THE PREVENTION OF MENINGOCEREBRAL ADHESIONS

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I. INTRODUCTION

In the Great War of 1914-1918 neurosurgery established its unassailable claim as a specialized branch of military surgery. The improvement of operative technique and the lowering of the mortality rate in all types of injuries of the central nervous system were due in large measure to the brilliance of Cushing, de Martel, Jefferson, Foerster, Sargent and other neurosurgeons. The greater number of surgical principles which they founded have been incorporated as "routine" in the modern treatment of brain, spinal cord and peripheral nerve injuries.

During the post-war years a widespread interest in the sequelae of injuries of the nervous system has developed. Outstanding among these complications are late abscess; disorders of speech, movement and sensation; mental disturbances and posttraumatic epilepsy. It is this last-named complication which has been of particular interest to Penfield and his associates in Montreal.

Penfield has repeatedly emphasized the importance of the adhesions between cerebral scars and overlying structures in the production of convulsive phenomena. In 1930 he collaborated with Foerster in a study of 12 cases of posttraumatic epilepsy. In many of these patients seizures were produced at the time of operation by tugging on the dura overlying a meningocerebral cicatrix. On the basis of these observations they suggested that a vasomotor reflex secondary to the traction may be responsible for the initiation of the seizures.

As further evidence for the importance of adhesions Penfield (1936) has pointed out the higher incidence of convulsive seizures following head injury in which penetration of the dura has occurred, as compared to those cases in which the dura was not penetrated. In an analysis of 452 cases of head injury sustained in the Great War, Rawling (1922) found the incidence of seizures following craniocerebral wounds of various types to be as follows:

Penetrating wound with hernia	54%
Penetrating wound	35%
Penetrating wound with foreign bodies retained	33%
Perforating wound	16%
Fractured base	14%
Non-penetrating wound	13%
Scalp wounds	10%

In a study of 377 cases of gunshot wound of the head, Wagstaffe (1928) found an incidence of 18.7% seizures in wounds with dural penetration and less than 2% in those cases where the dura was not penetrated. Stern, quoted by Schou (1933), found an incidence of 20 to 50% in open craniocerebral injury and 2 to 4% in closed injury.

The writer would object to acceptance of these statistics as evidence in favor of the importance of meningocerebral adhesions alone in the causation of seizures. While it is true that the incidence of adhesion formation would be much greater in the wounds with dural penetration, it is also likely that the destruction of nervous tissue was more

extensive under these circumstances. Furthermore, it is not improbable that in many of the non-penetrating injuries the lesions were confined to the superficial structures and did not involve the underlying brain.

A third point of evidence in favor of the importance of adhesions is Penfield's (1936) observation of the higher incidence of seizures in patients with meningocerebral cicatrix as compared to cerebral cicatrix. In the cerebral cicatrix, where there is little or no admixture of connective tissue, he believes the incidence must be much lower. In support of this contention he points out the infrequency of seizures in patients with cerebral scars resulting from vascular occlusion.

The importance of this study on the prevention of meningocerebral adhesions, with a view to a lowering of the incidence of posttraumatic epilepsy, is modified, therefore, by acceptance or rejection of the adhesion hypothesis. The solution to the problem requires adoption of a proven method for the prevention of adhesions, employing the technique in the treatment of craniocerebral wounds in the present conflict and, finally, an analysis of the incidence of posttraumatic epilepsy in patients so treated in later years.

II. REVIEW OF THE LITERATURE

A systematic approach to the problems involved in the prevention of adhesions between the brain and its coverings has two essential requirements. The first of these is knowledge of the factors involved in the evolution of the meningocerebral scar. The second requirement is an extensive review, with a critical analysis, of the methods which have been used in the past for this purpose. The data in this chapter consider both of these points.

The Meningocerebral Cicatrix.

A. Role of the Meninges.

Adherence to overlying structures is not the invariable component of cerebral injury. Any lesion, whether of a vascular, inflammatory or traumatic nature, which does not disturb the function or continuity of the arachnoid, is not followed by adhesions. Our knowledge of this protective role of the arachnoid is due to the investigations of Harvey and his associates.

