SERENDIPITY, SUPER GLUE AND SURGERY: CYANOACRYLATES AS HEMOSTATIC AIDS IN THE VIETNAM WAR

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SUMMARY: In 1942, Harry W. Coover (b. 1919) was working to develop a clear plastic for World War Two machine gunsights. The compounds he investigated; cyanoacrylates, proved unsuitable. After setting the formula aside for many years, Coover was inspired to rethink the use of the compounds, and explored their potential as strong, quick-drying glues. In 1951, 2-methyl cyanoacrylate or 'super glue' was first marketed as Eastman 910®. In 1964, Coover, in collaboration with the company Ethicon Co., applied for U.S. Food and Drug Administration (FDA) approval of cyanoacrylate glues for use as tissue adhesives. It was not until 1998 that the FDA approved cyanoacrylates for medical use; Coover's superglue is finally being used in America for a variety of medico-surgical applications. This paper will outline the aforementioned cyanoacrylate applications, discuss the outcomes of superglue use in American military surgery, and explain why it did not quickly achieve widespread usage in the United States until after 1998.

KEYWORDS: H. W. Coover, Tissue Adhesive, Cyanoacrylate, Super Glue, Haemostasis, Vietnam, Surgery.

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Introduction

The earliest record of wound closure dates back to 1100 B.C., when abdominal incisions on mummies were closed with leather ligatures.[1] Since then, physicians have innovatively addressed the problem of emergency wound closure using everything from leeches, fire ants, and

[1] Adam J. Singer and Henry C. Thode, "A Review of the Literature on Octylcyanoacrylate Tissue Adhesive," *Amercian Journal of Surgery* 187 (2004), pp. 238-248.

home-made molasses concoctions[2] to more conventional methods such as sutures, staples and adhesive tapes. One of the more recent innovations in wound closure and haemostasis is the long sought after use of tissue adhesives in medicine.

This paper traces cyanoacrylate tissue adhesive development from discovery to current medical uses. It focuses on H. W. Coover's (b. 1919) serendipitous discovery of cyanoacrylate glues, their medical development and remarkable performance in the Vietnam War, the challenges of obtaining U.S. Food and Drug Administration (FDA) approval, the extensive research and development of cyanoacrylates overseas, eventual approval of new formulations by the FDA, and the current medical uses of cyanoacrylates around the world. Making use of Coover's account of his involvement in super glue's development, medical publications from the Vietnam War, and a variety of peer-reviewed journal articles and books, this paper strives to highlight the successes and challenges that stemmed from a scientist's ability to see lifesaving potential in an accidentally discovered adhesive.

Harry W. Coover's Discovery

The road to discovering the cyanoacrylate formulation that is commonly known as '*super glue*' was a long journey, marked by serendipity and years of hard work. Coover first worked with cyanoacrylate compounds during World War Two in the Kodak Research Laboratories, while searching for an optically clear plastic that could be cast into precision gunsight lenses. These compounds showed some promise, but had the stubborn quality of sticking to everything they touched; thus cyanoacrylates were shelved at the end of World War Two, their adhesive properties quickly forgotten.[3]

It was not until 1951 when Coover was supervising a new project with the Tennessee Eastman Company that the full potential of cyanoacrylate adhesives was fully realized. This time, the research team was looking for heat-resistant polymers for use in jet plane canopies. When one of Coover's colleagues, Dr. Fred Joyner (b. 1923), was testing the optical properties of a sample of ethyl cyanoacrylate by putting a thin film of the monomer between two prisms of a refractometer, he was unable to

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[2] D.C. Wilson, *The Big-Little World of Doc Pritham* (Bangor, ME: Roberts Publishing, 1993), pp. 93-94.

[3] H.W. Coover, "Cyanoacrylate adhesives—a day of serendipity, a decade of hard work," *Journal of Coatings Technology* 55 (1983), p. 59.

separate the prisms after the test.[4] Reluctantly, Joyner reported to Coover that he had ruined a seven hundred-dollar piece of equipment; instead of becoming angry, Coover was able to see the great potential of cyanoacrylate adhesives:

> Any concern I had about the refractometer was swept away by the sudden realization that what we had was not a useless instrument, but a unique adhesive. Serendipity had given me a second chance but this time the mental process led to inspiration. Immediately I asked Fred for a sample of his monomer and began gluing everything I could lay my hands on […]. Everything stuck to everything, almost instantly, and with bonds I could not break apart. In that one afternoon, cyanoacrylate adhesives were conceived, purely as the result of serendipity.[5]

Although cyanoacrylate adhesives had revolutionary properties, there was still much work to be done before a marketable formulation could be found. Coover and his colleagues worked hard to elucidate the glue's mechanism of action and its most effective formulations. As well, the Tennessee Eastman Laboratory developed reliable methods for commercial production of cyanoacrylate adhesives. Finally, in 1958, they introduced a cyanoacrylate adhesive patented as Eastman 910® — the first super glue.[6]

Medical Development of Cyanoacrylate Adhesives

In the late 1950s, Coover realized that cyanoacrylate glues had the potential to be effective tissue adhesives, which had been long sought after by the medical community. It was well known that these adhesives formed strong bonds with human skin, as many laboratory workers had inadvertently experienced over the years of super glue's development. Consequently, in 1960, Coover partnered with Ethicon, a subsidiary of Johnson and Johnson, to investigate the possible medical applications of cyanoacrylates. Important considerations were the potential toxicity of cyanoacrylates, the efficacy of different formulations in various medical procedures, the ability to develop sterile packaging methods, and the

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[4] *Ibid*.
[5] *Ibid*.
[6] Harry W. Coover, "Cyanoacrylate adhesives—a day of serendipity, a decade of hard work," *Journal of Coatings Technology* 55 (1983), pp. 59-61; esp. p. 60.

design of effective applicators for the many potential medical uses of super glue.[7]

