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Surgical uses of a new tissue adhesive : Methyl 2-Cyanoacrylate

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SURGICAL USES OF A NEW TISSUE ADHESIVE, METHYL
2-CYANOACRYLATE

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Synthetic adhesives belong to a chemical group which has become increasingly important industrially but which, until recently, had not been widely investigated for biologic application. Although the potential usefulness of adhesives in surgery is apparent, previous materials of this type were impractical for several reasons. Most were ineffective on moist surfaces, such as those of living tissue. Many were chemically noxious. Almost all depended for their action upon either heating or the addition of toxic chemicals as solvents or catalysts.

The adhesive action of alkyl 2-cyanoacrylates was discovered during an investigation of a series of polymers derived from 1,1-disubstituted ethylenes. (4) A drop of highly purified ethyl 2-cyanoacrylate was placed between the prisms of a refractometer. When an attempt was made to open the refractometer, the prisms could not be pulled apart.

Conventional adhesives function by application of heat and pressure, addition of a catalyst, or evaporation of a solvent. The alkyl 2-cyanoacrylates are converted from the liquid to the solid state by anionic polymerization when pressed into a thin film between two adherends. This polymerization is apparently catalyzed by minute amounts of water or other weak bases present on the adherent surfaces. This effect on the bonding

action is enhanced by spreading the adhesive into a very thin film.

Alkyl 2-cyanoacrylates are produced by condensing formaldehyde with an alkyl cyanoacetate in the presence of a basic catalyst to yield first a poly (alkylcyanoacrylate). $\text{CH}_2=\overset{\text{C}\equiv\text{N}}{\text{C}}-\overset{\text{O}}{\text{C}}-\text{O}-\text{CH}_3$ Depolymerization of this material yields the alkyl 2-cyanoacrylate.

Monomeric alkyl 2-cyanoacrylate is quite fluid, clear, and colorless. Setting occurs within fifteen seconds to two minutes after the parts are joined. The effect depends upon the type of tissue and the kind and quantity of fluid on the surfaces to be bonded. Application of the adhesive on a fluid medium results in failure of the bond.

The adhesive acts by molecular attraction with smooth, dense surfaces (specific adhesion) and by the interlocking of set adhesive on irregular or porous surfaces (mechanical adhesion).

Water, dilute alkali, and steam have weakening effects on the bonds, but organic solvents have little or no effect. Dimethyl formamide will dissolve the material.

The material is self-sterilizing, probably because of its cyanide radical. In fact, it exhibits bacteriostatic activity when dropped on a culture medium inoculated with bacterial or fungal organisms. Dried

spores introduced directly into the adhesive could be recovered in a viable state for periods up to four weeks. (9)

VASCULAR Problems in vascular surgery remain. Even with the most careful placement of sutures, luminal narrowing is a problem. The success of direct arterial surgery in the past decade has been limited for the most part to the larger vessels of the body. Another major problem is the time required to repair the vessel in an exacting manner. Depending on the vessel undergoing repair, the time may or may not be critical. In order to overcome these problems, many attempts have been made to perfect a simplified nonsuture technique for the repair of blood vessels. Although many metal, alloy, and plastic prostheses have been tried, none has gained general acceptance in clinical application. If, therefore, a nonsuture technique can be developed which would facilitate direct surgical procedures upon the smaller arteries of the distal extremities as well as the coronary vessels of the heart, it might well prove useful.

Carton and his associates (3,6,7,8) did some of the earliest work in small blood vessel surgery with the adhesive. They described four methods of repair, using techniques of (a) Patch anastomosis, (b) Flanged ring, (c) Flanged vessel, and (d) Obturator anastomosis. In

their original report they described roof patching with 33 simple patches of 2 to 4 mm carotid arteries. Seven early hemorrhages occurred, and 20 vessels showed late aneurysmal dilatation. They concluded that external reinforcement of the patch would be needed to prevent hemorrhage and aneurysmal dilatation. In their second report they used external reinforcement consisting of vein, artery, fascia, Nylon, and plastic. Circumferential reinforcement with patching proved to be a simple procedure with a high and reproducible incidence of success. To date, in 390 repairs in the carotic, femoral, and mesenteric arteries of the dog using this method, patency has been achieved in 100 per cent of these patches, with verification by periodic angiography; some of the dogs were followed for two years.