In 1923 Sayad and Harvey published their observations on the reactions of the meninges to injury. They performed the first series of experiments on dogs. Discs of dura mater varying in size from 2.8 to 6.13 sq. cm. were excised. The leptomeninges were not injured. This dural defect was rapidly obliterated with blood clot, having only fibrinous attachments to the arachnoid. Within one week the arachnoidal surface of the clot was carpeted with a thin

layer of endothelial cells and the fibrinous attachment to the arachnoid disappeared. They therefore concluded that the dura mater will regenerate without adhering to the intact arachnoid.

The following year Lear and Harvey (1924) studied the regeneration of the injured pia-arachnoid of dogs. To ensure the intactness of the overlying dura they reflected it from the cortical surface in the form of a large flap. The leptomeninges lying directly beneath the center of the dural flap were injured with either a blunt instrument or the electrocautery. Dural adhesions occurred in all instances. This led them to postulate that, in the repair of the leptomeninges, the dura mater does not serve as a limiting membrane but enters actively into the healing process. This reaction of the intact dura to the injured pia-arachnoid has been offered by Harvey and Burr (1926) as one argument for the dual (mesenchymal plus neural crest) origin of the leptomeninges.

B. <u>The Formation of the Meningocerebral Cicatrix</u>.

The studies of Penfield (1924)(1927) and Rio-Hortega and Penfield (1927) have been outstanding contributions to the pathogenesis of the meningocerebral cicatrix. They have studied the sequence of events from within a few hours of the injury to the formation of the mature scar.

Within six hours of the injury the traumatic defect in the brain is filled with blood clot. The intensity of the fibroblastic-glial reaction which then ensues is

directly proportional to the amount of devitalized cerebral tissue which remains. Within twenty-four hours the neighboring microglia have an ameboid form and start their migration to the site of injury. At the end of the second day they are compound granular corpuscles and are actively phagocytizing debris. This phagocytosis continues until all of the unnecessary materials have been removed. It is not uncommon to find these cells, filled with products of destruction, within the interstices of the scar many years after the injury. Penfield (1941) describes one case in which fat-filled phagocytes were found in the border of a 28-year-old scar.

The astrocytes also play an important role in the repair process. At the end of the first day the astrocytes in the immediate neighborhood of the wound have undergone clasmatodendrosis. Those in the more distant zone show swelling, without fragmentation, of both cell body and processes. On the fourth day these swollen cells undergo amitotic division and begin to lay down fibrils at the margin of the wound. By this time fibroblasts from the overlying dura, muscle and blood vessels have permeated the clot and are soon intimately blended with the neuroglia fibrils of the wound edge. Blood vessels proliferate and penetrate the fibroblastic-glial meshwork and eventually form a rich anastamosis with the cerebral vessels.

The final stage, as Penfield points out, is one of contraction of the connective tissue core. This pull is

transmitted to the glial fibrils causing them to be orientated perpendicularly to the surface of the cerebral wound. At times this traction is so great that the sucker feet of astrocytes are displaced through the pia mater. A further indication of the pull is the migration of the lateral ventricle toward the site of the lesion.

In summary, therefore, there are two factors which influence the formation of the meningocerebral cicatrix. Most important is the damage to the arachnoid which predisposes the connective tissue invasion from the overlying structures. The second factor is the extent of brain damage, the density of the resulting scar being directly proportional to the volume of devitalized tissue.

The Prevention of Meningocerebral Adhesions.

The disturbances of bodily function due to adhesions are not confined to the brain and its coverings. The investigations related to this problem are few compared to those which concern the other serous spaces of the body, especially the peritoneal cavity. The prevention of adhesions in joint spaces, tendon sheaths and around sutured nerves has likewise attracted a great deal of attention. In Table I are listed the methods and materials which have been used for the prevention of adhesions between peritoneal surfaces. This list was compiled from the reviews of Richardson (1911) and Ochsner and Garside (1932).

