Fusiform Dilatation and Thrombosis of Arteries
Following the Application of Methyl 2-
Cyanoacrylate (Eastman 910 Monomer)*

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In previous reports from this laboratory, we demonstrated that the application of Eastman 910 monomer to the walls of relatively large arteries (i.e., femoral, axillary or common carotid arteries of dogs which measure 3–5 mm. in external diameter), produced fusiform dilatations of the entire segment to which it had been applied. On histological examination, this proved to be due to necrosis of the media. Subsequently, polymorphonuclear cell infiltration and small abscesses developed but, as the lesions healed, fibrosis of the arterial wall occurred with a return to normal, or near normal, appearance on subsequent arteriography. Although fibrinous deposition on the intima was seen in many of the large vessels, thrombosis was noted in only 1 out of 31 cases.

However, during the use of a prosthetic device in conjunction with the monomer methyl 2-cyanoacrylate (E-910) for small vessel anastomoses, thrombosis was seen to develop in all arteries with an external diameter of 2 mm. or less. This was in striking contrast to our experience with the same monomer applied to larger vessels. The question then arose whether the thrombosis was attributable to the prosthetic device or to changes in the arterial wall when the adhesive was applied.

Since the use of the adhesive had been considered particularly helpful in small vessel anastomosis when the conventional methods failed, a study was undertaken to investigate the effect of the adhesive on small vessels without the use of the prosthesis.

The simplest possible model was chosen, namely the coating of the 0.5 to 2.0 mm. branches of the femoral artery with a thin layer of the monomer. The fate of these vessels was then followed by arteriograms and histological examinations at varying intervals.

Method

Six mongrel dogs, varying in weight between 45 and 60 lbs., were anesthetized with Sodium Pentothal, intubated, and anesthesia maintained by intermittent intravenous Nembutal.

Maintaining strict surgical technique, the femoral arteries and their branches were carefully dissected. Considerable care was taken in preserving all side branches and stripping the loose adventitial tissue in a uniform manner for a distance of at least 5 cm. from their origin. The wound was bathed in a 1 per cent procaine hydrochloride solution to avoid arterial spasm. After an angiogram had been taken, a member of the team who had not been present during the dissection chose the segments of the vessels which were to be coated with the adhesive and those which were to serve as controls. Initially, all segments to be coated were marked with tantalum wire for identification on arteriography. However, since every segment which was coated developed aneurysmal fusiform dilatation, no markers were used in subsequent experiments.

Seventy-one arteries, varying in size from 0.5 to 2.0 mm. in external diameter were studied. Of these, 55 had the adhesive applied, while the remaining 16 vessels acted as controls.

Arteriography was performed in all dissections prior to coating of the vessels and repeated immediately, usually within 30 minutes, and at varying periods from 2 days to 8 weeks thereafter. Specimens were removed at varying periods in order to study both the acute and chronic histological changes.
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Results

Arteriography. Of the 55 arteries coated with adhesive, all showed fusiform dilatation on subsequent arteriograms. Dilatations of coated segments in some arteries were observed in the first film taken 30 minutes after application of the adhesive. In arteriograms which were taken about 14 days later, the dilatation had disappeared in all vessels and the lumen of the vessels had either returned to its original size, had become stenotic or had become completely occluded (Fig. 1). In some vessels which became stenotic but did not thrombose, late dilatations distal to the stenosis became evident in the 3rd week postoperatively. This dilatation was not located in the short segment immediately distal to the stenosis and, therefore, did not have the characteristics of a post-stenotic dilatation, but the vessels were dilated along their entire course and into their most distal ramifications (Fig. 2).

Those vessels which were found to be thrombosed following the initial dilatation subsequently showed a high degree of recanalization as demonstrated by arteriograms taken 24 to 30 days following the initial procedure.

Finally, a uniform dilatation of the control vessels, both proximal and distal to the coated vessels, developed slowly over the next 5 to 6 weeks, acting as collateral circulation to the areas where thrombosis was most marked. This is well demonstrated in the late arteriograms (Fig. 1).

Thrombosis occurred generally between the 4th and 10th postoperative day. Of 32 vessels which were followed for more than 10 days, 14 were found to be thrombosed, an incidence of 44 per cent.

All the control vessels were found to be patent on arteriography throughout the follow-up period.

Histology. Twenty-three vessels were removed during the first 4 days for histological examination. All were found to be patent. On gross examination, the wall was attenuated and the excised vessels collapsed, having like veins of similar external diameter. Identical slides were made of each specimen, which were stained with hematoxylin-eosin, Van Gieson Elastica and phosphotungstic acid hematoxylin (PTAH) in order to identify viable muscle tissue of the media.