They also present a case report of a 61 year old male in which they used the adhesive as an alternative to vessel sacrifice and repaired a hole at the site of an aneurysm in the internal carotid artery intracranially. (22) Using a linear patch of dura mater, they reinforced the patch with dura around three-quarters of the circumference of the vessel. They followed the patient for six months with no evidence of rebleeding. There was, however, some narrowing at the site, and they concluded that a roof patch should have been used rather than the linear patch, with the inevitable

narrowing resulting from pulling together the edges of the defect.

Healey et al (12, 13) designed a clamp for vascular repair which allows eversion of the vessels to form two cuffs. The clamps are simple to apply and allow rapid recirculation of blood, and are easily removable. Using these clamps with the adhesive applied to the cuff and polymerizing pressure applied with hemostats, they performed circumferential and linear repairs in common carotid, abdominal aorta, and inferior vena cava in dogs. In 170 repairs, only two animals bled from the anastomotic site.

They also used Eastman 910 in one human patient. (15) During the course of radical neck dissection, the severed ends of a large anterior jugular vein were sealed off with the plastic adhesive, and no ligatures were used. One month postoperatively no complications had arisen.

Braunwald and Awe (44) found the adhesive effective in controlling hemorrhages from the aorta in a series of heparinized and nonheparinized dogs when used in combination with a reinforcing muscle patch. They cemented patches of muscle, polyurethane foam, acrylate amide, or Teflon over 0.5 cm incisions in the thoracic aorta or epicardial surface of atria or ventricles.

They report one clinical case in which the adhesive was used in a seventeen year old patient with uncon-

trolled bleeding several hours after resection of a coarctation of the aorta. The thin aneurysmal wall was clamped, a muscle patch glued on as reinforcement, and the patient observed for recurrence. Eight months later the patient is doing well.

Hemorrhage from vascular suture lines in heparinized patients is often profuse until a heparin antidote is administered. Mechanical bypasses are frequently needed after completion of suture lines during resection of the ascending aorta, aortic arch, and descending thoracic aorta. A more direct method of controlling anastomotic hemorrhage would be a great technical advance. Garrett and Law (10) replaced a 3 cm segment of descending aorta with a Teflon graft in 20 heparinized dogs. In the ten dogs in which the suture lines were coated with cyanoacrylate blood loss was minimal or absent, while in the ten control dogs the hemorrhage was profuse and often fatal.

Other authors, using a variety of techniques, had less favorable results. Carton, using the flanged prostheses, found that he had difficulty everting small vessels, and that he had an incidence of late thrombosis of 48 per cent. Nathan (5) considers the material too inflexible and too irritating to tissues. Kessler (6) found clotting at the site of indentation of the vessel wall at the proximal or distal ends of the patches

where the resin forms an overhanging lip. Hafner (35) used polyethylene stents to prevent eversion of the edges of the defect and repaired femoral arteries. Linear closures were completely unsatisfactory, and end-to-end anastomoses were successful only 50 per cent of the time, comparable to the success rate of suture technique in arteries of the 3 to 4 mm size.

With the wide variance in the incidence of clinical success reported by the various investigators, it seems that further investigation toward improving techniques is necessary before a final judgement can be made of the ultimate role of the adhesive in vascular surgery.

LIVER Controlling immediate and delayed drainage of blood and bile from the cut surface of the liver is a problem in massive liver resections. Marable and Wagner (27) did massive resections in 12 dogs, deliberately transecting many large vessels and removing about one third of the liver. With manual compression and application of methyl alpha-cyanoacrylate, 11 of the dogs survived a month or longer. Just-Viera (30) and all did wedge resections and lobe resections of dog livers, also using the adhesive as a hemostatic agent. None of the animals whose cut livers were coated with the adhesive died, whereas 40 to 80 per cent of untreated animals died. However, dogs receiving large amounts of the plastic showed varying degrees of wound dehis-

cence, from partial skin separation to complete wound disruption. There was no evidence of obstruction, fistulas, secondary hemorrhage, abscesses, or bile extravasation in the animals tested.

Gross findings during the first days show a hyperemic adherent omentum covering the wound and the diaphragm firmly attached to the liver. The greatest amount of fibrosis and adhesion formation occurs during the first four weeks. Subsequently the adhesive appears isolated by a fibrous capsule and gradually disappears. The wound scar contracts until at seven months it is barely evident. Adhesions seem to diminish in number and degree with time.