During the first phases of research, Coover and many collaborating groups discovered that the original methyl cyanoacrylate (Eastman 910®) formulation, as well as ethyl cyanoacrylates, caused inflammation and were toxic to animal tissues.[8] These reactions were the result of several mechanisms. The polymerization of cyanoacrylate monomers is an exothermic reaction that releases heat to the surrounding tissue, which irritates the tissue upon application. When cyanoacrylate polymers are implanted into tissues with high blood flow, foreign body reactions often occur, causing chronic inflammation.[9] Finally, when these short-chain cyanoacrylates are broken down inside the body, their degradation products, notably formaldehyde and cyanoacetate, can reach concentrations high enough to have significant histotoxic effects. However, if used for a topical wound closure, methyl- and ethylcyanoacrylates degrade slowly enough that there will not be a significant release of toxic breakdown products before the adhesive sloughs off the skin.[10]

In addition to their toxicity, short-chain monomers like methyl- and ethylcyanoacrylates have other properties that limit their use as tissue adhesives. These monomers bead into droplets upon application to tissues and do not spread. Consequently, they cannot cover a large surface area of tissue and tend to polymerize slowly.[11] The inability of short-chain cyanoacrylates to spread also contributes to higher concentrations of toxic degradation products where the adhesive is applied, since a larger volume of adhesive is needed to close a wound. Another characteristic of short-chain cyanoacrylates is the formation of tight, brittle bonds that are susceptible to fracturing.[12] As a result, methyl- and ethylcyanoacrylates are not good candidates for surgical use, as they are hard to manipulate, damages tissue, and result in brittle, inflexible bonds. After conducting more experiments on dogs, Coover and his collaborators discovered a

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[7] Coover, *Cyanoacrylate Adhesives*, p. 60.

[8] John A. Collins et al., "Cyanoacrylate adhesives as topical hemostatic aids. I. Experimental evaluation on liver wounds in dogs," *Surgery* 65 (1969), pp. 256-259.

[9] James V. Quinn, ed., *Tissue Adhesives in Clinical Medicine* (Hamilton: BC Decker Inc., 2005), p. 27.

[10] *Ibid*.

[11] Teruo Matsumoto, *Tissue Adhesives in Surgery* (New York: Medical Examination Publishing Co., Inc., 1972), p. 8.

[12] Quinn, *Tissue Adhesives*, p. 28.

formula that did not demonstrate this deleterious effect on tissue. The laboratory workers at Eastman found that the same adverse reactions to methyl- and ethylcyanoacrylates were not seen in cyanoacrylates with longer side chains, such as n-butyl or isobutyl alkyl groups, which both contain four carbons.[13] In fact, the longer the alkyl group (four carbons and up), the less heat is released when the glue polymerizes and the longer it takes for the polymer to degrade. A smaller release of energy while the glue cures translated into less inflammation after application. Since it is the degradation of cyanoacrylate tissue adhesives in the body that releases toxins, longer degradation times result in less irritation of the tissue. Clinically proven, the toxic degradation products of longer-chain cyanoacrylates are barely detectable on extraction studies, such that they are widely considered non-toxic.[14] Some of the earliest studies on n-butyl- and isobutylcyanoacrylates in dog tissues revealed that no local or remote malignant changes were observable one year to twenty-one months after researchers applied the adhesives to open wounds of a dog liver.[15]

On top of the medical advantages of longer chain cyanoacrylate adhesives are their desirable physical properties – butylcyanoacrylates which are much easier to apply medically than short-chain cyanoacrylates. These compounds are able to spread, and can cover a greater surface area of tissue. This property allows them to polymerize faster, making them able to staunch bleeding and effectively close wounds in minimal time.[16]

Another clear benefit of long-chain homologues over short-chain homologues is their flexibility after they are cured. In general, researchers discovered that the longer and more complex the side chain of the cyanoacrylate, the more flexible the polymer.[17] Such added flexibility and tensile strength is an important consideration for the use of butylcyanoacrylates in wound closure, where the adhesive must move with the body – and withstand the shear stresses between the adhesive and the tissue.

Overall, it was shown that the longer-chain cyanoacrylates (butyl and higher) were less toxic and irritating to living tissue, polymerized faster, were easier to apply, and were more durable once cured.[18] Several studies

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[13] Yoshito Ikada, "Tissue Adhesives," in: *Wound Closure Biomaterials and Devices*, ed. C.C. Chu, A. Von Fraunhofer and H.P. Griesler (Boca Raton, Florida: CRC Press, 1997), p. 332.
[14] Quinn, *Tissue Adhesives*, p. 29.
[15] Collins et al., *Cyanoacrylate Adhesives*, p. 259.
[16] Matsumoto, *Tissue Adhesives in Surgery*, p. 8.
[17] Quinn, *Tissue Adhesives*, p. 30.
[18] Collins et al., *Cyanoacrylate Adhesives*, p. 258.

published in the early 1960s concluded, based on desirable medical and physical characteristics of the glues, that the preferred monomers for surgical use were n-butyl- or isobutylcyanoacrylates.[19] As far as using these compounds to stop active internal bleeding, Collins et al. (1969) concluded in their study on dogs that "longer chain alkyl-2-cyanoacrylates are significantly more effective topical haemostatic aids on open wounds of the liver in dogs than standard suturing techniques or methyl-2 cyanoacrylate."[20]

Using these new formulations, researchers began to experiment with cyanoacrylate tissue adhesives in suture-less surgery, the rejoining of vessels and intestines, several procedures in ophthalmology, the sealing of bleeding ulcers, the reparation of soft organ damage and in dental and periodontal surgery.[21] The promising qualities of this '*medical super glue*' led Coover and Eastman to submit their initial application for new drug approval to the FDA in 1964.[22]