Table I.

A list of methods and materials which have been used to prevent the formation of peritoneal adhesions [compiled from the reviews of Richardson (1911) and Ochsner and Garside (1932)].

MATERIALS PRIMARILY MECHANICAL IN ACTION DUE TO:

A. SEPARATION OF DENUDED OR TRAUMATIZED SURFACES

1. VIABLE ANIMAL MEMBRANES

PERITONEAL GRAFTS AND FLAPS
OMENTAL GRAFTS AND FLAPS

2. NON-VIABLE ANIMAL MEMBRANES

GOLDBEATER'S SKIN (SEROSA OF OX CAECUM)
SHARK PERITONEUM
CARGILE MEMBRANE (OX PERITONEUM)
WOVEN CATGUT
HUMAN AMNIOTIC MEMBRANE
BEEF AMNIOTIC MEMBRANE
BEEF ALLANTOIC MEMBRANE
CALF PERITONEUM

3. LUBRICANTS

MUCILAGE OF GUM ARABIC
LANOLIN
PARAFFIN
OLIVE OIL
LIQUID PETROLATUM
VASELINE OIL
CAMPHORATED OIL
HUMANOL
MUCIN

4. MISCELLANEOUS FILMS

ARISTOL (THYMOL IODIDE)
AGAR
GELATIN (PLAIN AND FORMOLIZED)
AGAR GELATIN
CARRAGEN (ISLAND MOSS)
COLLODION
VITREOUS HUMOR OF CALF EYE
EGG ALBUMIN
GUTTA PERCHA SOLUTIONS
SILK PROTECTIVE
SILVER FOIL

5. LIQUIDS

RAW MILK
PEPTONIZED MILK
HYPERTONIC SALINE
HYPERTONIC GLUCOSE
NORMAL SALINE

6. GASES

OXYGEN
NITROGEN WITH AIR

B. EFFECT ON THE MOTILITY AND MOBILITY OF THE GASTROINTESTINAL TRACT

1. THROUGH PERISTALTIC ACTION

CATHARTICS
PHYSOSTIGMINE
PHYSOSTIGMINE WITH STRYCHNINE
GASTRIC LAVAGE

2. THROUGH VARIOUS PHYSIOTHERAPEUTIC MEASURES

MASSAGE OF THE LOWER ABDOMEN
POSTURING TO SEPARATE TRAUMATIZED SURFACES
PERIODIC DISTENTION OF THE COLON WITH OXYGEN OR ENEMATA
PERIODIC DISTENTION OF THE BLADDER WITH BORIC ACID SOLUTION
LOCAL HEAT TO THE ABDOMEN

MATERIALS PRIMARILY CHEMICAL IN ACTION DUE TO INHIBITORY EFFECT ON ADHESION FORMATION:

1. SUBSTANCES USED ORALLY

SYRUP OF HYDRIODIC ACID
THIOSINAMINE
FIBROLYSIN (THIOSINAMINE WITH SODIUM SALICYLATE)
PHOSPHOROUS

2. SUBSTANCES USED HYPODERMICALLY

PEPTONE
PHYSOSTIGMINE

3. SUBSTANCES USED INTRAPERITONEALLY

5-20% SOLUTION OF MAGNESIUM SULPHATE
NORMAL SALINE WITH ADRENALIN
AMMONIUM OXALATE SOLUTION
SODIUM CITRATE SOLUTION CONTAINING GUM ARABIC
SODIUM CITRATE SOLUTION CONTAINING SODIUM CHLORIDE
HIRUDIN SOLUTION
FIBROLYSIN SOLUTION
PEPTONE SOLUTION
AMFETIN (AMNIOTIC FLUID)
PEPSIN-PREGL IODINE SOLUTION
PAPAIN SOLUTION
TRYPSIN SOLUTION

There is a purpose in presenting this impressive array of methods and materials. It is testimony to the existing confusion in the prevention and treatment of peritoneal adhesions. A new method or material will have been successfully employed by one, or, frequently, a number of observers and then failed in the test of time and trial. Similar circumstances have held for adhesion prevention in the other serous spaces of the organism. The problem remains unsolved.