Thus the substance would seem to be a useful adjunct to conventional methods in minimizing the morbidity in liver resections.

KIDNEY Retention sutures placed into renal parenchyma result in destruction of renal tissue, distortion of the parenchyma, and subsequent fibrosis. Mathes and Terry (32) believe that if an acceptable adhesive could be found it would allow faster, more exact approximation in nephrostomy, overcoming many of the disadvantages of suturing.

Dog kidneys were bivalved, in one group of six the two cut surfaces were approximated with sutures. In the other group of eight, no sutures were used

at all. Fourteen of the sixteen kidneys closed with adhesive alone held fast with no active bleeding, two required additional capsule sutures.

At autopsy all incisions were well healed with a healthy fibrous tissue scar, moderate adhesions between kidney and surrounding tissues were noted in most cases. Sections taken 3 to 4 months postoperatively demonstrated ample fibrosis and minimal inflammatory reaction.

The authors concluded that the adhesive should be very helpful in closing nephrotomies and in producing watertight closures of pyelotomy and ureterotomy incisions with or without suture augmentation, as well as in ureteral anastomoses and pyeloplasties.

INTESTINES O'Neill and Healey (28) performed nonsuture end-to-end anastomoses in 26 animals. There were five failures, four of which occurred in the large intestinal group and one in the small intestinal group. The failures in the large intestinal group presented a common finding of necrosis of the entire intestinal wall on either side of the anastomosis and complete disruption of the anastomosis, leading to generalized peritonitis and death.

It is believed that the necrosis was produced by undue compression of the walls of the intestine by the anastomats. The possibility of the adhesive producing an obliterative endarteritis of the vessels at the site

of anastomosis, thereby resulting in ischemia, should be considered, but the authors produced no evidence to substantiate or rule this out.

The technique used was eversion of the edges, curettement of the mucosa from the submucosa for a distance of one centimeter or so, coating of one of the surfaces, then approximation and gentle pressure with non-toothed forceps for about one minute. Both excessive compression of the intestines by the anastomat while maintaining the transected ends in position for application of the adhesive, and excessive amounts of the adhesive must be avoided.

SKIN Plastic surgeons are ever looking for a method of skin closure which would minimize wound scars.

Ashley (20, 39) used the adhesive to close skin lacerations and to perform nonsutured grafting of skin. In lacerations, the edges were carefully approximated and the adhesive applied over the edges. Scars were smooth, linear, and almost invisible. In comparing the width of residual scar to those left by suturing and skin clipping, he found that the scar from the adhesive technique was approximately $1/3$ that of the sutured laceration and $1/2$ that of the clipped laceration.

Fischl (29) found that, in his work, wounds closed with the adhesive healed without incident and grossly and histologically resembled conventional wounds after two weeks.

Ashley found that the survival time of skin homografts was doubled by using adhesive as opposed to the skin clip technique. He attributed this to the relatively nontraumatic technique involved with the adhesive, and the more adequate approximation and adaptation of skin edges.

Cramer (26) reported uniform success in using the adhesive to bond 2 cm square grafts in paired animals. He reports neither delayed healing nor postoperative infection.

Yoshimura (51) found that in measuring anti-tension the adhesive was inferior to silk thread suture between the fourth to sixth day, but became equal after the seventh day.

LUNG The problem of blood loss and air leakage from cut lung surfaces at times leads to lobectomies or pneumonectomies in cases which otherwise might only require a wedge or segmental resection. Vasko and Sawyers (49) used 20 dogs, performing on each either a segmental or extensive wedge resection of the lung. The raw surfaces were sealed with the adhesive without the use of ligatures or sutures. The dogs were sacrificed from two to six months after the procedures. Complete sealing was effected in all 20 dogs.

Healey and his associates (24) evaluated the use of the adhesive as an adjuvant in bronchial stump

closure. Three groups of dogs were utilized, in each of which a left pneumonectomy was performed. Five dogs in which the bronchus was sutured all lived. 15 dogs were treated by two or three sutures and plastic adhesive. 10 dogs were treated by closure with the adhesive only. Two of these died, one of tension pneumothorax, and one of empyema and mediastinitis from a sponge left in the pleural cavity.

It seems that probably the use of the adhesive as an adjuvant will be the more useful method, and may reduce the incidence of leakage from the stump.