Soon after the initial medical experimentation on cyanoacrylate tissue adhesives had begun, the United States Army Medical Biomechanical Research Laboratory took notice of the great potential for cyanoacrylate tissue adhesives in military medicine. They involved themselves in the early phases of product research and were the first to develop a sterile, disposable, freon-propelled n-butyl cyanoacrylate spray applicator.[23] By the mid 1960s, there had been many experimental successes in the spray application of butylcyanoacrylates. The adhesive was generally sprayed on using a spray gun nozzle and pressurized nitrogen gas, which left a thin, uniform layer of polymer on the tissue surface that dried into a flexible sheet. Yet this technique was not portable, as it involved large tanks of pressurized gas. Another drawback was that this spray technique required cautious and meticulous cleaning of the spray gun's nozzle and Teflon tip after every procedure; otherwise the glue would permanently occlude the nozzle and it could not be reused.[24]

Since the spray gun method was clearly not suited for use on the battlefield, the U.S. Army Biomechanical Research Laboratory took on the formidable task of designing a disposable aerosol n-butylcyanoacrylate

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[19] Matsumoto, *Tissue Adhesives in Surgery*, p. 9.
[20] Collins et al., *Cyanoacrylate Adhesives*, p. 259.
[21] Coover, *Cyanoacrylate Adhesives*, p. 59-61.
[22] Frederic B. Jueneman, "Stick it to 'em," *Industrial Research & Development* (Aug 1981), p. 19.
[23] Robert M. Hardaway, "The problem of acute trauma and shock," *Surgery, Gynecology and Obstetrics* 133 (1971), pp. 799-806; esp. p. 801.
[24] Matsumoto, *Tissue Adhesives in Surgery*, p. 14.

spray unit. The first challenge that needed to be addressed was the optimal ratio of cyanoacrylate adhesive to propellant, in this case Freon®. Experimentally, the maximum haemostatic and bonding actions of n-butylcyanoacrylate were found when the monomer was 60-70 percent by weight of the spray solution. If the monomer was present in concentrations greater than 80 percent, the spray action was not satisfactory. Thus it was determined that a concentration of propellant higher than 30 percent was ideal for proper spray action.[25] The second challenge needed to make an aerosol cyanoacrylate spray was the design of the container. The ideal container had to be sterile, able to withstand pressurized contents, and nonreactive with the chemical components of the spray. The biggest challenge proved to be selecting a gasket that would not be damaged or glued during use of the canister. Fortunately, an ingeniously-designed gasket valve was found which prevented the sensitive components of the gasket from being damaged by the chemical contents of the spray. In addition, this design prevented the build up of adhesive in the canister's dipping tube, which allowed the spray to be used with fewer occlusions and greater reliability. Finally, the container was made to have a disposable actuator (nozzle) that could be easily replaced should it become sealed with adhesive.[26] Once a satisfactory sterile aerosol spray canister was available, the U.S. Army conducted several studies on its efficacy and safety. In dogs, the spray was shown to achieve successful haemostasis of wounds to the liver and kidney, as well as quick anastomosis of intestines. There were no pathological findings in the subsequent histological examination of tissues that had received an application of cyanoacrylate spray and no toxicity was apparent. Several advantages of the Freon-propelled n-butylcyanoacrylate, in addition to the simplicity of its application, were also noted: the spray allowed for controlled application of the monomer, the cooling effect of Freon caused vasoconstriction and aided in haemostasis, and the immediate evaporation of the Freon gas from the sprayed surface created a porous film that was thought to accelerate its degradation in vivo.[27] The cyanoacrylate spray technology was available and the opportunity to save lives in the battlefields of Vietnam was quickly recognized. In 1966 a special surgical team was equipped with and trained to use the aerosolized cyanoacrylate adhesives, and was dispatched to the war effort in Vietnam.[28]

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[25] *Ibid*., p. 15.
[26] *Ibid*., pp. 16-17.
[27] Matsumoto, *Tissue Adhesives in Surgery*, pp.16-18.
[28] Coover, *Cyanoacrylate Adhesives*, p. 61.

Cyanoacrylate Use in the Vietnam War (1955-1975)

In military medicine, the main concern of the physician is to quickly stop any life-threatening bleeding; cyanoacrylates were able to address this problem in two ways: First, during the Korean and Vietnam Wars, many soldiers died of blood loss en route to field hospitals, because efficient treatment of traumatic and hemorrhagic shock was not available.[29] Having field medics equipped with cyanoacrylate spray allowed a simple spray of the adhesive to instantly stop bleeding, allowing time to treat the wounds by conventional means once the injured could be transported to a treatment centre.[30] Secondly, after serious trauma, many casualties suffered persistent internal bleeding, despite the best efforts of military trauma surgeons using conventional surgical techniques. In these situations, cyanoacrylate sprays could be directly applied to the bleeding surface, achieving instant haemostasis and saving the patient's life.[31] It is this second use of cyanoacrylates that is best documented and that saw the most dramatic application in military medical practices during the Vietnam War.

The US Army's cyanoacrylate spray was used in about thirty documented cases of surgically untreatable haemorrhage resulting from wounds to the liver, kidneys or retroperitoneal space.[32] In life-threatening situations, or those in which the patient's organ would otherwise have been sacrificed due to uncontrolled bleeding, cyanoacrylate spray adhesive was used according to the following methods. Initially, the blood supply to the involved organ had been occluded via digital pressure or a vascular clamp to achieve temporary haemostasis.[33] (Note that non-arterial bleeding and the ability to achieve a temporarily dry surface were relative requirements for this surgical use of cyanoacrylates).[34] Then a sterile polyethylene sheet, with a hole cut in it to expose the area where the glue was to be applied, was draped over the surgical field. After carefully drying the oozing area, the spray could either be applied to the organ surface and allowed to polymerize by itself or pressure could be applied during polymerization via another polyethylene sheet, a piece of omentum,

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[29] Hardaway, *The Problem of Acute Trauma and Shock*, p. 799.
[30] Coover, *Cyanoacrylate Adhesives*, p. 61.
[31] Hardaway, *The Problem of Acute Trauma and Shock*, p. 801.
[32] *Ibid*.
[33] Charles A. Heisterkamp et al., "Solid Organ Injuries in Vietnam. Emergency Hemostasis with n-butyl Cyanoacrylate Adhesive," *Archives of Surgery* 100 (1970), p. 109-112.
[34] Collins et al., *Cyanoacrylate Adhesives*, p. 261.

