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Review article

The histotoxicity of cyanoacrylates

A selective review

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Summary. Cyanoacrylates, a group of rapidly polymerizing adhesives, have found widespread uses in oral and general surgery as well as surgical subspecialties, for example as hemostatic and anastomotic agents. They have been utilized most recently as materials for embolotherapy of complex cerebral and extra-cerebral vascular anomalies. The histopathology that results from their deposition in human tissues is thus an important consideration, and the subject of this review. Particular attention is given to the fate of cyanoacrylates in cerebral lesions after iatrogenic embolization procedures. The apparent toxicity of these plastics on blood vessel walls is discussed in relation to experimental observations. It is imperative that clinicians who use this group of substances evaluate their potential functions in the light of the pathologic findings.

Key words: Cyanoacrylate - toxicity - blood vessels - embolization

Chemistry

The adhesive action of alkyl 2-cyanoacrylates was discovered in the course of experiments carried out to characterize polymers derived from 1,1-disubstituted ethylenes [1]. Two refractometer prisms became accidentally glued together and could not be separated. Eastman 910 adhesive was developed shortly thereafter. Several methods are available for preparing alkyl cyanoacrylate [1-3], e.g. by reacting formaldehyde with alkyl cyanoacetate to obtain a polymeric material and then depolymerizing the material by heating to distill off the liquid monomer. A crucial problem during preparation is that of removal of water, which is known to cause the monomer to polymerize. Several liquid and vapour phase polymerization inhibitors are used, the most common being phosphorous pentoxide, O-sulfobenzoic anhydride, nitric oxide and sulfur dioxide.

The alkyl 2-cyanoacrylates belong to a class of vinyl monomers known as 1,1-disubstituted ethylenes, and are represented by the structural formula

$$C_2H=C\begin{matrix}^{X}\\_{Y}\end{matrix}$$

where X and Y may be any of several electronegative groups. For instance, when X is the nitrile group ($-CN$) and Y is alkoxycarbonyl ($-COOR$), the resultant compound is a rapidly polymerizing adhesive. It is possible to prepare several other compounds based on alterations of the X and Y groups, some of which have poor adhesive properties. Some alkyl cyanoacrylates (e.g. methyl 2-cyanoacrylate) polymerize at room temperature when spread as a thin film and polymerization is directly affected by the presence of available humidity.

An exothermic reaction occurs with alkyl cyanoacrylate polymerization, which can be initiated (e.g. in the case of methyl 2-cyanoacrylate) by free radicals or anions [1]. Isobutyl 2-cyanoacrylate (IBC) polymerizes upon contact with an ionic solution or endothelium. With methyl 2-cyanoacrylate, a thin water film may be the initiating agent. The necessary chemical bonds form much less rapidly on a slightly acidic surface (e.g. oak wood) than on an alkaline surface (e.g. glass).

The speed of polymerization in a given compound is a function of the alkyl side chain [4, 5]. Alkyl cyanoacrylates with 4 or 6 carbon atoms have the ability to polymerize within seconds of contacting tissue. The length of the side chain also affects other physico-chemical properties, e.g. wettability and

flexibility. The methyl compound (short chain) is a highly flexible material, while the butyl type is less so. In general, cyanoacrylates generate heat as they are transformed from monomeric to polymeric form, a fact that may be of substantial importance in considering their histotoxicity.

Detection of cyanoacrylates in tissue sections may be troublesome because they are partly or totally dissolved by routine histological processing and embedding procedures. Cyanoacrylates fail to stain with regular histological stains. However, a technique has been formulated whereby the materials can be detected histologically [6].

Use of cyanoacrylates outside the CNS

Animal studies have investigated possible uses of cyanoacrylates for a range of surgical functions that includes the closure of incisional wounds, the placement of skin grafts, and the anastomosis of tubular organs [7-9]. O'Leary studied the hemostatic properties of isobutyl cyanoacrylate after total abdominal hysterectomy in dogs, concluding that although hemostatic properties are acceptable, the tensile strength of the material is not [10]. Studies utilizing methyl 2-cyanoacrylate reported successful hemostasis for wounds of the liver, kidney, lung, spleen and pancreas [11-14]. Likewise, many experiments carried out in the 1960's reported the successful use of various cyanoacrylate monomers for hemostasis in experimental surgery of the gastrointestinal tract, kidney and liver [15]. An early symposium reviewing several other potential uses for cyanoacrylates in the body, and some of the observed histotoxicity, has been published [16].

Today, the major indication for use of cyanoacrylates is in patients for whom bleeding cannot be stopped by conventional means and life is threatened. Frequently, this occurs in patients who have suffered massive trauma or have developed leaks from anastomotic vessels that are inadequate. Cyanoacrylates have been used in sutureless anastomosis of small vessels, and in selected patients with solid visceral injuries, particularly of the liver and kidney. In ophthalmic surgery, they have been used in cases of stromal melting of the cornea, for sealing of corneal perforations and lacerations, and for repair of conjunctival fistulas [17]. Cyanoacrylates have been used in plastic and reconstructive surgery, e.g. in skin grafting [18]. In otologic surgery, they have been used in reconstruction after ossicular disruption [19].

Widespread use of these materials in dentistry and oral surgery led to some of the earliest histopathologic data. Animal and human studies have examined the use of cyanoacrylates in areas of surface dressing after soft tissue surgery and in pulp capping techniques, where the plastics may be a component of the filling material [20-23]. They have been used for conventional periodontal dressings, and were administered using a spray gun [24]. They have been used as a spray covering for biopsy sites, after minor surgical procedures or extractions, and in therapy of oral and skin ulcers [25-27]. Cyanoacrylate adhesives have been used for mucosal grafts, by application to both donor and recipient sites, thus expediting adhesion of the graft as well as successful healing [28].