OPHTHALMIC Bloomfield (36, 41, 42) has studied the adhesive in many areas of ocular surgery.

Lids Simple incisions and grafts in the lids of rabbits were closed by approximation and application of the adhesive. All results were good. Through and through lid incisions closed with the adhesive alone, however, showed lid notching at five weeks postoperatively.

Conjunctiva The bulbar conjunctiva was incised and the glue applied to a few mm on either side of the conjunctival surface and the margins pressed together. Difficulty was encountered because of the rapid dispersion of the low viscosity adhesive, but the results were satisfactory and the inflammatory reaction "moderate".

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Muscle The recti muscles of four rabbits were divided from their insertions, the adhesive applied to a new insertion site, and the muscle reattached. The new attachments appeared firm and the inflammatory reactions appeared equal to those using conventional gut sutures.

Corneal and Limbal Incisions Corneal incisions were made and the monomer used for closure, but since the edges were continually moistened by the aqueous, adhesion was produced only 25 per cent of the time. Using a Dacron mesh patch coated with the adhesive worked well in the closure of limbal incisions, with the patch holding following the injection of air into the anterior chamber up to a pressure of 50 mm Hg.

Scleral and Detachment Surgery Partial penetrating scleral flaps were dissected and then pasted back in position with the monomer, resulting in uneventful healing. Dacron patching was also acceptable. Thus the adhesive may be helpful in detachment surgery, any inflammatory reaction possibly aiding in keeping the retina in position if the glue is applied to the choroid.

Evisceration The glue was applied inside the sclera and a polyethylene sponge deposited, with immediate adhesion, showing possible use in evisceration surgery in which an implant is used.

Bloomfield states that closure of limbal incisions after cataract extraction is often marred by complications generally attributable to faulty closure of the incision. In order to avoid these unhappy occurrences, more numerous corneoscleral sutures are frequently advised, but multiple sutures also present hazards because of the close tolerances necessary for apposition, and the everpresent reaction and infection.

He found an effective method to consist of closing the incision with the smallest number of corneoscleral sutures necessary for loose approximation of the wound edges. The external surface of the incision is then lightly coated over its entire length with the adhesive. A previously formed limbal-based conjunctival flap is then smoothly pressed lightly onto the surface of the wound for two minutes.

The postoperative inflammatory reaction in the eyes with the adhesive did not seem significantly greater clinically than in the eyes without the adhesive.

This technique is faster than the suture methods now used, and the strength of such closures was tested and compared with that of similar incisions conventionally closed and found to be significantly stronger and more impervious to leakage.

DURAL Three basic purposes of dural substitutes are to prevent leakage of cerebrospinal fluid, to replace

membrane affected by injury or disease, and to prevent adhesions between brain and overlying soft tissue.

Albin et al (17) used Teflon patches coated with the adhesive to close dural defects in two groups of dogs. In group I, in which total or partial lobectomy was performed, there were adhesions to the cortex, but in group II, in which no cortical tissue was removed, there were no adhesions. In both groups a thick fibrous neomembrane formed, encapsulating the Teflon, and providing a firm seal of the defect. No damage to the underlying brain occurred that could be attributed solely to the use of the adhesive.

BONE Lighterman and Farrell (21) treated surgically induced fractures of mandibles of dogs by gluing with methyl cyanoacrylate. The fractured segments remained stable and the dogs gained weight after an initial drop. With the adhesive there appears to be a physical bond between the bone fragments for about 20 to 50 days. Then it seems the adhesive is partially removed by enzymatic action, leading to refracture. This material does not seem to be acceptable for bone gluing.

LIMB IMPLANTATION MacDonald (25) used the adhesive as an adjunct in reimplantation of dog limbs, achieving a success rate in the range of 80 per cent by stapling blood and lymphatic vessels and then coating with the adhesive.

NEURAL TISSUE Kline and Haynes (45) coated 3 cm segments of peroneal and radial nerves in dogs with the adhesive. They demonstrated increased thresholds, and tubular demyelination with axon fragmentation. The same investigators instilled the material into the cortex. One dog died two weeks postoperatively of a sterile occipital abscess showing extensive cortical necrosis with neuronal and glial degeneration. Five dogs survived with only small cortical infiltrates of lymphocytes and plasma cells surrounding the adhesive. Their work therefore seems to demonstrate that the adhesive has neurotoxic qualities.