or a cooptation of the organ itself. Polymerization took twenty to thirty seconds; if bleeding recurred after polymerization, the polymerized adhesive could be easily removed in one sheet before its seal to the organ is complete and the process could be repeated to achieve total haemostasis.[35]

Collins et al. published a review of the clinical use of cyanoacrylate adhesives as topical haemostatic aids in seven combat casualties in the Vietnam War, which outlined the early successes of super glue in the battlefield. In four of these patients, standard surgical procedures had failed to stop their internal bleeding and each patient had already been given twenty to fifty units of blood prior to application of the adhesive. All four demonstrated diffuse, oozing bleeding from the liver or kidney. The three remaining cases were not as urgent, but resulted in cyanoacrylate use to stop mild, but continued bleeding of one liver and two poorly localized retroperitoneal bleeds during surgical wound repair. The results were promising: "In none of the seven patients was there any indication that the adhesive failed to stop bleeding or that the bleeding recurred at the site of application." Although three of the seven patients died, one of kidney failure and two of septic complications, the use of cyanoacrylate was determined as not being a cause of death. Of the four patients who survived, twelve day to seven month follow-up studies failed to show any renal or liver impairment, even where the spray was applied directly to these organs.[36]

A second, more comprehensive review of emergency haemostasis with n-butylcyanoacrylate adhesives on solid organ injuries in Vietnam was published by Lieutenant Colonel Charles A. Heisterkamp et al. in 1970. This document reviews twenty three combat casualties, of which ten patients received cyanoacrylate treatment for liver wounds, three for kidney wounds, five for retroperitoneal bleeding and five for vascular anastomosis reinforcement. In nineteen of these twenty three cases, rapid haemostasis with cyanoacrylate spray was very successful. Of the four unsuccessful cases, there was one difficulty in stopping a liver haemorrhage where several hepatic vessels were necessarily ligated before cyanoacrylate mediated haemostasis could be achieved; prolonged clamping of the renal pedicle during debridement and haemostasis resulted in a nephrectomy in another patient; one patient died of profuse abdominal bleeding that could not be stemmed long enough through adhesive polymerization; and one patient died of post-operative hemorrhagic and

[35] Heisterkamp, *Solid Organ Injuries in Vietnam*, pp. 109-110.
[36] Collins et al., *Cyanoacrylate Adhesives*, pp. 261-262.

septic complications unrelated to cyanoacrylate use.[37] A typical case report of a Vietnam War casualty treated with cyanoacrylate is as follows:

> A 24-year-old soldier was wounded by a bullet which entered the right flank, fracturing the right kidney, the right hepatic lobe, gallbladder, and then entered the hemithorax. Right nephrectomy and right hepatic lobectomy were performed. The larger vessels within the liver substance were individually ligated but persistent oozing remained. At this point more than 25 units of blood had been utilized during resuscitation and operation. Blood pressure was 80/40mm Hg and pulse 120 beats per minute with the patient under anaesthesia. Application of cyanoacrylate spray after temporary occlusion of the Porta hepatis was followed by complete cessation of bleeding from the liver surface.[38]

Both of these reviews concluded that the rapidly polymerizing of the n-butyl cyanoacrylate spray adhesive was a successful haemostatic aid in cases where traditional surgical techniques had failed to control soft organ bleeding. Although none of the deaths in casualties treated with cyanoacrylate sprays were attributable to the use of cyanoacrylate, both authors cautioned that insertion of foreign bodies (i.e. non-degradable cyanoacrylate polymers) into living tissue could increase the risk of long term complications, and that their use should be reserved for life threatening situations.

FDA Disapproval

After the initial application for n-butyl cyanoacrylate tissue adhesive for FDA approval in 1964, Coover and his team worked for six years testing and retesting for product safety. Despite the positive results and follow-up from cases in Vietnam, as well as laboratory and clinical research, the FDA was concerned about the potential carcinogenicity of cyanoacrylates.[39] Would surgical superglue, so effective in emergency situations on the Vietnam battlefield, possibly cause cancer in patients if it was introduced into widespread surgical practice? The only evidence for potential carcinogenicity was an FDA animal study in rats, where implantation of polymerized cyanoacrylate disks in rats resulted in tumour formation; however, this reaction was not seen in other animal trials or in humans. According to Coover, this test did not accurately represent the long term

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[37] Heisterkamp, *Solid Organ Injuries in Vietnam*, pp. 110-112.
[38] *Ibid*., p. 110.
[39] Coover, *Cyanoacrylate Adhesives*, p. 61.

risks of cyanoacrylate implantation for two reasons: First, the doses of cyanoacrylate given to the rats were over hundred times higher than what would ever be used in humans. Second, it was well described in scientific literature that rats commonly develop tumours in response to almost any implanted foreign bodies that were not sufficiently porous, including FDA approved prosthetic devices in use at the time. Nonetheless, the FDA required another, very costly, long-term study to settle the dispute before granting their approval to cyanoacrylates.[40]

Medical researcher Coover and the pharmaceutical company Ethicon now faced a serious dilemma; either to carry out a multi-million dollar study that would overshadow all product revenues for years to come, or to abandon their project. Reluctantly, they decided on the latter course of action, as the long term study did not seem to be an attractive gamble and there was no guarantee that the FDA would grant their approval even if the results were favourable.[41] Despite the American experimental successes of n-butylcyanoacrylate tissue adhesives in neurosurgery, plastic surgery, otolaryngology, and ophthalmology; FDA approval was not to be granted at this juncture.[42] As Coover notes in his version of the events, "by 1972, after twelve years of technical success and a record of saving lives, the cyanoacrylate medical adhesive was, for all practical purposes, dead."[43]