The observations on methods and materials employed to prevent adhesions between the brain and its enveloping structures are but few when compared to the total literature on adhesion prevention. The majority of the available reports concern various substances which have been utilized primarily to repair dural defects. These methods of duroplasty have been reviewed by von Saar (1910), Buné (1933), de Bernardis (1935), Caporale and de Bernardis (1936) and Glaser and Thienes (1938).

The experiments on duroplasty are of great interest and value in the present study. The reaction of the surrounding tissues to these materials, especially when the arachnoidal barrier is broken, has served as a guide in the selection of the proper substances for this investigation. For purposes of review and discussion these materials may be classified as follows:

A. Metals.
B. Viable animal membranes.
C. Non-viable animal membranes.
D. Miscellaneous.

A. Metals.

The debut of the modern period in the surgery of posttraumatic epilepsy, which was pioneered by Horsley in the latter part of the 19th century, was followed by the first reports on the use of materials to prevent meningocerebral adhesions. Horsley excised the epileptogenic cicatrices but did not cover the area of removal with protective materials. Beach is accredited with the first suggestion to use these substances. In 1890 he reported a case of posttraumatic epilepsy treated by lysis of the meningocerebral adhesions. At this time he stated that should the seizures recur he would reoperate and implant gold foil between the brain and dura. In 1897 he reported that this plan was effected at a second craniotomy in 1892. The patient's attacks recurred but with diminished frequency and intensity. No further observations on the condition of the foil were reported.

The popularity of the metallic foils in the surgery of epilepsy was maintained well into the first decade of the twentieth century. The observations of Beach on gold foil were followed by the reports of Oliver (1896), Estes (1896), Summers (1897) and Woolsey (1897) on this metal and those of Ray (1901), Harris (1904) and Prime (1909) on silver foil and Morehead (1896) and McCosh (1898) on platinum foil. Chao, Humphreys and Penfield (1940) have recently reported their experiences with silver foil, aluminum foil, nickel plate and stainless

steel plate. The results of all of these observations are outlined in Table II.

One feature common to all of these metals is encapsulation. The intensity of cellular reaction is variable and would seem dependent on the degree of electrolysis of the metal. The good clinical results are overshadowed by the finding of dense adhesions between the brain and dura in all of the cases where direct observations on the condition of the membrane were possible.

B. Viable Animal Membranes.

At the close of the first decade of the twentieth century the metallic substances were being discarded in favor of viable and non-viable animal membranes. The viable membranes have generally been employed for the closure of dural defects and not for the prevention of meningocerebral adhesions. This work originated with Kirshner (1909) who, in 1909, used autoplastic fascia lata for dural restoration in dogs. The first human duroplastic operation with fascia lata was performed by Körte in 1910. A variety of viable membranes have since been employed. Among the autoplastic tissues are dura (Brüning 1911), periosteum (Rohde 1933, Buné 1933), and fat (Rehn 1913, Denk 1914, Chao et al. 1940). Homoplastic hernia sac was successfully used in man by Finsterer (1910). Burger (1939) attempted to replace the dura mater in cats with human amniotic membrane obtained in the fresh state at Caesarian section but his results were inconclusive. Chao, Humphreys and

Table II.

The Metals.