Mechanisms of toxicity

In examining the literature some general principles emerge from the mass of investigations carried out on cyanoacrylates: methyl 2-cyanoacrylate stimulates an acute severe inflammatory response, the length of the alkyl chain determines toxicity, the higher homologues are in general less toxic (e.g. when applied to peripheral nerves) and the higher homologues are degraded more slowly [29-33]. Effects of various cyanoacrylate plastics on rats, guinea pigs, rabbits, cats, dogs, pigs, chimpanzees, and human patients, as well as cultured fibroblasts and bacteria, have been assessed. A broad range of tissues, organs and bodily fluids has been examined. Effects of the adhesives on blood vessels have been studied with renewed interest, and the relevant findings will be presented in the next section in view of their special relevance to cyanoacrylate embolotherapy.

Because of their potential use in ophthalmic surgery, cyanoacrylate monomers (octyl, decyl, isobutyl) were applied to the denuded cornea of rabbits and guinea pigs and injected into the corneal stroma of guinea pigs [34]. Initially a severe polymorphonuclear cell infiltration of the corneal stroma appeared around the adhesive, followed by severe neovascularisation and areas of granulomatous response. These changes were seen between the 5th and 21st days and were similar for all three polymers.

Because of the potential usefulness of an innocuous tissue adhesive in treating soft tissue wounds, the histotoxicity of methyl, hexyl, and decyl-2-cyanoacrylate on various soft tissues in the rat was examined [29]. It was found that methyl 2-cyanoacrylate was intensely necrotising and pyogenic when applied as a monomer and polymer to the cut surface of the liver, subcutaneous fat and muscle and femoral bone marrow and the tissues were examined from 6 h to 63 days later. The methyl monomer evoked this in-

tense reaction in only 6 h in subcutaneous tissue. Later, granulation tissue encapsulated the polymer and became wider and more vascular. By 63 days part of the polymer mass had disappeared, yet phagocytosis was not seen. The polymer mass was always surrounded by a zone of necrotic tissue elements which separated it from the inflammatory cells and by this time polymer fragments and cell debris were appearing, imprisoned in a capsule of granulation tissue. The same kind of response was seen in the liver beneath the site of application of the adhesive, commencing with a zone of coagulation necrosis and haemorrhage at 6 h. By 63 days, the methyl polymer was no longer visible and the site was marked by a narrow fibrous scar. Similarly, in the marrow cavity there was at first widespread necrosis, haemorrhage, and intense inflammation about the methyl polymer. By 28 days the mass was extruded from the marrow cavity and then healing took place.

Hexyl- and decyl-2-cyanoacrylate homologues evoked only mild transient inflammation in subcutaneous tissue so that by 3 days the hexyl homologue implantation site was surrounded by a narrow zone of mononuclear and plasma cells, and by 14 days there was a conspicuous foreign body giant cell (FBGC) reaction with subdivision of the mass into irregular amorphous masses, different from the uniform rhomboid plates of the methyl polymer. Fibroblasts and collagen had appeared. The decyl homologue evoked similar changes.

In the liver, hexyl and decyl application sites were at first surrounded by a transient acute inflammatory cell response that was followed by a FBGC reaction isolating the polymer mass from the parenchyma. In the marrow cavity there was only transient inflammation in response to the hexyl and decyl polymers so that by 7 days marrow elements could be found next to polymer masses, by 28 days little polymer remained, and by 63 days cortical bone had been restored.

Implanted hexyl and decyl polymer discs induced far less inflammatory reaction than the corresponding monomer and there was inconspicuous chronic inflammatory cell reaction and circumferential fibrosis with FBGC's being rarely seen, in contrast to the monomer injections described above.

N-alkyl -cyanoacrylates form tightly adherent coatings when sprayed or otherwise applied directly to the skin and the question arises (as it does in relation to other organs) as to whether there is any absorption of the monomer or its degradation products. By tagging methyl, n-butly and n-heptyl α-cyanoacrylate with ^{14}C, Ousterhout et al. [35] demonstrated that in rats there is absorption of these substances from intact skin and split-thickness skin graft donor sites, proved by radioactivity in the urine. Urinary radioactivity was three times greater when the adhesive was applied to a split-thickness skin-graft donor site. The data also showed that urinary ^{14}C activity was in the order methyl > n-butyl or n-heptyl which is consistent with the known fact that higher homologues are degraded more slowly than lower ones. Whether urinary radioactivity was due to degradation products or absorption of intact monomer, which is fat soluble and not water soluble, was not investigated.

Perhaps a by-product or a diffusible substance produced by isobutyl polymer causes varying degrees of growth inhibition when isobutyl monomer is placed on a Petri dish streaked with pure cultures of bacteria. Growing colonies of streptococcus were actually destroyed by the polymer. Definite zones of inhibition were found around the polymer and from the physical appearance of the zones it was postulated that some diffusible substance containing a bacteriostatic agent, was present [36]. Similar conclusions were reached in other experiments [37].

Soluble degradation products of cyanoacrylate adhesives have been implicated in causing cell death in mouse fibroblast tissue cultures. Galil et al. [38] compared the effects of an industrial cyanoacrylate compound (KG) not authorised for biological use, and n-butyl 2-cyanoacrylate, a biological tissue adhesive authorised by Canadian but not USA authorities. Using the agar overlay tissue culture technique, filter paper discs containing the polymerised cyanoacrylate were implanted on fibroblast monolayers. Around the KG disc the cells were totally killed within 12 h and around the n-butyl 2-cyanoacrylate, the zone of cell death progressed at a slow rate to a maximum in 4 days.