Worldwide Cyanoacrylate Development and Clinical Use

Although the fight for approval of surgical superglue was indefinitely suspended by Ethicon in the United States, there had been much research and development devoted to cyanoacrylate tissue adhesives elsewhere in the world. By 1972, there was already a large body of experimental and clinical research on medical cyanoacrylates that had been established by scientists in Japan, Austria, Germany, and several other European countries.[44] As early as 1965, the Japanese Ministry of Public Welfare had already approved an ethylcyanoacrylate adhesive, known as "Aron Alpha", as a commercially available surgical material. Approval of this admittedly imperfect tissue adhesive stimulated many investigators to either use or broadly examine the medical potential of tissue adhesives. The widespread adoption of tissue adhesives in the Japanese surgical

[40] *Ibid.*
[41] *Ibid.*
[42] Matsumoto, *Tissue Adhesives in Surgery*, pp. 226-331.
[43] Coover, *Cyanoacrylate Adhesives*, p. 61.
[44] Matsumoto, *Tissue Adhesives in Surgery*, pp. 332-429.

community resulted in the development of new tissue adhesive formulations, more research on the characteristics and long term effects of the already approved adhesives, as well as expanding the use of cyanoacrylate tissue adhesives to new surgical procedures.[45] The early Japanese interest in the development of tissue adhesives may have stemmed from their cultural beliefs, as blood loss and the need for transfusions are extremely emotive issues.[46] Perhaps an effective tissue adhesive could reliably obtain haemostasis and close wounds where sutures were ineffective or undesirable.

The two main tissue adhesive products used with relative success in Japan were Aron Alpha, and BioBond; a mixture of Eastman 910®, a polyisocyanate, and nitryl gum that was used successfully to encase intracranial aneurysms.[47] Much research was done on their effects in animal and human tissue; although, similar results to Ethicon's findings on methyl- and ethylcyanoacrylate toxicity and inflammatory properties were reported, the benefits of their clinical application were judged to outweigh the risks. The Japanese successfully used Aron Alpha in humans to stop bleeding and rejoin blood vessels, reinforce vascular, intestinal, pulmonary, and cleft palate suture lines, obliterate bronchofistulas, perform suture-less closure of skin incisions and attach skin grafts.[48] In the 3,000 patients treated with Aron Alpha in Japan by 1972, no acute systemic toxicity was observed, although, surface toxicity was found in 5-6 percent of patients, and no carcinogenicity was detected at the site of application within a follow-up period of 10 years.[49]

In Austria, medical cyanoacrylate development blossomed after an international Symposium on Tissue Adhesives was held in Vienna, Austria, in September 1967. Austrian scientists developed a new method of synthesising n-butylcyanoacrylate adhesive and their experiments with tissue adhesives primarily investigated the properties and applications of this Austrian-made adhesive. Vulnocoll® was an n-butylcyanoacrylate that was synthesised without the use of an organic solvent. This new procedure resulted in a greater yield of purified product in a shorter amount of time. The properties of this tissue adhesive were found to be

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[45] *Ibid*., pp. 339-390.

[46] P. Driscoll, *New Wound Closures Get Seal of Approval, Advanced Medical Technologies (2008)*; retrieved 27 June 2009 (http://mediligence.com/blog/2008/02/11/wound-sealant/).

[47] Matsumoto, *Tissue Adhesives in Surgery* (New York: Medical Examination Publishing Co., Inc., 1972), pp. 339-340.

[48] *Ibid*., p. 339.

[49] *Ibid*., pp. 393-402.

similar to traditionally synthesised n-butylcyanoacrylates; they are less toxic than shorter-chain cyanoacrylates, degrade more slowly, polymerize faster and result in the formation of flexible bonds.[50]

Most notably, Austrian clinical research on n-butylcyanoacrylate resulted in the development of a "grid adhesion" technique for binding two tissues together. Since longer chain cyanoacrylate polymers do not degrade significantly in vivo, using these tissue adhesives to bond two layers of tissue together does not allow for proper healing and integration of the two layers.[51] Thus, for procedures such as skin grafts, a protocol was developed where a roller (similar to a paint roller) covered in tiny projections could be coated in glue and rolled onto the tissue, depositing a grid of adhesive droplets. The graft could then be placed atop the adhesive-covered tissue and allowed to heal. Since a discontinuous layer of n-butylcyanoacrylate held the two layers together, the graft could heal around the glue particles and satisfactorily integrate itself with the recipient's tissue. Grid adhesion techniques proved to be very successful in closing wounds in both animals and humans, organopexy (fixation of a floating organ) procedures, and to reinforce suture lines by gluing a layer of tissue over the sutures.[52]

In Germany, contribution to tissue adhesive research was marked by the development of Histoacryl Blue®, which was introduced into the German medical market in early 1968. Developed in the early 1960s by Dr. Bernd Braun (1906-1993), completely independent from work done by Coover, Histoacryl Blue® was an n-butylcyanoacrylate adhesive originally designed for topical use.[53] Still being marketed today, Histoacryl Blue® is delivered in sterile plastic capsules that have a fine plastic capillary tube through which the adhesive can be applied. There are several applicator tips to choose from, as well as a spray formulation. Histoacryl Blue® is named for the blue colouring of the glue, which allows physicians to accurately judge and control the amount of adhesive they apply without tattooing or permanently colouring the patient's tissue.[54]

Although, first marketed as a topical tissue adhesive, Histoacryl Blue® was applied experimentally to an array of clinical applications. This German surgical glue was used to close thousands of small wounds on the head, face and hands; it was noted to be especially useful in children as it

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[50] *Ibid*.
[51] Matsumoto, *Tissue Adhesives in Surgery*, pp. 402-403.
[52] *Ibid*., pp. 404-414.
[53] *TissueSeal, History – 40 Years of Histoacryl®, TissueSeal LLC. (2005); retrieved 20 June 2009* (http://www. tissueseal. com/history.html).
[54] Matsumoto, *Tissue Adhesives in Surgery*, pp. 446-447.

could be applied painlessly without local anaesthesia.[55] Experimental uses of Histoacryl Blue® in Germany included reinforcing and waterproofing suture lines, closing tracheal lesions, performing oesophageal, vascular and nerve anastomoses, and sealing pancreatic and kidney resections.[56] By 1972, when Coover's efforts to obtain FDA approval for n-butyl cyanoacrylate tissue adhesives were abandoned, Histoacryl Blue® was being widely used for topical wound closures in Germany and additional research was being conducted on its potential applications in invasive procedures.

