerebral aneurysms in rats are similar to spontaneous aneurysms in man with regard to the site of origin, the natural history, and the histopathologic findings. Aneurysms that are not related to arterial branches also are frequently found in experimental rats.

Several other techniques for the experimental production of cerebral aneurysms have been reported.

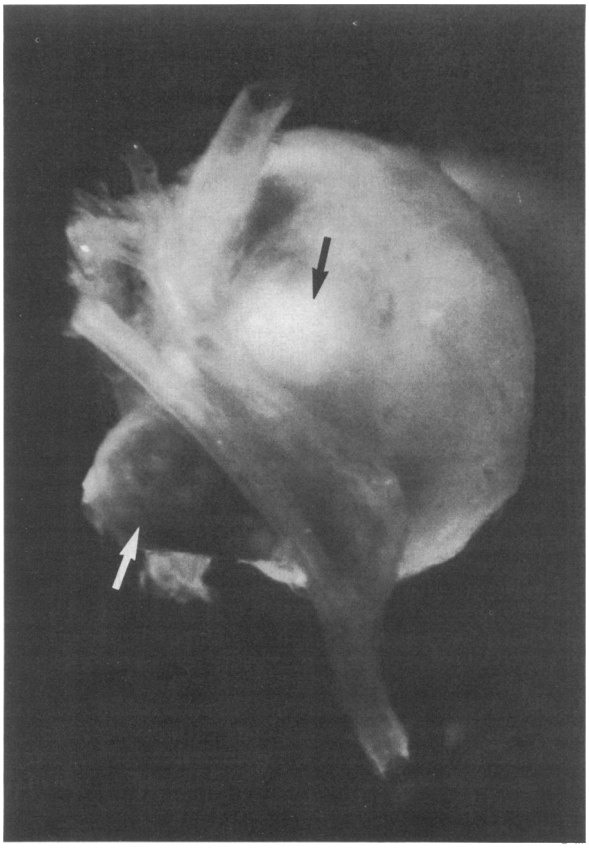

Figure 1—A large aneurysm originating from the anterior cerebral-anterior communicating arterial complex. Note the "daughter" aneurysm (*white arrow*) and plaque (*black arrow*).

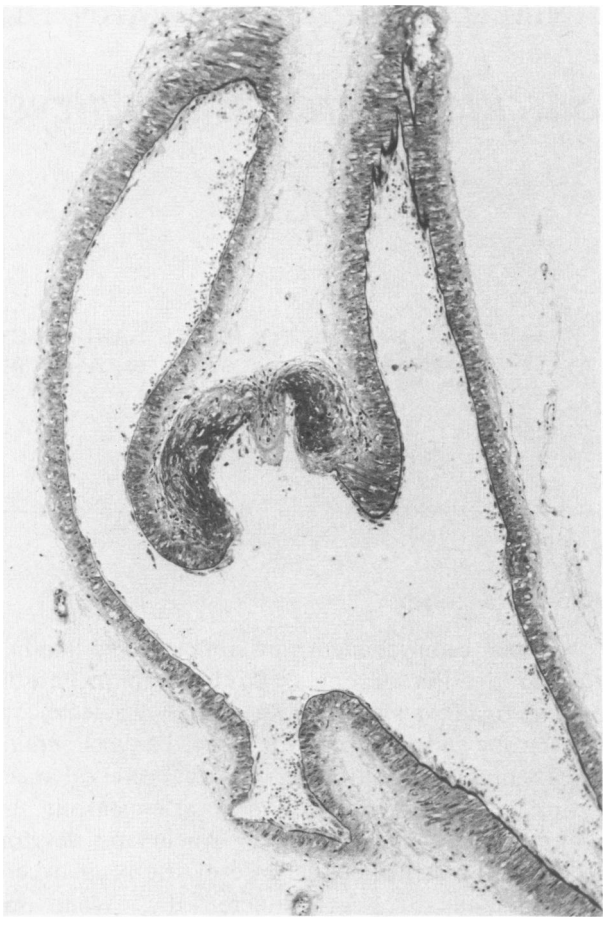

Figure 2—Photomicrograph illustrating abrupt termination of internal elastic membrane at the opening of an aneurysm originating at the apex of a bifurcation.

These include intramural injection of a variety of solutions[9] or insertion of a vein pouch.[10] However, these aneurysms differ greatly from naturally occurring, saccular cerebral aneurysms and contribute little to the study of the cause and development of spontaneous aneurysms.

In human aneurysms of the anterior communicating artery, inequality of the proximal segments of the anterior cerebral arteries are commonly found. In cases of arteriovenous malformations, cerebral aneurysms are frequently found on the vessels involved in the development of a lesion. In experimental rats, a focal increase of hemodynamic stress is achieved by carotid ligation. Hemodynamic alterations and hypertension may accelerate degenerative changes on certain portions of the circle of Willis. A relationship between hemodynamic alterations and aneurysmal development has been clearly demonstrated in rats.[3,4] The animal model may be useful in investigating whether the development of aneurysms in humans is related to hemodynamic stresses.

When hypertension and β-aminopropionitrile are not used, about 1 year is needed to induce aneurysms in rats only with carotid ligation.[5] Hypertension has been shown to accelerate aneurysmal development and increase the incidence of the lesion.[5] The fragility of the vessel wall is also considered to be one of the predisposing factors in the development of cerebral aneurysms in humans, such as occurs with connective tissue disorders. Increased fragility of cerebral vessel walls is produced experimentally by the administration of β-aminopropionitrile, which markedly increases the incidence of aneurysms in rats.[2] Possible contributory mechanisms in the development of cerebral aneurysms in humans may be elucidated by further studies with this experimental model.

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