Mutagenicity of cyanoacrylates has been investigated [39]. Both isobutyl and n-butyl-cyanoacrylate were demonstrated to have a mutagenic capacity using the standard Ames test. In this test, as in any mutagenicity assay, the observed mutations are related to a small part of the bacterial genome. A positive result implies that the product under study is mutagenic for man, and the test is a reliable method for detecting carcinogens. Yet the clinical impression remains that cyanoacrylates are in general non-carcinogenic.

Cyanoacrylates in neurosurgery and neuroradiology

Suggested and proven functions of cyanoacrylates in this field have included (a) use as adhesives to coat or reinforce berry aneurysms, (b) use as a glue to treat dural cerebrospinal fluid (CSF) leaks, (c) use as

Table 1. Tissue reactions to IBC emboli: experimental studies

Animals and lesions embolized	Post-embolization interval	Pathology	Reference
1. Porcine GIT	3–5 months	Thrombus and FBGCs; lymphocytes, plasma cells in and around thrombi; i. e. l. variably disrupted; ulcers, infarcts, abscesses near IBC.	[105]
2. Canine GIT	1 month	Mild fibroblastic inflammatory reaction extrinsic to muscularis; focal areas of inflammation with partial replacement of media	[106]
3. Canine A-V fistulas, vein pouch aneurysms, normal renal arteries	Up to 3 months	PMNs initially; fibrosis, FBGCs at 2 months; "rare degenerating endothelial cell"; denting of i. e. l.; media--"shrinking and hyperchromatism of few nuclei adjacent to i. e. l."	[109]
4. Normal canine cerebral vessels	5 min to 5 months	Acutely--endothelial loss; chronic--FBGC; normal vessel wall layers indistinct with variable fibrosis, mild focal inflammation	[110]
5. Porcine iliac artery	14–35 days	Chronic inflammation; destruction of intima; FBGCs; intact elastica with loss of "undulations"	[107]
6. Canine splenic artery	2–7 weeks	Thrombus formation only	[108]

Abbreviations: GIT = gastrointestinal tract, FBGC = foreign body giant cell, i. e. l. = internal elastic lamina, A-V = arteriovenous, PMN = polymorphonuclear leukocyte

Table 2. Tissue reactions to IBC emboli: human pathologic studies

Lesions embolized (specimens/patients treated)	Post-embolization interval	Pathology		Reference
		Inflammatory	Vascular	
1. GIT neoplastic and other (6/14)	2–196 days	nil or FBGC	nil	[113]
2. GU abnormalities neoplastic and other (3/14)	3 h to 4 months	FBGC in IBC casts (4 months)	nil	[115]
3. GIT non-neoplastic (2/16)	16 days	nil (IBC and thrombus)	nil	[114]
4. Medical splenectomy (splenic a.) (2/15)	3 weeks	nil	nil	[117]
5. AAA repair (iliac, hypogastric a.) (1/3)	6 weeks	nil	nil	[116]
6. Cerebral aneurysms (2/20)	3 years	aneurysm occluded by IBC "no evidence of aneurysm wall necrosis compatible with chronic inflammatory change"		[72]
7. Cerebral AVM (1/3)	56 days	nil	nil	[94]
8. Cerebral AVM (2/2)	42 days, 1 year	FBGC in lumen, mononuclear cells around	?	[118]

Abbreviations (also see Table 1): GU = genitourinary, a = artery, AAA = abdominal aortic aneurysm, AVM = arteriovenous malformation

a chemical 'suture' material in the re-anastomosis of severed nerves or blood vessels, and (d) use as embolic material in the therapeutic embolization of encephalic arteriovenous malformations (AVMs), carotid-cavernous fistulas (CCFs) and, less commonly, berry aneurysms. Though this section will deal primarily with these techniques and the related histotoxicity, other pathologic data (from both animal experiments and observations in human lesions) will be reviewed, as they may have direct relevance to the CNS lesions.

Several reports have described coating of aneurysms or leaking cerebral vessels with cyanoacrylates (e. g. ethylcyanoacrylate, methyl 2-cyanoacrylate) for purposes of reinforcement [40–43]. A cyanoacrylate coating may be used to strengthen classically clipped aneurysms [44, 45]. Though there has been little reported histopathologic follow-up, one patient developed thrombosis of the parent vessel 20 days after aneurysm coating with ethylcyanoacrylate [41]. Methyl 2-cyanoacrylate has been found to cause necrosis of a middle cerebral artery (MCA) aneurysm wall [46] producing fatal subarachnoid hemorrhage 3 days after the coating procedure, and in another instance without pathologic documentation [47] late thrombosis of the MCA aneurysm and feeding vessel. Extensive clinical experience with ethyl 2-cyanoacrylate has suggested minimal overt vascular his-

