Bucrylate was injected directly into the cerebral cortical arteries of mongrel dogs. Preparations for light and electron microscopy were obtained from 5 min to 5 months after the introduction of the polymer. A mixed pattern of damage to arterial endothelium was seen, including electron microscopic documentation of stripping away of the endothelium. Acute effects include a subocclusive thrombogenic matrix, which causes partial or complete thrombosis. The long-term reactions are those of a chronic inflammatory response to a foreign body.

Isobutyl 2-cyanoacrylate (Ethicon, Somerville, NJ) was injected into the intracranial arteries in two groups of mongrel dogs. In the initial group, the adhesive was injected through a Kerber calibrated leak balloon microcatheter [1] after fluoroscopic positioning within the internal carotid artery. Cerebral cortical vessels were injected directly in the second group of dogs. Histopathologic studies were performed on autopsy tissue.

Materials and Methods

An initial group of seven mongrel dogs was catheterized under general anesthesia, using the Kerber calibrated leak balloon microcatheter technique (fig. 1). Localizing injections with several filings placed the catheter in the internal carotid artery. The amount of 0.01–0.25 ml of isobutyl 2-cyanoacrylate (bucrylate) was injected using a 1 ml syringe followed by a flush of 5% distilled water. The catheter was immediately removed from the internal carotid artery and a contrast injection of the common carotid artery was subsequently obtained.

A second group of nine mongrel dogs underwent right parietal craniotomy using pentobarbital general anesthesia. The dura was opened and a superficial parietal cortical artery was isolated (fig. 2). This vessel was cannulated with a 27 gauge needle under

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Fig. 1.—Kerber calibrated leak balloon microcatheter technique in mongrel dogs under general anesthesia.

Fig. 2.—Isolation of superficial parietal cortical artery in mongrel dogs under general anesthesia.

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microscopic visualization. Sufficient isobutyl 2-cyanoacrylate was injected to occlude cortical vessels in the microscopic field. The operative wound was closed using standard neurosurgical technique. All dogs of this group were sacrificed at intervals from 24 hr to 5 months. The brains that were prepared for light microscopy were fixed for 2 weeks in 10% formalin. Bucrylate-injected brains obtained for electron microscopic studies were fixed in glutaraldehyde immediately after sacrifice of the animal.

**Results**

Results of the initial group of dogs were divided into immediate (less than 5 min after injection) and acute (24–36 hr). Results of the second group of dogs were all chronic studies, sacrificed 2–5 months after direct cortical injections.

Electron micrographs of arteries fixed immediately after bucrylate injection show intravascular profiles of the polymer. In some vessels, such profiles apose apparently intact endothelial cells (fig. 3). In other vessels widespread stripping away of arterial endothelial cells was observed (fig. 4).

Light microscopic study of arteries in dogs acutely sacrificed showed intraluminal meshworks of bucrylate polymer (fig. 5), which variably occluded the lumen and in some animals were associated with thrombotic occlusion. Acute ischemic neuroparenchymal damage was seen in the corresponding arterial territories.

The long-term light microscopic histopathologic reactions in small leptomeningeval arteries to intraluminal bucrylate polymer are those of a chronic inflammatory response to a foreign body. While the normal layers of the vessel wall become indistinct with variable fibrosis, collagenization, and mild focal lymphohistocytic infiltrates, the cellular reaction is a marked multilayered proliferation of cells immediately apposed to the intraluminal bucrylate (fig. 6). Neoplastic changes were not seen.
Discussion

The direct surgical approach to the introduction of bucrylate resulted in a more effective localization of the polymer than did internal carotid artery catheter injections. This direct approach resulted in less extensive neurologic deficits. Sacrificing the animals at specific time intervals was thus achieved.

Lehman et al. [2] studied the toxicity of alkyl 2-cyanoacrylates in mongrel dogs and chimpanzees. In their series radial and peroneal nerves were exposed and subsequently coated with the monomer. A second study by Lehman et al. [3] included coating of the entire exposed brain cortex with cyanoacrylate. The animals were sacrificed from 3 days to 36 weeks. Light microscopic study of tissue obtained in both series revealed various degrees of inflammatory reaction. Their studies of a series of cyanoacrylate monomers found that isobutyl cyanoacrylate exhibited the least histotoxicity and was the most slowly degraded monomer. They also found no evidence of tumor formation with long-term implantation studies of isobutyl cyanoacrylate.

White et al. [4] clinically evaluated the effects of isobutyl 2-cyanoacrylate on human visceral arteries and arterioles. Histologically there were areas of a nonstaining, slightly refractile network surrounded by large numbers of foreign body giant cells and organized thrombus. There were varying degrees of chronic inflammation containing lymphocytes and plasma cells in the thrombus and surrounding vascular tissues. The vascular outlines were unremarkable, although the internal elastic lamella was often focally disrupted. Freeny et al. [5] also used bucrylate to occlude visceral arteries and they found that injected vessels had intact internal elastic membranes with no reactive changes in the media or adventitia. The histiocytic giant-cell reaction was confined to the vessel lumen.

Vinters et al. [6] described the histology of bucrylate embolization in two patients after surgical resection of arteriovenous malformations of the brain. One patient underwent surgery 42 days after embolization. Arterial thrombosis and inflammatory giant-cell reaction was seen. The second case was followed for 1 year subsequent to embolization. Light microscopy showed chronic inflammation in and around the vessel walls. Reactive gliosis in the surrounding parenchyma was noted. Walls of injected vessels were thickened.

Zanetti and Sherman [7] studied the effects of bucrylate on mongrel dog renal arteries, surgically constructed arteriovenous fistulas, and vein pouch aneurysms. The authors reviewed the histology of acute and chronic occlusion lesions. They concluded that the adhesive causes permanent intravascular blockage. In acute occlusions the adhesive was focally in contact with the intima. The chronic occlusions, however, showed fibrous tissue formation and chronic inflammation.

Hood et al. [8] reviewed the direct effect of carbohexoxyethyl 2-cyanoacrylate upon the cat cerebral cortex. The animals were sacrificed at 4 and 7 days after the application of this new adhesive. Meningeal necrosis, astrocytosis, vascular wall degeneration, hemorrhage, and inflammatory reaction was seen.

Our results indicate a mixed pattern of damage to arterial endothelium in which the endothelium appears intact in many vessels, but is stripped away in other vessels. Whether such stripping reflects the toxic effects of bucrylate or mechanical artifacts of intraarterial injection is not verified by our data. The immediate effects of bucrylate relate to the amount of ischemic neuroparenchymal damage after occlusion of arteries by the bucrylate.

Acute effects showed multiple arteries and arterioles within the cerebral hemispheres containing irregular meshworks of polymerized bucrylate. Endothelial stripping was seen. The bucrylate polymer provides a subocclusive thrombogenic matrix that causes partial or complete thrombosis. Acute neuroparenchymal damage consisted of ischemic cortical neurons showing a distinct eosinophilic change in the territory of the injected vessel. This finding presumably reflects the pattern and degree of arterial occlusion rather than possible toxic effects of bucrylate on vessels or parenchyma. Electron microscopic findings revealed gross disruption and stripping of endothelial cells by the polymer.

The long-term histopathologic reactions are those of a chronic inflammatory response to a foreign body. The normal layers of the vessel wall become indistinct with variable amounts of fibrosis, collagenization, and mild focal lymphohistiocytic infiltrates. However, the main cellular reaction is a marked multilayer proliferation of cells immediately exposed to the intraluminal bucrylate. This chronic inflammatory response is common to many foreign bodies. Neoplastic changes were not seen.

REFERENCES