METALS

MATERIAL	OBSERVERS	YEAR	ANIMAL	LOCATION	PURPOSE	RESULT
GOLD FOIL	BEACH	1892	MAN	CORTICAL SURFACE	PREVENT ADHESIONS	CLINICALLY FAIR-NO AUTOPSY
	OLIVER	1895	MAN	CORTICAL SURFACE	PREVENT ADHESIONS	RE-OPERATED AND RESULT GOOD
	ESTES	1896	MAN	CORTICAL SURFACE	PREVENT ADHESIONS	CLINICALLY GOOD-NO AUTOPSY
	SUMMERS	1897	MAN	CORTICAL SURFACE	PREVENT ADHESIONS	CLINICALLY GOOD-NO AUTOPSY
	WOOLSEY	1897	MAN	CORTICAL SURFACE	PREVENT ADHESIONS	ENCAPSULATION & ADHESIONS
SILVER FOIL	RAY	1901	MAN	CORTICAL SURFACE	PREVENT ADHESIONS	CLINICALLY GOOD NO AUTOPSY
	HARRIS	1904	MAN	CORTICAL SURFACE	PREVENT ADHESIONS	CLINICALLY GOOD-NO AUTOPSY
	PRIME	1909	DOG	CORTICAL SURFACE	PREVENT ADHESIONS	ENCAPSULATION & ADHESIONS
	CHAO HUMPHREYS PENFIELD	1940	CAT	CORTICAL SURFACE	PREVENT ADHESIONS	DENSE ADHESIONS AND MARKED CELLULAR REACTION
PLATINUM FOIL	MOREHEAD	1896	MAN	CORTICAL SURFACE	PREVENT ADHESIONS	NOT STATED
	McCOSH	1898	MAN	CORTICAL SURFACE	PREVENT ADHESIONS	NOT STATED
ALUMINUM FOIL	CHAO ET AL.	1940	CAT	CORTICAL SURFACE	PREVENT ADHESIONS	DENSE ADHESIONS AND MILD CELLULAR REACTION
NICKEL PLATE	CHAO ET AL.	1940	CAT	CORTICAL SURFACE	PREVENT ADHESIONS	DENSE ADHESIONS AND MARKED CELLULAR REACTION
STAINLESS STEEL PLATE	CHAO ET AL.	1940	CAT	CORTICAL SURFACE	PREVENT ADHESIONS	DENSE ADHESIONS & ENCAPSULATION

Penfield (1940) present the only experimental data on the use of viable membranes to prevent meningocerebral adhesions specifically. Both fat and fascia lata were used over brain wounds in cats. Adhesions occurred in all of the experiments.

An analysis of the data outlined in Table III allows certain conclusions to be drawn. From the standpoint of dural repair the autoplastic, viable membranes have been uniformly successful. However, when the cortex was damaged and subsequent examination of the tissues was carried out, meningocerebral adhesions have been invariably noted.

C. Non-viable Animal Membranes.

A large number of materials classifiable in this category have been employed over the intact and wounded cerebral cortex. In 1898 Freeman described two experiments, one on a dog and the other on a rabbit, in which the vitelline membrane of the hen egg was placed over the wounded cerebral cortex. The wound in the dog suppurated, vitiating his results. The rabbit was killed at the end of two months. The brain was yellow at the site of the laceration but was smooth and non-adherent except by a few trivial and delicate adhesions around the edge of the dural opening. Greer (1901) and Prime (1909) subsequently reported their observations on this membrane. Prime noted adhesions in his dogs in every instance when the cortex was damaged.

Table III.

The Viable Animal Membranes.