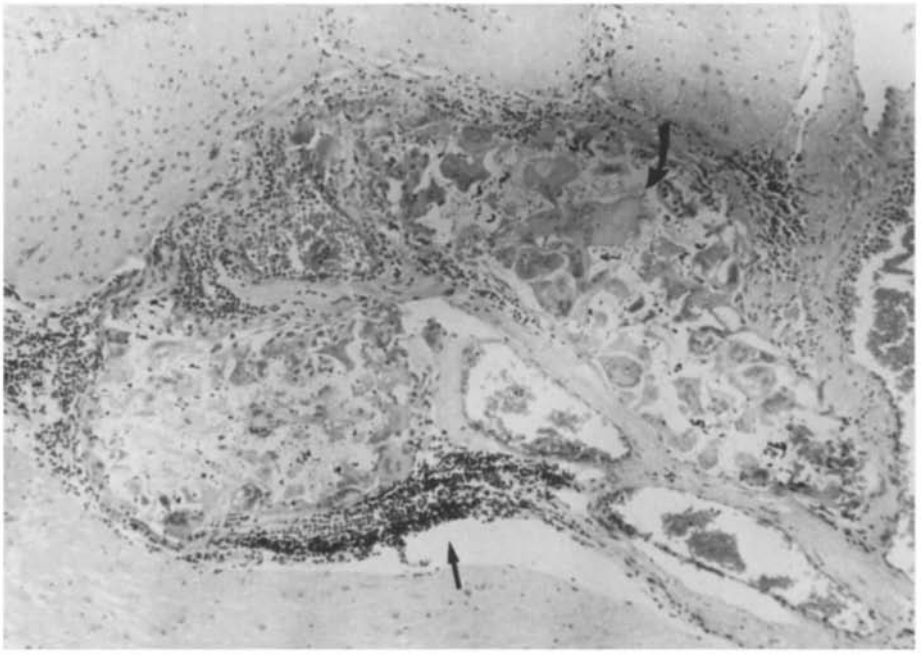

Fig. 1. Section from an AVM embolized 16 months prior to resection. IBC-tantalum mixture, portions of which appear extravascular, surrounded by many FBGC's *(curved arrow)* and focally pronounced mononuclear inflammatory infiltrate in and around vessel wall *(straight arrow)*. Hematoxylin and eosin, × 135

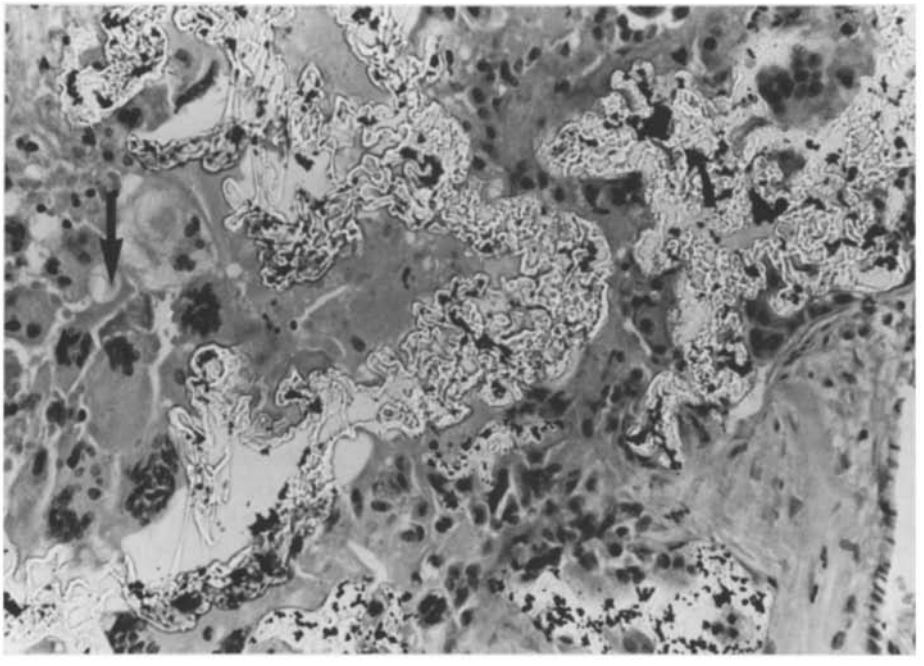

Fig. 2. Section from a left temporal AVM embolized with IBC-tantalum more than a year prior to resection. IBC thrombus appears as serpiginous material, often in thin strands, which is slightly refractile. Irregular black particles are tantalum *(curved arrow)*. FBGC's and histiocytes *(straight arrow)* surround the material. Hematoxylin and eosin, × 300

totoxicity [40], i.e. there is a low incidence of rebleeding or vasospasm. Much animal work has been carried out to assess possible toxic effects of the materials when they are applied to the cerebral cortex and adventitial vascular surfaces. Results with ethyl 2-cyanoacrylate and ethylcyanoacrylate have been rather contradictory, but in the worst situation show consistent inflammation, degeneration, and necrosis in the adventitia and media of normal vessels with thrombosis, and non-specific necrotic cortical and meningeal alterations in the cat [40, 48–50] as well as false aneurysm formation at the sites of arteriotomy [51, 52] in rats. Comparable findings, though of somewhat lesser severity, have been noted with a newer adhesive, carbohexoxy-methyl 2-cyanoacrylate [53].