The histological appearance was the same in all vessels which were removed during the first 24 hours. The entire wall of the coated vessel was noted to be markedly thinner and the lumen wider than normal (Fig. 3). This was in keeping with the arteriographic appearances. Nuclei were absent throughout the entire thickness of the vessel wall except occasionally in the region immediately below the intima, i.e., a point furthest away from the application of the adhesive (Fig. 4). The internal elastic membrane appeared to be intact, though thinned out and un-ruffled in all sections; however, there were no disruptions of any of these vessels observed either in the histological picture or on clinical examination. Sections stained with PTAH duly demonstrated necrosis of the entire muscular wall which is in keeping with the scarcity of nuclei in hematoxylin and eosin stained sections. A few viable muscle cells were seen at the sub-intimal level; under high power magnification many of these contained pyknotic nuclei which were pleomorphic and in a stage of karyolysis. The adventitia did not present any unusual appearance, except that there was a scarcity of nuclei and a thinning out of the entire layer in keeping with the general dilatation of the vessel. Refractile crystals of the polymer were easily identified. Later sections taken between the 4th and 14th day showed marked polymorphonuclear infiltration, both in the adventitia and in the media of the coated segment; this appearance, including micro-abscesses, resembled that seen in the larger vessels in previous studies. Sections stained for bacteria disclosed none. All previous changes, including the flattening of the intima and the loss of crenations of the internal elastic membrane were recognized. However, in the regions where the media was still intact, as demonstrated by PTAH stain, the crenations of the intima
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FIG. 1. Composite angiogram of left femoral artery and its branches 2, 9 and 48 days after application of the adhesive to tributaries, at their point of takeoff. Note aneurysmal dilatation (2 days), followed by thrombosis (9 days), and recanalization and stenosis (48 days). Note the distortion of the femoral artery due to extensive perivascular fibrosis. "C" denotes control vessel, dissected in a similar manner but left uncoated. Numbers 1-10 denote the vessels studied. Vessels 1, 2, 3, 7, 8 and 9 thrombosed as seen at 9 days while 7 and 8 show recanalization.
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Fig. 2. Composite angiogram showing a 2 mm. branch at various stages of follow-up (vessel numbered 1), namely (a) control prior to application of adhesive, (b) 4 days after application, aneurysmal dilatation of coated region (demarcated by arrows), (c) 28 days after application. Area now stenotic with obvious uniform post-stenotic dilatation which includes its most distal ramifications, (d) 70 days after application. Dilatation more marked in distal segment. In vessel numbered 2, dilatation, stenosis and post-stenotic dilatation are also clearly seen.

were still present (Fig. 4). Those vessels which were found to be thrombosed showed all the histologic features in the arterial wall mentioned above (Fig. 5B).

Specimens removed between 2 and 8 weeks showed varying degrees of perivascular fibrosis and intimal proliferation. In some of the vessels, these factors had resulted in stenosis of the entire segment, while in others it led to complete thrombosis (Figs. 5A and 5B). Some of the originally thrombosed vessels were now recanalized. The entire muscularis was found to be replaced by dense fibrous tissue as evidenced by the PTAH-stained sections which showed no viable muscle cells.

Sections made through the regions of late dilatation distal to the stenosis showed no abnormality. No attempt was made to stain the vasomotor nerves selectively.

Discussion

Anastomosis of vessels 2 mm. or less in diameter still presents a technical challenge, whether suture or non-suture techniques are employed. In evaluating a method for end-to-side anastomosis of vessels of this size, a prosthetic device was developed in which
FIG. 3. Histological sections through normal (control) arterial wall (A and C) and that of coated vessel (B and D) of a similar size after 24 hours. Sections A and B stained with H. & E., Sections C and D stained with PTAH (X275). Note the marked thinning and the obvious acellularity of the wall of the coated arteries B and D as compared to A and C. Arrow points at crystals of the polymer still present at this stage.
the vessels to be anastomosed were glued to the inside of the prosthesis by means of a polymerizing tissue adhesive.⁹ The results were most disappointing, with thrombosis occurring in almost all instances. The question arose as to whether the thrombosis was caused by the prosthetic device or by the adhesive, though the adhesive was applied only to the outer wall of the vessel to be anastomosed.

In previous experiments vessels of 3 to 5 mm. in size (i.e., carotids and femorals) did not exhibit thrombosis when coated with the adhesive; however, when the intact smaller branches of femoral arteries were coated with a thin layer of the monomer, it became apparent that these vessels reacted differently from the larger ones. Application of the adhesive to vessels 0.5 to 2 mm. in diameter caused 44 per cent of the vessels to thrombose eventually.

Though the final result was different, the immediate reaction observed in both small and large vessels was the same, namely dilatation, which in the case of the small vessels occurred as early as 30 minutes following application of the adhesive. This coincided histologically with necrosis of the vessel wall in all specimens removed within the first 24 hours. The elastic tissue appeared to be the only structure left intact, which seemed to account for the fact that despite the advanced destruction of the arterial wall disruptions of the vessels were never encountered. Therefore, it is possible that repair of vascular structures deficient in elastic tissue may well prove hazardous. Carmichael,¹ in an extensive study of non-inflammatory cerebral aneurysms, emphasizes that the muscular coat ended more or less abruptly near the neck of the aneurysm, as did the elastic tissues, which rarely extended for more than 1 mm. into the sac. If elastic tissue was present in the fundus, this was always fragmented and never continuous. Our results, therefore, cast some doubt on the advisability of using the adhesive for the repair of cerebral aneurysms.