VIABLE ANIMAL MEMBRANES

MATERIAL	OBSERVERS	YEAR	ANIMAL	LOCATION	PURPOSE	RESULT
FASCIA LATA	KIRSCHNER	1909	DOG	DURAL DEFECT	DUROPLASTY	FIRM UNION WITH DURA
	DAVIS	1910	DOG	DURAL DEFECT	DUROPLASTY	FIRM UNION WITH DURA CORTEX UNINJURED AND NO ADHESIONS
	KIRSCHNER	1913	DOG	DURAL DEFECT	DUROPLASTY	FIRM UNION WITH DURA IN 45 DAYS. NO ADHESIONS TO PIA
	CHAO ET AL.	1940	CAT	CORTICAL SURFACE	PREVENT ADHESIONS	MODERATE ADHESIONS AND CELLULAR REACTION
AUTOPLASTIC PERIOSTEUM	FINSTERER	1910	DOG	DURAL DEFECT	DUROPLASTY	DENSELY ADHERENT TO WOUNDED CORTEX
AUTOPLASTIC TEMPORALIS FASCIA	BUNE	1933	DOG	DURAL DEFECT	DUROPLASTY	ADHESIONS IF CORTEX DAMAGED
AUTOPLASTIC PERITONEAL TISSUES	ROHDE	----	DOG	DURAL DEFECT	DUROPLASTY	ADHESIONS IF CORTEX DAMAGED
	BUNE	1933	DOG	DURAL DEFECT	DUROPLASTY	ADHESIONS IF CORTEX DAMAGED
AUTOPLASTIC FAT	REHN	1913	DOG	DURAL DEFECT	DUROPLASTY	ADHESIONS EVEN THOUGH PIA UNDAMAGED
	DENK	1914	DOG	DURAL DEFECT	DUROPLASTY	DENSE ADHESIONS TO DAMAGED PIA
	CHAO ET AL.	1940	CAT	CORTICAL SURFACE	PREVENT ADHESIONS	DENSE ADHESIONS AND MARKED CELLULAR REACTION
HUMAN AMNIOTIC MEMBRANE	BURGER	1939	CAT	DURAL DEFECT	DUROPLASTY	RESULTS INCONCLUSIVE

Other non-viable animal membranes which have been subjected to investigation are Cargile membrane (Craig and Ellis 1905, Prime 1909, Chao et al. 1940), prepared hernia sac (Finsterer 1910, von Saar 1910), human amniotic membrane (Chao et al. 1940, Odom 1940), beef allantoic membrane (Chao et al), catgut membrane (de Bernardis 1935, Caporale and de Bernardis 1936, Chao et al. 1940), sheep peritoneum (Hanel 1909) and calf artery (Ritter 1910). The results of these observations are presented in Table IV.

These non-viable membranes have shown the greatest promise in the prevention of meningocerebral adhesions. This is especially true of amniotic and allantoic membranes. While both materials promote cellular reaction and are eventually encapsulated, these reactions have been generally minimal. Adhesions have been trivial or absent in a great number of instances. Caporale and de Bernardis have had excellent results with catgut membrane. In their rabbit experiments the membrane was adherent to the brain wound but not to the overlying structures. However, their good results were not confirmed in the experiments of Chao and his colleagues.

D. Miscellaneous Membranes.

These membranes are outlined in Table V. Various substances of plant or mineral origin are included in this group. The experience with these materials has been generally unsatisfactory. Encapsulation and adhesion formation have occurred in practically all instances.

Table IV.

The Non-viable Animal Membranes.

NON-VIABLE ANIMAL MEMBRANES

MATERIAL	OBSERVERS	YEAR	ANIMAL	LOCATION	PURPOSE	RESULT
EGG SHELL MEMBRANE	FREEMAN	1898	DOG RABBIT	CORTICAL SURFACE	PREVENT ADHESIONS	INCONCLUSIVE
	GREER	1901	MAN	CORTICAL SURFACE	PREVENT ADHESIONS	INCONCLUSIVE
	PRIME	1909	DOG	CORTICAL SURFACE	PREVENT ADHESIONS	ENCAPSULATION AND ADHESIONS IF CORTEX INJURED
CARGILE MEMBRANE	CRAIG & ELLIS	1905	DOG	DURAL DEFECT	DUROPLASTY	INCONCLUSIVE
	PRIME	1909	DOG	CORTICAL SURFACE	PREVENT ADHESIONS	ENCAPSULATION AND ADHESIONS IF CORTEX INJURED
	CHAO ET AL.	1940	CAT	CORTICAL SURFACE	PREVENT ADHESIONS	DENSE ADHESIONS AND MODERATE CELLULAR REACTION
PREPARED HERNIA SAC	FINSTERER	1910	DOG	DURAL DEFECT	DUROPLASTY	FIRM UNION WITH DURA. NO CORTICAL INJURY-NO ADHESIONS
	VON SAAR	1910	DOG RABBIT GUINEA PIG	DURAL DEFECT	DUROPLASTY	ADHESIONS IN MOST CASES
HUMAN AMNIOTIC MEMBRANE	CHAO ET AL.	1940	CAT	CORTICAL SURFACE	PREVENT ADHESIONS	NO ADHESIONS IN MOST CASES FINE ADHESIONS IN OCCASIONAL CASE
	ODOM	1940	CAT	CORTICAL SURFACE	PREVENT ADHESIONS	ADHESIONS IN MOST CASES
BEEF ALLANTOIC MEMBRANE	CHAO ET AL.	1940	CAT	CORTICAL SURFACE	PREVENT ADHESIONS	FEW ADHESIONS AND SLIGHT CELLULAR REACTION
CATGUT MEMBRANE	CHAO ET AL.	1940	CAT	CORTICAL SURFACE	PREVENT ADHESIONS	MODERATE ADHESION FORMATION AND MODERATE CELLULAR REACTION
SHEEP PERITONEUM	HANEL	1909	DOG	DURAL DEFECT	DUROPLASTY	MEMBRANE RESORBED AND DURA-LIKE MEMBRANE SUBSTITUTED. NO ADHESIONS
CALF ARTERY	RITTER	1910	DOG	DURAL DEFECT OVER SPINAL CORD	DUROPLASTY	NO ADHESIONS.