Several studies have addressed the issue of methyl 2-cyanoacrylate toxicity when the material is applied to peripheral or central nervous system (PNS, CNS) tissue (considering that even minimal cytotoxi-

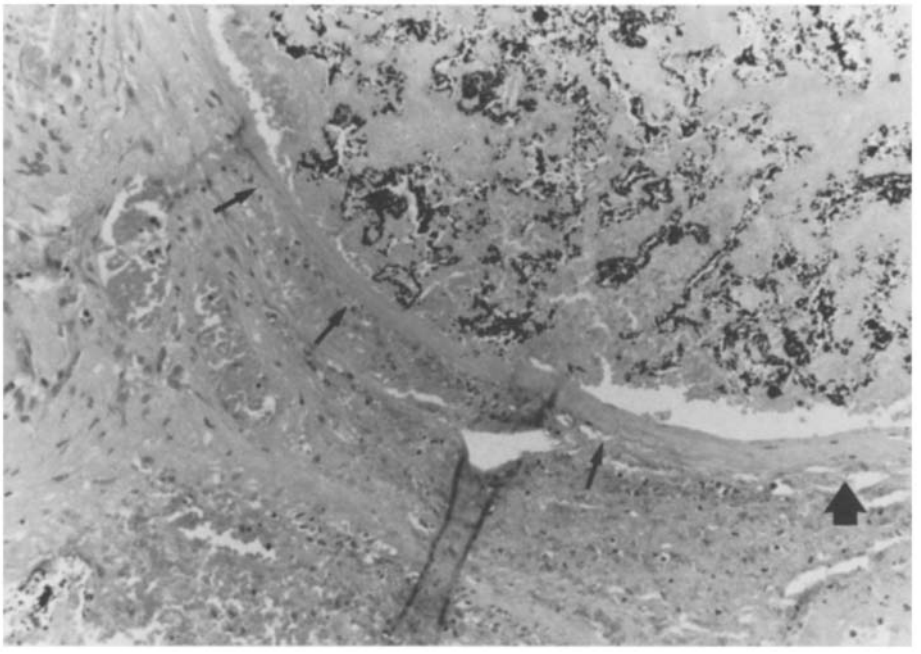

Fig. 3. AVM embolized 7 days prior to resection. IBC-tantalum mixture in lumen of a vessel *(upper right)*. Most of the adjacent vessel wall *(arrows)* shows necrosis with loss of medial nuclei. Neuroglial parenchyma adjacent to necrotic vessel wall also shows necrosis with karyolysis. A few residual nuclei are identified in portion of vessel wall *(arrowhead)*. Hematoxylin and eosin, × 215

city might result in neurological sequelae) and/or the vascular adventitia in a variety of animal species. The importance of specifying the exact form of the plastic used in experiments has been emphasized [54]. Observed neurotoxicity has included neuronal necrosis and gliosis in the CNS as well as perineural inflammation, neurilemmal and non-specific axonal damage in the PNS [54, 55]. Granulomatous inflammation was noted. When a series of cyanoacrylates (methyl, n-butyl, n-propyl, n-heptyl, n-octyl and isobutyl) were tested on canine radial and peroneal nerves, the methyl compound produced the most severe changes. Nerve fibers showed a gradient of degeneration up to digestion chambers in the myelin sheaths, the pathology being greatest peripherally in the area closest to the adhesive coating [31].

Vascular damage has taken the form of severe adventitial and medial necrosis or erosion of large arteries, sometimes with delayed and deficient healing [54, 56, 57]. Perhaps suprisingly, few instances of thrombosis were encountered in large arteries (3–5 mm external diameter). However, damage to small arteries (0.5–2 mm) may also consist of severe medial necrosis with replacement of the media by fibrous tissue and resultant intimal proliferation [58]. Only the elastica has shown pronounced resistance to the toxic effects of the plastic, again suggesting caution in the use of this substance to reinforce berry aneurysms, which are already deficient in elastica. The vascular wall damage in these smaller vessels has produced fusiform dilatation and frequent thrombosis in long-term follow-up. A material with optimal properties for aneurysm coating appears to be needed if this procedure is to become an adjunct to, or substitute for clipping.

IBC has been successfully used to treat CSF leaks [59–61] but the only histology available in follow-up of these patients [59] showed (3 weeks after surgical application of the material) a few scattered foci of inflammatory cells near the adhesive.

Cyanoacrylates would seem to be ideal materials for use as chemical 'sutures' in the re-anastomosis of traumatized nerves or blood vessels and patching of arteriotomies [62–65]. Yet animal studies with methyl 2-cyanoacrylate in peripheral nerve repair [66] suggest few benefits over standard suture repair. With all cyanoacrylates, a brisk inflammatory reaction and axonal damage within the nerve have been identified [49, 50, 66]. Methyl 2-cyanoacrylate, when used together with microsurgical reconstruction of small arteries, resulted in the expected medial necrosis and histiocytic inflammatory response, but an overall acceptable outcome [64]. Alpha ethyl cyanoacrylate has been shown to cause negligible vessel damage when applied to arteries of 1 mm outside diameter [65]. Rat aortas cut and rejoined using IBC, when examined up to 6 weeks postoperatively, showed degeneration of the media with focal calcium deposition, and a more intense and prolonged FBGC reaction than in sutured vessels [67]. The observed toxicity was attributed to the adhesive's heat of polymerization and/or the degradation products of the fission of the polymer, which include formaldehyde and alkyl cyanoacetate. When a series of cyanoacrylate adhesives