TRACHEA Shaff, a veterinarian, covered traumatic tracheal defects with fascial patches applied by using only the adhesive. All three animals survived the procedure without complications. (43)

DERMATOLOGY Keddie et al (46) used a small film of the monomer pressed between the surface of the skin and a glass slide to remove stratum corneum and hair roots for examination for tinea versicolor.

TOXICITY Studies on the toxicity of Eastman 910 have been made by Fassett (52). He showed that the size of a mass of the material injected subcutaneously in the guinea pig gradually diminished and there was a mild cellular foreign-body reaction without injury

to the animal. There was no demonstrable toxicity, but he advises avoidance of contact with the eyes.

Lewers et al (38) studied the potential systemic toxicity of the plastic by introduction of the cement into the liver and peritoneal cavity of mice, causing immediate death. Introduction of both non-polymerized and polymerized forms cause death, ruling out polymerization per se as a factor. The mechanism of death is unknown, and the lethal dose per unit of body weight given, when extrapolated to dogs or man, becomes quite large.

It appears that the adhesive has a distinct toxic effect.

Questionnaires are in the mail at the time of this writing inquiring of all known investigators using the adhesive any allergic phenomena they may have noted. Results will be tabulated in part II of this paper.

TISSUE REACTIONS Liver Histologic changes were noted after sacrifice at varying lapses of time post-operatively. Sections from the 3 hour specimen show acute localized hemorrhage only at the surface near the plastic. At 48 hours changes of marked, acute inflammation are evident, with fibrin, polymorphonuclear cells, and some proliferation of fibroblasts from the underlying liver. At three days extensive

hemorrhage and necrosis distort the architecture of the liver parenchyma at the site of application, the reaction extending about 0.5 cm into the liver substance.

Portal triads widen because of increased connective tissue and infiltration of inflammatory cells, predominately mononuclears. In the junction between the area of necrosis and remaining well-preserved hepatic parenchyma there is continuing organization by connective tissue.

At one week necrosis is diminished and the acute inflammatory reaction is less. A layer of organized connective tissue divides the inflamed and normal zones. In some areas between the organizing connective tissue and the necrotic zone multiple foreign body granulomas appear and surround the plastic; some even contain fragments of the plastic.

One month after the operation the acute inflammatory reaction is minimal whereas the chronic inflammatory changes are more in evidence. Numerous foreign body granulomas, organizing connective tissue, and macrophages can be encountered and at this time the encapsulation of the plastic by fibrous tissue is completed.

Seven months after operation the pinkish areas are separated from normal hepatic parenchyma by definite

bands of well-organized connective tissue. Small areas of foreign body reaction can still be found and there are numerous small foci of calcification.

Arterial Extensive fat necrosis was found in all specimens where the agent was applied subcutaneously as a liquid or as dry pellets of polymerized material. On microscopic examination, the adhesive was found to be severely irritating to subcutaneous tissues and arterial walls. There was an acute inflammatory reaction in its immediate vicinity with a polymorphonuclear leukocyte response which persisted for as long as one month wherever the monomer had been placed.

Observations were directed toward determining the fate of the plastic in tissue. This was not handled uniformly in every instance, possibly due to variables involved in the polymerization, possibly to tissue differences. The plastic was brittle and after three months disintegrated into particulate form. Usually at three months the inflammation had subsided and particles of plastic remained in the media and adventitia of vessels, encased in foreign body cells and fibrous tissue. The reaction to the adhesive was indistinguishable from the reaction to Teflon patches or silk sutures.

Intestinal The reparative process following nonsuture anastomosis is similar in both large and small

intestines. The anastomotic area rapidly becomes infiltrated and surrounded by an inflammatory exudate composed of polymorphonuclears and plasma. As the reaction regresses over the next three to five days, it is replaced by a rapidly proliferating vascular fibrous tissue mixed with many lymphocytes and plasma cells. Small granulomatous nodules form around the more deeply placed particles of adhesive. Organization begins in the serosa and muscularis and proceeds inwards. The reestablishment of mucosal continuity is usually the first phase of healing. The inflammatory cells disappear gradually over a period of two to three weeks, leaving the bowel wall restored by fibrous tissues of diminishing vascularity.