Table V.

Miscellaneous Materials.

MISCELLANEOUS

MATERIAL	OBSERVERS	YEAR	ANIMAL	LOCATION	PURPOSE	RESULT
RUBBER TISSUE	ABBE	1897	MAN	CORTICAL SURFACE	PREVENT ADHESIONS	DENSE ENCAPSULATION
CELLULOID	HANTSCH	1922	RABBITS DOGS	SKULL DEFECT WITH DURA EXCISED AND BRAIN DAMAGED	STUDY OF REACTION	ENCAPSULATION WITH ADHESIONS TO CORTEX
PARCHMENT	OBERNIEDERMAYER	1928	RABBIT	DURAL DEFECT	DUROPLASTY	ENCAPSULATION WITH ADHESIONS TO CORTEX
MICA	CHAO ET AL.	1940	CAT	CORTICAL SURFACE	PREVENT ADHESIONS	DENSE ADHESIONS AND MODERATE CELLULAR REACTION
CELLOPHANE	CHAO ET AL.	1940	CAT	CORTICAL SURFACE	PREVENT ADHESIONS	DENSE ADHESIONS AND MILD CELLULAR REACTION
OLIVE OIL	PRIME	1909	DOG	CORTICAL SURFACE	PREVENT ADHESIONS	DENSE ADHESIONS EVEN THOUGH CORTEX NOT WOUNDED

The Ideal Membrane.

The analysis of the results obtained with the materials outlined previously has been invaluable in the selection of substances for the present series of experiments. The difficulties in the past have been due to cellular reaction leading to encapsulation of both the resorbable and non-resorbable membranes. Adhesions have occurred from the inner layer of the capsule to the cortical wound. It is probable that the presence of the membrane has served to aggravate, rather than retard or prevent, the formation of adhesions.

The membrane, selected for the prevention of adhesions, should have certain characteristics. First in importance should be its inertness, that is, a tendency to promote but minimal reaction in the surrounding tissues. This reaction includes both the mobilization of inflammatory cells and the proliferation of fibroblasts. Second in importance would be its resorbability. However, this last quality is dispensable if the material were entirely inert in the tissues.

The ideal membrane should remain intact and check the ingrowth of fibrous tissue from the surrounding structures during the period required for complete covering of the wound in the brain by the arachnoid. The period of time required for this repair will vary according to the site, size and nature of the lesion. Chao et al.(1940) noted in their experiments that when small cerebral lesions were produced

the arachnoid was completely healed at the end of 30 days.