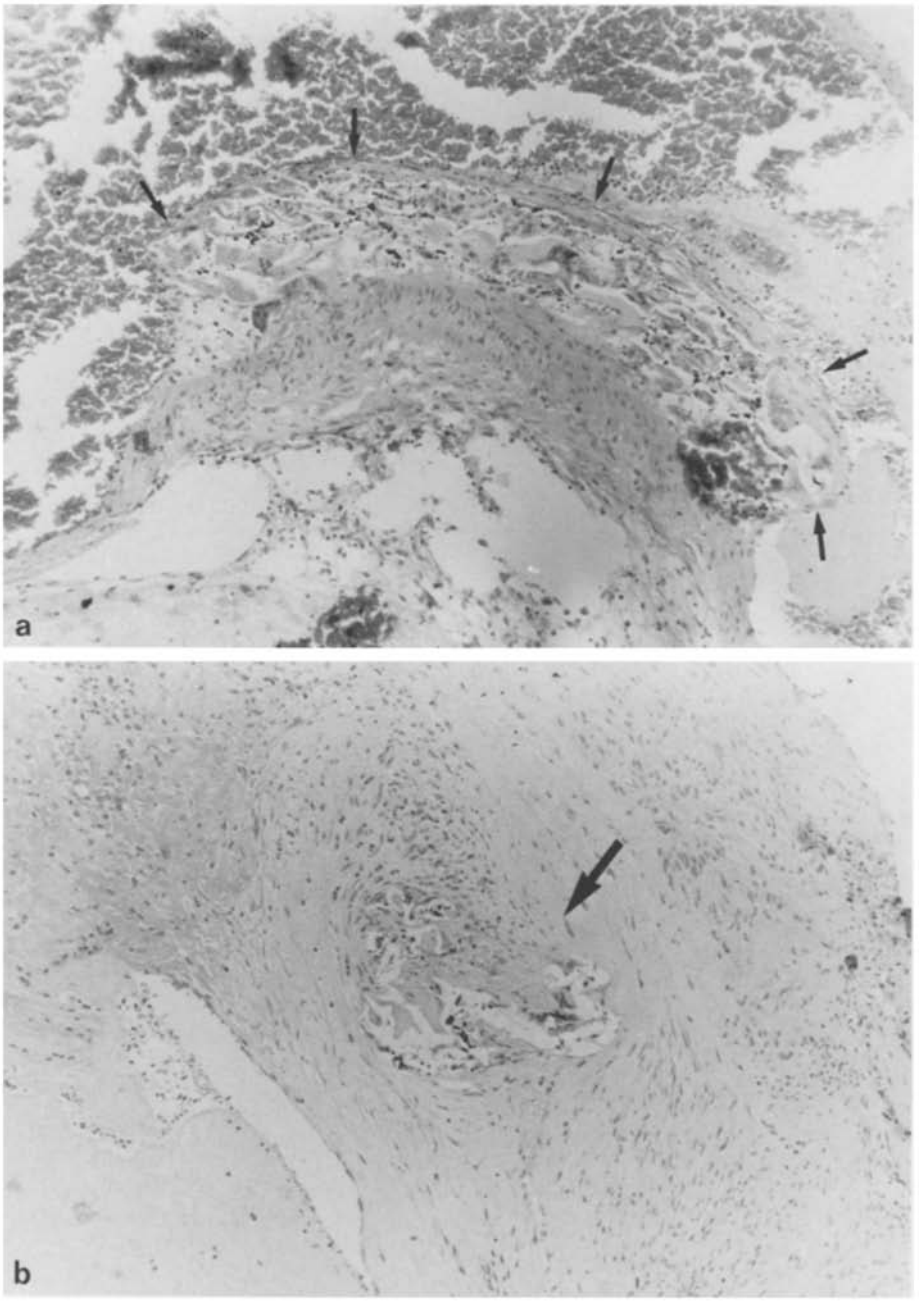

Fig. 4 a and b. Sections of AVM's embolized 2 weeks (**a**) and 4.5 months (**b**) before resection. In **a,** IBC is noted to be adherent to luminal surface of a vascular channel, and is lined by endothelium *(arrows).* RBC's in lumen seen at top. In **b,** IBC-tantalum mixture *(arrow)* is embedded in fibromuscular cushion of a thickened channel wall. Hematoxylin and eosin, A × 110, B × 130

was tested for local toxicity (e.g. presence of leukocyte infiltration, extent of medial necrosis and mural calcification) on rabbit aortas, the butyl adhesive was consistently found to be less toxic than cyanoacrylates with methyl and ethyl radicals [68].

Therapeutic embolization of cerebral vascular lesions with plastic adhesives is now a relatively common procedure in specialized centres. IBC is essentially the only cyanoacrylate to be used for this purpose. Though CCFs [69–71] and even berry aneurysms [72] have been treated by IBC embolotherapy, the largest experience has been with embolization of cerebral or spinal cord AVMs [71, 73–83]. Embolization is performed either as the primary therapy or in conjunction with surgical resection, and may be carried out by the femoral approach or at craniotomy in the case of encephalic lesions. Clinical indications for the best approach for embolizing the AVM in a given patient have been thoroughly discussed [73, 78–95]. The advantages and disadvantages of IBC over other embolotherapy materials for both CNS and non-CNS lesions has been presented