Another interesting lesion observed in these small vessels was stenosis which developed within 10 to 14 days after application and resulted from the gross perivascular fibrosis, replacement of the media by fibrous tissue and proliferation of the endothelium. Though the same histological changes were seen in the larger vessels⁵ stenosis had not

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*Fig. 4. A 1.5 mm. artery, 24 hours after coating with adhesive. Note crenations of intima in region where a few normal and pleomorphic muscle fibre nuclei have survived (arrows). PTAH X70.*
been previously observed. It is an established fact that the presence of a stenosis encourages the development of a post-stenotic dilatation. However, the dilatation of the vessels seen was not confined to the poststenotic segment, but involved the entire peripheral course and reached into the finest ramifications of the involved vessels.

Though its cause was not definitely established, no sections having been specifically stained to identify the perivascular neuronal network, it is likely that the dilatation resulted from destruction of this neuronal network within the arterial wall leaving the vessels denervated. This view is supported in the study by Kline and Hayes\textsuperscript{11} in which it was shown that the application of this adhesive to peripheral nerves produced marked neuronal damage. Since none of these changes were seen in the control vessels surgical trauma was excluded as the cause of the changes.

More recently the adverse effects of the monomer have been demonstrated in other tissues. Extensive necrosis of the liver tissue,\textsuperscript{10} necrosis of healing skin incisions,\textsuperscript{14} and inflammatory reactions in blood vessels,\textsuperscript{13} have all been reported. Previous studies with the use of this adhesive in vascular surgery have, on the whole, been encouraging;\textsuperscript{2, 4, 6, 8, 12} however, it is important to note that all the previous studies were confined to larger vessels, such as the femoral or carotid artery of dogs. In arteries of this calibre, suture techniques consistently give results comparable to, or even better than, those reported with the aid of this adhesive. Despite all the changes which we have de-
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Fig. 6. Sections through human aneurysm which had been coated with E-910 over its dome and re-enforced with temporalis muscle (1). Note the attenuation of the elastic fibres in the wall of the aneurysm (2) as compared to those at the orifice at the right (3). Most of the aneurysmal wall shows a complete absence of both elastic and muscle fibres with marked polymorphonuclear cell infiltration where the adhesive had been applied. Note the absence of interposing aneurysm wall (arrow) and lack of muscle nuclei in wall distal to orifice. Elastic van Gieson ×12.

scribed and attributed to the application of the adhesive, larger arteries remain essentially patent. Smaller vessels, however, are unable to withstand the insult and thrombosis occurs in a large percentage of cases. This finding is also supported by data from the literature. Carton et al. described the patching of the internal carotid artery with survival of the patient. Subsequent angiography revealed patency of the internal carotid artery while the considerably smaller anterior cerebral artery failed to fill and can, therefore, be presumed to have thrombosed. Similarly, Coe and Bondurant have reported late thrombosis within an aneurysm of the middle cerebral artery and its parent vessel, occurring 5 weeks postoperatively. Though they do not implicate the monomer directly, they considered that secondary shrinkage of the coated vessel was a possible cause since arteriograms demonstrated marked narrowing and stretching of the siphon of the internal carotid artery. Though they have no histological evidence, our data would support their conclusions.

A human post-mortem specimen* demonstrated the possible relationship of these observations to the treatment of aneurysms in man. An aneurysm of the anterior communicating artery had proved too large for clipping or ligation during surgery, and the fundus was therefore coated with E-910 and

* Montefiore Hospital, autopsy No. 17667.
re-enforced with a piece of temporalis muscle. Death occurred 24 hours postoperatively. Histological sections showed complete necrosis of the muscle patch with marked polymorphonuclear cell infiltration and necrosis of the wall of the aneurysm where the adhesive had been applied (Fig. 6). All the features seen in dogs could be seen in this specimen.

**Summary**

1. Methyl 2-cyanoacrylate (E-910), when applied to the walls of healthy arteries varying in size from 0.5 to 2.0 mm., produced fusiform aneurysmal dilatation in all cases.
2. Methyl 2-cyanoacrylate is nontoxic to the entire vessel wall except the elastica, continuity of the vessels seemingly being maintained by persistence of this layer.
3. Thrombosis occurred in 44% of vessels followed over periods greater than 4 days. Control vessels treated similarly in every way, except for the application of the adhesive, developed no thromboses, a fact which also excluded surgical trauma as a contributing thrombogenic factor.
4. All treated vessels which did not thrombose demonstrated localized stenosis due to intimal proliferation, replacement of the muscularis by dense fibrous tissue, and extensive perivascular fibrosis. Marked dilatation distal to the stenosis and affecting the entire vascular tree was demonstrated.
5. It has been stressed that small arteries (0.5 to 2 mm. in diameter) react differently from larger arteries (3 to 5 mm. in diameter) when coated with this adhesive.
6. Reasons have been advanced to explain why this adhesive has failed to re-enforce an intracranial aneurysm and why it has consistently led to the failure of small vessel anastomoses.

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**References**