By 1980, Histoacryl Blue® was approved for medical use in Canada, Europe, Israel and Japan.[57] Primarily, the glue was used topically for skin incisions and the closure of small wounds; it was also used for middle ear procedures, to close cerebrospinal leaks and to affix skin grafts.[58] However, n-butylcyanoacrylates did not gain widespread popularity in these regions of the world, despite their availability. Even though butylcyanoacrylates were superior to their short chain homologues, physicians still found that they could be difficult to manipulate, had variable clinical outcomes and were mildly histotoxic, with largely unknown long term complications.[59] Nevertheless, by the late 1980s, butylcyanoacrylates had been used topically and internally in tens of thousands of patients worldwide without a single report of carcinogenicity.[60]

Meanwhile, in the United States, the FDA had not yet approved any cyanoacrylate tissue adhesives. In the late 1970s, the FDA granted n-butyl- and isobutylcyanoacrylates an "Investigational Drug and Device Exemption" (IDE). Although Coover and Ethicon had formally ended their development of cyanoacrylates in 1972, they provided cyanoacrylates free of charge to any researchers in the United States who had submitted a protocol to the FDA and obtained an IDE for their study.[61] The FDA's experimental exemption, however, did not make cyanoacrylates widely

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[55] *Ibid*., p. 449.
[56] *Ibid*., pp. 449-492.
[57] Quinn, *Tissue Adhesives in Clinical Medicine*, p. 19.
[58] William H. Eaglstein and Tory Sullivan, "Cyanoacrylates for skin closure," *Dermatologic Clinics* 23 (2005), pp. 193-198.
[59] Tanja Fernandez and Val Bliskovsky, *Cyanoacrylate Technology, Stay Glued," Pharmabiz.com (2003)*; retrieved 10 June 2009 (http://www.pharmabiz.com/article/detnews.asp?articleid=13609&sectionid=46).
[60] Alex Berenstein and Grant Hieshima, "Clinical versus experimental use of isobutyl-2-cyanoacrylate," *Journal of Neurosurgery* 67 (1987), pp. 318-320.
[61] *Ibid*.

available to surgeons; Coover claims that some American surgeons without IDEs risked using commercial grade cyanoacrylates on their patients under special circumstances.[62]

FDA Approval of Octylcyanoacrylate Tissue Adhesives

The long awaited FDA approval of cyanoacrylate tissue adhesives began in the laboratories of Tri-Point Medical Corporation, a small technology company in Raleigh, North Carolina. Tri-Point scientists worked for years to develop medical cyanoacrylate formulations that could be used to seal topical skin incisions and lacerations. By the mid 1980s, Tri-Point released its first tissue adhesive, Nexaband®, to the market. It was an octylcyanoacrylate adhesive approved for veterinary use.[63] By the mid 1990s, Tri-Point had formulated an octylcyanoacrylate adhesive for human use.[64] Octylcyanoacrylates have an eight carbon alkyl group, which gives it several advantages over intermediate (i.e. butyl) or short (i.e. methyl or ethyl) side chains. The octyl chain produces an adhesive with greater flexibility, which has four times the three-dimensional breaking strength of n-butylcyanoacrylate.[65] The long alkyl chain also results in virtually no toxic degradation products, while plasticizers and stabilizers are included to control the polymerization rate and viscosity.[66]

With a promising new tissue adhesive in clinical testing, "Tri-Point Corporation" renamed itself "Closure Medical Corporation", and in 1996 entered into a renewable eight year supply and distribution agreement with Ethicon. This agreement gave Ethicon exclusive worldwide rights to market, distribute and sell the new octylcyanoacrylate formulation, named "Dermabond®".[67] On August 26, 1998, Closure Medical Corporation received FDA approval for market release of Dermabond® Topical Skin Adhesive; the first class III adhesive device approved for topical skin approximation.[68] Dermabond® has become available in sterile, single-use plastic ampoules that can be used on their own or attached to a variety of different applicators in order to topically approximate the edges of a wound. Since octylcyanoacrylate does not

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62 Coover, *Cyanoacrylate Adhesives*, p. 61.
63 Fernandez and Bliskovsky, *Cyanoacrylate Technology*; retrieved 10 June, 2009.
64 *Ibid*.
65 Eaglstein and Sullivan, *Cyanoacrylates for Skin Closure*, p. 194.
66 Quinn, *Tissue Adhesives*, p. 30.
67 Fernandez and Bliskovsky, *Cyanoacrylate Technology, Stay Glued*; retrieved 10 June, 2009.
68 Quinn, *Tissue Adhesives*, p. 19.

degrade in vivo, it is important not to get the adhesive in the wound, but only seal together the surface edges. Otherwise, cyanoacrylate adhesive between the two sides of the wound would impede the healing process and become permanently implanted in the wound. To achieve maximum strength, the wound edges should be held together and a few layers of Dermabond® should be applied to the skin surface. If the wound is deep, sometimes subdermal sutures will be required before the wound edges can be sealed effectively with adhesive.[69] When used experimentally to seal incisions and lacerations, Dermabond® was able to close wounds twice the length of those closed in previous studies with n- butylcyanoacrylate. It was also shown to be less irritating to the skin and as effective in closing wounds as 5.0 monofilament sutures.[70]