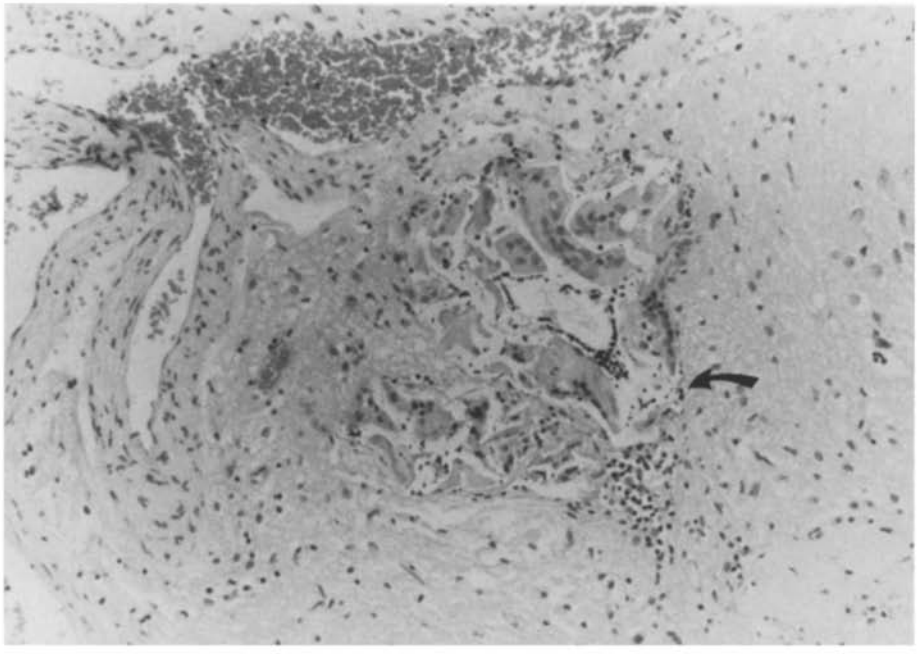

Fig. 5. Section from AVM embolized 3.5 months before resection. IBC-tantalum mixture with FBGC's and lymphocytes is seen lying in neuroglial parenchyma, totally outside vessel lumen, which can be identified at left. Interface between embolized material and parenchyma *(arrow)* shows no vessel wall remnants. Hematoxylin and eosin, × 210

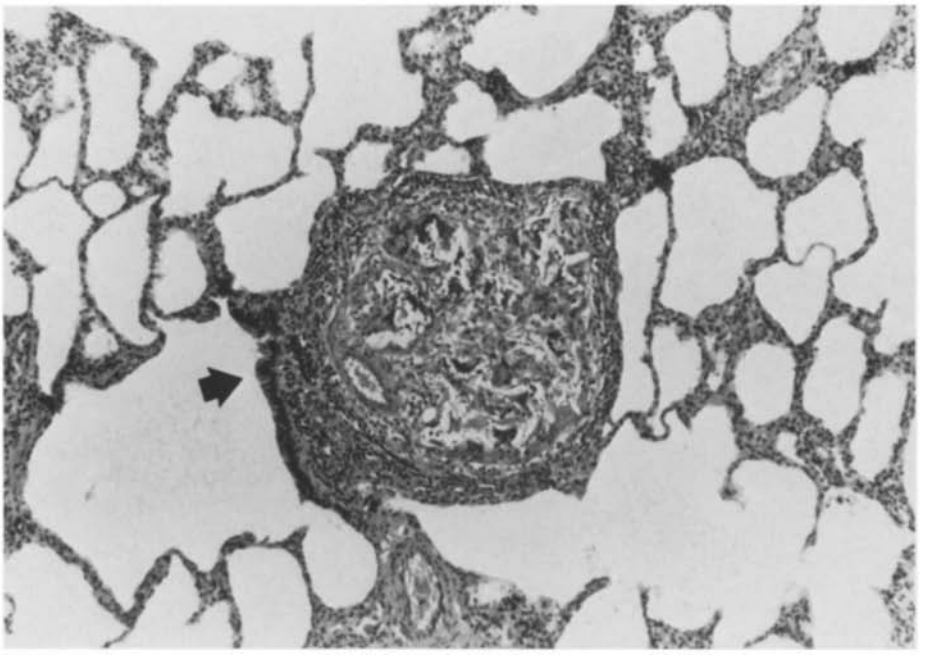

Fig. 6. Section of lung from a patient with a large thalamic and mesencephalic AVM embolized (with IBC-tantalum) on several occasions, as early as 33 days prior to death. IBC and tantalum is seen in a pulmonary vessel, surrounded by FBGC's and lymphocytes *(arrow)*. No IBC identified in adjacent alveolar spaces. Hematoxylin and eosin, × 130

[96–104]. A discussion of these is beyond the scope of the present review.

Though almost all authors stress the need for animal experimentation with IBC (given its unusual physical properties) prior to human use, relatively few studies have discussed pathologic changes induced by IBC when it is used specifically as an endovascular agent (Table 1). Examination of porcine [105] and canine [106] gastrointestinal tract up to 5 months post-embolization has shown thrombi with FBGCs and chronic inflammatory cells in and around occluded vessels with focal disruption of the elastica [105], as well as parenchymal lesions attributed to ischemia. Porcine internal iliac arteries with IBC emboli have shown, after 14–35 day follow-up, chronic mural inflammation, luminal FBGCs, patchy intimal disruption, and 'straightening' of the elastica [107]. Experimental obstruction of canine splenic arteries resulted in no inflammation when IBC was used, but a marked transmural necrosis

when flucrylate (trifluorinated isopropyl ester of cyanoacrylate) was employed [108].

In an experimental model of arteriovenous fistulas and vein pouch aneurysms in dogs [109] that might be expected to have greatest relevance to the treatment of human cerebral vascular anomalies, the authors have described a sequence of inflammatory changes beginning with a polymorphonuclear infiltrate and progressing to fibrosis and FBGC formation 2 months after IBC occlusion. A "rare degenerating endothelial cell" was described at points of contact with IBC, and there was denting of the elastica and subtle alteration of the media. Canine cerebral arteries examined up to 5 months after IBC injection have shown possible endothelial stripping acutely (a mechanical artifact could not be excluded), and in later follow-up, a chronic granulomatous and lymphohistiocytic inflammatory response with variable mural fibrosis [110].