The fate of the adhesive is difficult to determine. Histologically, it can be recognized under reduced illumination as transparent refractile plates in early specimens. That which is nearest the internal surface disappears within the first week, while the adhesive can be found in the muscularis and serosa as late as the twenty-first postoperative day. It seems likely that the adhesive from the internal portion of the anastomosis may be cast off into the lumen along with some of the acute inflammatory exudate. That which is more deeply placed appears to be removed by histiocytes and foreign body cells which are components of

the granulomas.

Eye Both severe reactions and routine healing were seen histologically, and there appeared to be a correlation between the amount of monomer used and the intensity of the subsequent reaction. The most marked inflammatory response of the rabbit eye to the adhesive occurred after topical application to the conjunctiva. One drop of the monomer instilled subconjunctivally or in the lower cul-de-sac uniformly produced a severe response. When placed in the anterior chamber there was an absence of significant inflammatory response both clinically and microscopically.

DISCUSSION The ideal tissue adhesive must have a number of qualities: (1) Quick adhesion with adequate shear strength in a short period of time.

(2) Adhesion to moist living tissue and stability within body temperature range.

(3) Innocuous to human tissue, non-allergenic, noncarcinogenic, and not a deterrent to healing.

(4) Sterile, or capable of sterilization.

(5) Assurance of functional healing by histologic study.

Methyl 2-cyanoacrylate appears to meet many, but not all, of the above criteria. It bonds in less than two minutes, has excellent shear strength, is sterile, and adheres to tissue with a minimum of moisture.

It seems nonallergenic from reports to date. However, it forms a brittle granular bond in tissue, and is reported as having properties which cause moderate to severe inflammatory reactions in many tissues.

The absence of studies on the tumor-producing potential of this plastic and the lack of long-term studies constitute an important warning. Anyone noting the recent dampening of the initial enthusiasm for "bone gluing" cannot but advocate restraint in the clinical use of these plastics until further experimental work is completed.

Oppenheimer et al (1) reported carcinogenesis induced by certain plastics, including Teflon and methyl methacrylate. It is difficult to transpose results obtained in experimental animals to humans, but certainly these studies did not deter anyone from the clinical use of Teflon. Oppenheimer also demonstrated that the polymers, tagged with radioisotopes, decomposed at a minute rate, and excretion began after a latent period. The carcinogenic effect perhaps resides in the macromolecule itself, and the question was raised of a chemical or physicochemical interaction between the polymer or its degradation products and some basic cell constituent of the organism. Juhlin (2) described the retention of spherical particles of methacrylate by the reticuloendothelial system and their excretion in

bile. Further studies of the fate of implanted cyanoacrylate are obviously essential.

TECHNIQUE Several points are absolutely essential to adequate bonding with the adhesive. Primary among these is the necessity for adequate drying of the tissues to be bonded. Sponging alone is not sufficient, and most investigators are in addition using a stream of oxygen, helium, or compressed air. Addition of a millipore filter system in the line to assure sterility seems desirable, and a needle attached to the system would allow fine control of the stream of air.

Extreme care must be utilized in vascular surgery not to allow any of the adhesive to enter the lumen of the vessel, for thrombosis inevitably results.

The minimal amount of adhesive necessary to cover the desired area should be applied. An excess of the adhesive causes severe reactions, may be toxic, and causes the resultant bond to be weaker than that formed with a minimal amount.

Instruments in contact with the adhesive should be siliconized to minimize undesired bonding.

Shelf life of the adhesive at this time is considered to be six months or less. Tests are now underway to determine the best method of storage and the deterioration curve of the adhesive.

Coloring, to aid in application of the adhesive,

and smaller "one dose" packages would seem desirable for practical use of the adhesive.

SUMMARY The discovery of the adhesive properties of methyl 2-cyanoacrylate by Coover and his coworkers in 1959 presented the medical world with the first tissue adhesive to prove practicable in the progress toward the ultimate goal of sutureless surgery.

Numerous workers have used the adhesive in experimental procedures designed to test the applicability of the material toward performing such diverse procedures as blood vessel anastomosis, sealing the cut surfaces of organs, bowel anastomoses, skin closure, dural patching, and ophthalmic surgery. The adhesive is not the final answer for all these problems, but it does seem to have enough merit to warrant further investigation.