Dermabond® was proven to be an effective wound closure device, but would it be shown to be a cost effective option versus traditional suturing techniques? Although one ampoule of Dermabond® is more expensive than basic suture materials, studies conducted in both Canadian and British emergency departments have shown that total cost per patient is as low as half the cost of sutures.[71] This discrepancy in cost can be attributed to the time required for wound closures, the number of surgical instruments required, the need for anaesthetics, and whether or not follow-ups are required. Four randomized controlled trails found that skin closure was 3.6 minutes faster with octylcyanoacrylates than with standard wound closure devices.[72] In addition, wound closure with Dermabond® required no additional surgical equipment, unlike suturing procedures, and usually did not require a local anaesthetic.[73] Finally, octylcyanoacrylate tissue adhesives usually sloughed off the skin five to ten days after application and eliminated the need for follow-up visits to remove non-dissolving sutures.[74]

Another benefit of octylcyanoacrylates is their optimal cosmetic outcome. In several clinical trials, the cosmetic results of superficial wound closure with Dermabond® were judged to be equivalent or superior

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[69] Quinn, *Tissue Adhesives*, pp. 41-43.

[70] Marjorie E. King and Anita Y. Kinney, "Tissue Adhesives: A New Method of Wound Repair," *Nurse Practitioner (Oct 1999)*; retrieved 5 June 2009 (http://findarticles.com/p/articles/mi_qa3958/is_199910/ai_n8875194/).

[71] *Ibid*.

[72] A.J. Singer and H.C. Thode, "A Review of the Literature on Octylcyanoacrylate Tissue Adhesive," *American Journal of Surgery* 187 (2004), p. 239.

[73] King and Kinney, *Tissue Adhesives: a New Method of Wound Repair*; retrieved 5 June 2009.

[74] Quinn, ed., *Tissue Adhesives in Clinical Medicine*, p. 42.

to those achieved with sutures. For example, a prospective study evaluated the treatment of skin lacerations and elective head and neck incisions, finding no cosmetic difference between using octylcyanoacrylate adhesives or traditional sutures.[75] Dermabond® use correlates with high patient satisfaction, as one study found that 98 percent of individuals (or their parents), whose wounds were treated with tissue adhesives, said that they would "again choose this method for convenience, comfort, and results compared with past experiences with suturing".[76] Topical octylcyanoacrylate tissue adhesives have been shown to be more resistant to infection after wound closure than sutures, due to three different mechanisms. Because suturing inherently introduces foreign material into a wound, octylcyanoacrylate has a natural advantage in preventing an infection due to its topical application, most notably with clean contaminated wounds.[77] In addition, cyanoacrylates themselves have antimicrobial properties, especially against gram-positive organisms such as Staphylococcus aureus.[78] The third mechanism for preventing infection is the fact that Dermabond® creates a waterproof barrier over the wound that is also successful in keeping out bacteria. In January 2002, Dermabond® received FDA approval to be market as an adhesive that acts as a barrier to microbial penetration.[79]

Nexaband® and Dermabond® are not the only FDA-approved octylcyanoacrylate products marketed by companies such as Closure Medical and Ethicon after 1998; Band Aid Brand Liquid Bandage (Liquiderm®) and Soothe-n-Seal® are two octylcyanoacrylates available as over-the-counter tissue adhesives. Liquiderm® adhesive was shown in clinical trials to stop active bleeding, speed wound healing and reduce pain associated with superficial cuts and abrasions, while providing a protective antimicrobial barrier. It is currently the only FDA-approved consumer tissue adhesive on the market. On the other hand, Soothe-n-Seal® is an oral tissue adhesive for wound and ulcer protection. With a market of 40 million households in the United States by 2003, it is currently the only FDA-approved over-the-counter device designed to treat canker sores.[80]

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[75] Eaglstein and Sullivan, *Cyanoacrylates for Skin Closure*, p. 194.
[76] King and Kinney, *Tissue Adhesives: A New Method of Wound Repair*; retrieved 5 June 2009.
[77] Eaglstein and Sullivan, *Cyanoacrylates for Skin Closure*, p. 194.
[78] Quinn, *Tissue Adhesives*, p. 34.
[79] Fernandez and Bliskovsky, *Cyanoacrylate Technology, Stay Glued*; retrieved 10 June, 2009.
[80] *Ibid*.

In the years following FDA approval of octylcyanoacrylate tissue adhesives, two n-butylcyanoacrylate tissue adhesive formulations were approved for medical use in the United States. On September 25, 2000, the FDA approved the first cyanoacrylate monomer, "Trufill®" n-butylcyanoacrylate, for neurologic embolization. It is a three compound system of n-butylcyanoacrylate, ethiodized oil, and tantalum powder, which polymerize into a solid embolic agent when mixed. The principle behind the device is to use a microcatheter to deliver the mixture to a cerebral arteriovenous malformation (AVM), and block the blood flow to the lesion with the adhesive before the AVM can be removed surgically.[81] Since Trufill® is only used pre-operatively, it does not constitute a permanent foreign body, and thus the FDA approved it without having to consider its potential long term effects in the human body.

On May 22, 2002, Indermil® tissue adhesive became the second cyanoacrylate approved for topical wound approximation by the FDA. Thirty six years after Coover's original application for approval of a butylcyanoacrylate tissue adhesive, and after n-butylcyanoacrylate products had been used in millions of patients worldwide without any serious adverse effects, the FDA was finally beginning to be convinced of the safety and medical utility of n-butylcyanoacrylates.[82]

Current and Future Uses of Cyanoacrylates in Medicine

Physicians have long sought a tissue adhesive that could not only be used in wound closures, but anywhere that sutures would be difficult or impractical to use. Butyl- and octylcyanoacrylates have proved themselves worthy tissue adhesives that are used around the world for a variety of procedures. Selections of reported uses include: skin, cartilage, and bone grafting; tympanoplasty and ossiculoplasty in otologic surgery; as a sealant for cerebrospinal fluid leaks and for bowel and vascular anastomosis; as an embolizing agent for arteriovenous malformations, and gastric and esophageal varicose; as a periodontal dressing and temporary dental sealant; as a haemostatic agent in visceral injuries; as a dressing for burns, abrasions, and blisters; and as a delivery vehicle for chemotherapeutic agents and antibiotics. They have also been used as a temporary sealant for injured teeth with exposed nerve endings and for apthous ulcers.[83]

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[81] Quinn, *Tissue Adhesives*, pp. 21-22.
[82] *Ibid*., pp. 20-21.
[83] Quinn, *Tissue Adhesives*, p. 36.