Studies on the effects of IBC on human tissues (Table 2) have been few. Surprisingly, several opportunities to examine IBC-embolized organs have been passed up or if material was examined, results have not been reported [111, 112]. Lesions (neoplastic and non-neoplastic) that cause genitourinary and gastrointestinal hemorrhage are now commonly embolized with IBC [113–115]. Pathologic follow-up for as long as 196 days has shown a characteristic FBGC reaction in the IBC thrombus but negligible vascular changes. Large artery IBC embolizations in conjunction with abdominal aortic aneurysm repair [116] or for purposes of medical splenectomy [117] have produced negligible vascular pathology.

In one patient who died 3 years following iatrogenic berry aneurysm thrombosis with IBC [72], there was "no evidence of aneurysm wall necrosis compatible with chronic inflammatory change", and the point of aneurysm sac breakdown did not contain IBC. One case of a cerebral AVM resected 56 days after embolization failed to show any reaction to IBC [94]. However, we have reported the findings in two embolized AVMs removed 42 days and 1 year after embolotherapy [118]. Both showed a typical FBGC reaction and a perivascular lymphocytic inflammatory infiltrate.

We have subsequently undertaken a detailed examination of sub-serial sections of AVMs previously embolized with IBC [119]. In nine cases (including the two previously reported), embolotherapy was performed from 7 days to 16 months before surgery. Though detailed results of the study will be published elsewhere, we have continued to observe a pattern similar to that initially described [118], i.e. a brisk FBGC reaction that is noted within 5–7 days of embolization and persists for up to 16 months (Fig. 1). A mononuclear inflammatory response, somewhat variable in intensity, is present around embolized vessels. The inflammatory response as we observe it may be modified by the commonplace administration of steroids to patients pre- and postembolization. The IBC itself persists and can be demonstrated using a modified oil red 0 stain [120], though fortuitously tantalum powder added to the IBC for purposes of angiographic visualization serves a double function in acting as a histologic marker. In the absence of tantalum or without special stains, IBC appears as a slightly refractile substance on routine light microscopy (Fig. 2).

This detailed histologic analysis of IBC-embolized AVMs has furthermore provided some intriguing new observations [119]. Patchy transumural necrosis of portions of some vessels can be identified within days to weeks of IBC embolotherapy (Fig. 3). Some vessels containing IBC and thrombus undergo recanalization. In other vessels, the IBC thrombus becomes lined by endothelium and, with time, there is actual smooth muscle cell hyperplasia between the endothelial lining and the IBC (Fig. 4). We have also observed, in AVMs resected months after embolization, IBC lying within the neuroglial parenchyma adjacent to AVM vessel lumens (Fig. 5). The possible relationship of these latter two findings to the previously described angionecrosis will be discussed in detail elsewhere [119]. Clearly, however, the fact that IBC can produce focal vessel wall necrosis (whether by a mechanism secondary to its heat of polymerization or some other physicochemical property) may explain some of the complications of IBC embolotherapy [80]. As indicated above, vascular medial necrosis and lumen narrowing with intimal proliferation is a documented effect of several cyanoacrylates when applied to circle of Willis' vessels experimentally [121], though IBC is more benign in this respect than ethyl cyanoacrylate.

Postembolization cerebral hemorrhage is a rare but well-documented and potentially devastating complication of IBC embolotherapy [122]. A proposed mechanism for this bleeding is that partial obliteration of venous drainage occurs, with preservation of one patent arterial feeder. This might produce a sudden increase in pressure in the residual AVM nidus, with rupture of some of the abnormal vessels. Such an event would, obviously, be all the more likely if portions of the AVM vasculature were necrotic, as our data indicate they are. In some AVM patients, deposition of IBC in the nidus of the malformation appears to lead to progressive thrombosis which may in turn produce total occlusion of the nidus and/or thrombosis of the draining veins [123]. Whether these individuals are actually cured of their lesions will be

settled by meticulous long-term follow-up. Indeed, we cannot exclude the possibility that AVM's with subtle structural differences 'handle' IBC in different ways. The group of AVM's we have examined in detail consists of malformations in which IBC embolization was *not* curative, nor was it intended as definitive treatment in all cases. Given the highly abnormal structure of vascular channels within AVM's [124] experimental studies on the effects of IBC in *normal* cerebral vessels [110] may have relatively little to contribute to settling this specific issue.

Clinicians using IBC embolization techniques must also be aware of the potential for this material to embolize to the lungs [125] after passage through an arteriovenous fistula. This has now been pathologically documented (Fig. 6), and the suggestion has been made that, depending on the extent of pulmonary vascular occlusion, pulmonary hypertension could in theory become a complication of the treatment modality [126].

To date, there is no evidence that IBC is carcinogenic. In fact, its direct toxicity on brain tissue in experimental systems consists of focal inflammatory and degenerative reactions, together with fibrosis and chronic FBGC inflammatory change [121].

In summary, it is apparent that enough morphologic evidence of IBC effects in animal and human studies is now available to allow for a more thorough assessment of its histotoxic properties. Whether the pathologic findings will lead to a review of IBC's usefulness as an embolotherapy agent remains to be seen. In the meantime, it is important that all pathologists, when confronted with the opportunity to carefully inspect organs (at necropsy or surgery) embolized or treated with any of the cyanoacrylates, take advantage of this opportunity [127]. The result will be a more thorough appreciation of the tissue effects this interesting group of materials may produce. Clearly, there is now a population of patients who will harbor IBC fragments within embolized lesions or adjacent normal tissues for many months and even years. It is incumbent on clinicians and pathologists alike to document any possible long-term effects of the polymer.

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