Conventional adhesives function by the application of heat and pressure, addition of a catalyst, or evaporation of a solvent. Methyl 2-cyanoacrylate is converted from the liquid to the solid state when pressed into a thin film between two adherends. Polymerization is apparently catalyzed by minute amounts of water or other weak bases present on the surface of the adherends. Polymerization seems to occur in 15 seconds to 2 minutes, depending on the surfaces to be joined. The adhesive is

self-sterilizing. The bond formed withstands most organic solvents, and is dissolved only by dimethyl formamide.

The adhesive is a clear, colorless fluid which is available in 15 cc polyethylene dispensers. The viscosity is about that of water, and it has little odor.

Bond strength seems excellent, several investigators reporting that blood vessels anastomosed with the adhesive withstood intraluminal pressures up to 300 mm Hg. The bond eventually turns brittle and granular in tissues and is probably ultimately phagocytized.

The adhesive produces inflammatory reactions of mild to moderate severity in various tissues, with small foreign body granulomas reported by almost all investigators.

Toxic effects have been demonstrated, but were induced by amounts of the adhesive which, if extrapolated to humans, would be much in excess of amounts needed for most procedures.

The fate of the implanted adhesive in tissues, its possible carcinogenic properties, and its shelf life are among the questions awaiting answers before it joins the medical armamentarium.

CONCLUSIONS Methyl 2-cyanoacrylate meets many, but not all, of the criteria for a tissue adhesive. It is self-sterilizing, forms strong bonds without catalysts, pressure, or heat, and bonds in less than two minutes.

Investigations have proved it practical in many procedures, e.g. bowel and blood vessel anastomoses, skin closure, and sealing the cut surfaces of organs.

Possible carcinogenesis, fate of the adhesive in tissue, and shelf life must yet be determined.

I believe the adhesive will find use in surgical procedures, primarily as an adjunct, and will provide a stimulus for further investigation and development of new and better tissue adhesives.

A RAPID METHOD OF MICROSCOPICALLY EXAMINING TUMOR BEDS
UTILIZING A PLASTIC ADHESIVE: AN EXPERIMENT

The aim of this experiment was to develop a method of excising the tumor bed in toto for frozen section microscopic examination. We wanted to devise a system for holding the tissues together during the removal and subsequent staining.

The rapid microscopic examination of tumor beds for residual malignancy is hampered by several factors:

1. Tissue, especially fatty tissue, is too friable to permit excision of a thin layer without frequent shredding and tearing.

2. Polychrome and other one-step staining techniques commonly used for frozen sections produce slides which are of poor quality and which are not permanent sections.

3. If the tumor bed is large, each piece of tissue removed must be coded immediately upon removal to allow later identification.

Technique After surgical extirpation of the tumor, hemostasis was obtained by applying trichloroacetic acid with a cotton tipped applicator. Cauterization by this acid minimized possible absorption of the material, thereby protecting against a possible allergic reaction.

Gauze mesh (surgical sponge unfolded to form a

single layer) was then placed over the tumor bed and coated with the adhesive, applied either by a small brush or tongue blade.

Five minutes were allowed for polymerization, and an attempt was made to dissect the entire tumor bed free as a 1 mm thick specimen backed by the gauze. The specimen was subdivided with scissors, and the edges of the segments were marked using differentially colored vertical and horizontal lines. A map was made showing the location of the pieces in the wound bed. Colored borders identified the top and bottom, right and left sides of the sections. Each piece was then submitted separately for frozen section utilizing the hematoxylin and eosin technique described by Mohs. (50) Such frozen sections yield permanent slides of good quality.

Results To date, experiments utilizing the adhesive have been erratic. We have found that any application of a strongly ionic agent such as trichloroacetic acid or zinc chloride causes failure of bonding.

Since we have obtained excellent bonding with post mortem tissue, and the method is a complete success using such tissue, we believe moisture present in living tissue, (blood and tissue fluids) to be the probable reason for our failure thus far. Improved tissue drying by compressed air jet prior to application

of the adhesive may resolve the problem.

Work continues in an attempt to create a satisfactory technique; the ability to make repeated sweeps across a tumor bed until it is proven to be tumor free would have obvious advantages.

A survey was taken of all known investigators currently using the material to determine if allergic reactions had been noted by them. This must be considered since moderate amounts of the adhesive are utilized in our procedure. Questionnaires returned by ten of these investigators show that in 2741 procedures in animals and 93 procedures in humans, no allergic reactions have been noted.

Conclusions The method described for rapid excision and staining of tumor beds for microscopic examination has thus far proved impracticable in our hands.

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