Whether or not these procedures are widely available or remain experimental varies widely and mainly depends on national regulatory approval. In the United States, cyanoacrylate products are only approved for temporary and topical applications; the FDA still maintains that there is not enough evidence to prove the safety of long term implantation.[84] What does the future hold for tissue adhesives in medicine? Around the world there is ongoing research on how to improve cyanoacrylate formulations for various surgical purposes. Further research into finding adhesive compounds that will polymerize into porous sheets or safely degrade in vivo would allow for more effective wound closure and could eliminate the risks of implanting a permanent foreign body, respectively.[85] Perhaps one of the most interesting applications of cyanoacrylates, which is currently being researched, is topical drug delivery of chemotherapy and antibiotics. By using butylcyanoacrylate nanoparticles as drug carriers, adhesive applied to the skin can slowly release a drug to the affected area and will slough off in 5-10 days.[86] The medical potential for cyanoacrylate use is staggering, and the applications we see now are likely the beginning of a long tradition of super glue in medical procedures.

Conclusions

Without Harry W. Coover's ability to realize the great potential of cyanoacrylates as adhesives, we would be without a valuable medical tool. Moreover, it was Coover's creativity that allowed him to envision that his commercially sold glues could potentially save many lives where traditional medical practices could not. Although it was a long road, marked with many disappointments, the investigations of the physician Coover and the research support of the pharmaceutical company of Ethicon helped save many lives in Vietnam and around the world even though they were forced to abandon the project. In Japan, early cyanoacrylate tissue adhesives were approved, which resulted in a flurry of innovative research; in Austria new n-butylcyanoacrylate synthesis methods and grid adhesion techniques were developed; and in Germany, Histoacryl Blue® was first marketed in 1968 and has become available in Canada, Europe, Israel and Japan since 1980.

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[84] George J. Mattamal, "US FDA Perspective on the Regulations of Medical-Grade Polymers: Cyanoacrylate Polymer Medical Device Tissue Adhesives," *Expert Review of Medical Devices* 5 (2008), pp. 41-49; esp. p. 48.
[85] Ikada, *Wound Closure Biomaterials and Devices*, p. 327.
[86] Eaglstein and Sullivan, *Cyanoacrylates for Skin Closure*, p. 194.

In 1998, Coover's dream to market cyanoacrylate tissue adhesives in the United States came true when the FDA finally granted their approval to octylcyanoacrylate medical adhesives, and later, to two n-butylcyanoacrylate adhesives. Today we benefit from Coover's efforts, as well as the efforts of those who continued cyanoacrylate research and persevered in creating new formulations with countless medical uses. It is important to ask what we can learn from this tale of serendipity, super glue and surgery. As Coover put it;

> This should serve as a reminder to all of us to be open-minded and curious enough to pursue unexplained events and unexpected results which may unlock new secrets and lead to the new and exciting discoveries of the future.[87]

Because Coover was able to see the medical potential of his super glue, various formulations are now used in a variety of procedures from incision closure to corneal transplants.

However, we must also realize that prevalent political and regulatory climates play an enormous role in the adoption of new technologies. If the testing of cyanoacrylate adhesives did not occur with the backdrop of the Vietnam War, its success as a haemostatic aid in trauma surgery may never have been explored to its fullest potential. Once the research and development of new tissue adhesives caught on, different regulatory bodies in different parts of the world served to both help and hinder the progress of cyanoacrylate tissue adhesives. In countries such as Japan, the tissue adhesives were approved very early after their medical potential become apparent; their availability led to increased interest and research into formulating the ideal adhesive. Similarly, in Germany, Histoacryl Blue® was marketed before any long term studies had been done on n-butylcyanoacrylates. Its acceptance by the medical community led to the development of a huge diversity of surgical applications for cyano-acrylates. On the other hand, the FDA has been the most conservative regulatory body, demanding a larger burden of evidence on the long term safety of cyanoacrylates.

Many critics have questioned the FDA's apparent overregulation of the American drug approval process, especially in relation to their longstanding failure to approve medical cyanoacrylates. In 1962, two years before Coover's first proposal for cyanoacrylate approval, the FDA introduced the "Kefauver Harris Amendment" which required companies to prove the long term safety and efficacy of their drug or device before it

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[87] Coover, *Cyanoacrylate Adhesives*, p. 61.

was approved.[88] This amendment was a response to the Thalidomide tragedy of the late 1950s, where thousands of children worldwide were born with birth defects because their mothers had taken the drug for morning sickness. Although the intent of the amendment was praiseworthy, drug development declined significantly after 1962, and the wait for new life-saving drugs increased to more than a decade by the end of the 1970s.[89] Whether or not the FDA's tight regulation on cyanoacrylates truly considered the best interests of patients or the best interests of the FDA is up for debate.

Clearly serendipity and open-mindedness both play a role in new discoveries, but the success of these discoveries is largely determined by the point in history that they are implemented, where they are implemented, and how tightly regulated they are. In the end, it was the ambition and perseverance of investigators around the word that have made the widespread medical use of cyanoacrylate tissue adhesives a reality.

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[88] Sam Peltzman, "An Evaluation of Consumer Protection Legislation: the 1962 Drug Amendments," *Journal of Political Economy* 81, (1973), p. 1051.

[89] Daniel B. Klein and Alexander Tabarrok, *History of Federal Regulation: 1902 – Present, The Independent Institute (2008)*; retrieved 27 June 2009 (http://www.fdareview.org/history.shtml).