The materials used in the present study are both resorbable and non-resorbable. They were selected on the basis of one or more of the following characteristics: (1) Availability of supply, (2) Inertness, (3) Delayed resorption, (4) Successful employment in the past. They are:

1. Human amniotic membrane.
2. Beef allantoic membrane.
3. Cargile membrane.
4. Tantalum foil.
5. Polymerized vinyl alcohol compounds.

Amniotic Membrane.

The earliest reference to the use of amniotic membrane for the prevention of adhesions between serous surfaces is that of Schmerz (1911a). He reported the successful treatment of disabling adhesions in three cases of gunshot wound of the tendon sheaths and a fourth case of ankylosis of the elbow joint. In all of these cases the traumatized surfaces were covered with amnion. The membrane he used was prepared by fixation in formalin, preservation in absolute alcohol and sterilization by immersion in boiling water or exposure to live steam. It is interesting that in this report he mentions the possible value of amniotic membrane in myolysis, neurolysis and duroplasty. In a later communication (1911b) he described the successful recovery of function in a case of ankylosis of the knee joint treated by interposition of this material.

In 1914 Lyman and Bergtold used human amniotic membrane, treated by washing in water and then preservation in a 0.5% solution of formaldehyde in 70% alcohol, to prevent postoperative peritoneal adhesions in seven human cases. While they reported success their experience was entirely clinical. No subsequent surgical or pathological observations were made.

The successful use of amniotic membrane reported in these earlier papers apparently aroused but little enthusiasm. No further observations on this material are recorded until 1933 at which time Lyons reported the satisfactory epithelialization of two postoperative mastoid cavities lined with fresh, sterile amniotic membrane obtained at Caesarian section. In 1937 Davis and Aries reported their observations on the use of both beef and human amniotic membrane for the prevention of adhesions around repaired nerves and tendons and between the denuded peritoneal surfaces of dogs. The human amniotic membrane was used in the fresh state, having been obtained at Caesarian section and placed temporarily in sterile physiological saline solution. The beef amnion was rendered non-viable by sterilization. The tendon and nerve experiments were unsuccessful but excellent results were obtained in the peritoneal cavity, especially if the mucoid surface overlying the epithelial layer of the amnion was intact. Johnson (1937) had previously reported good results with human amniotic membrane in avoiding adhesions between the traumatized peritoneal surfaces of rabbits.

However, he notes that the membrane was treated as a foreign body by the contiguous tissues.

The studies of Burger (1937, 1939) on the potentialities of human fetal membranes have opened new doors to the art of plastic surgery. In 1937 he reported three cases of successful reconstruction of the human vagina with fresh fetal membranes obtained at Caesarian section. In these procedures the chorion was placed against the wall of the prepared tract; the amnion serving as the inner lining. Subsequent biopsies showed the repaired vagina to be lined with stratified squamous epithelium. Comparison with other cases in which the vagina was repaired with a tube of intestine, and in which the epithelium permanently retained its glandular structure, led Burger to assume that the stratified squamous epithelium represented a transformation of the cellular layer of the amnion and not an ingrowth of epithelium from the vaginal orifice. In a later communication (1939) Burger mentions that he and his associates had used living human fetal membranes to replace the dura in cats. He notes "In one of the cases the adherence was satisfactory, still this lone case was not sufficient for the solution of our problem."

The first observations on the use of amniotic membrane to prevent adhesions between the brain and its coverings were those reported by Chao, Humphreys and Penfield (1940). These workers reported success with amnioplastin, a specially-treated form of human amniotic membrane. This membrane is prepared as follows: After

separation from the chorion by finger dissection, the amnion is thoroughly washed in running water, preserved in 70% alcohol and sterilized by either boiling or autoclaving. This membrane was placed over the wounded cerebral cortex and leptomeninges of cats. The animals were sacrificed at appropriate intervals up to 60 days. Their results were uniformly good. The membrane caused only a slight cellular reaction and was completely resorbed at the end of 30 days. Within this 30-day period the pia-arachnoid had covered the cerebral wound and adhesions to the overlying structures did not occur. Their consistently good results led these observers to recommend amnioplastin "as a preventative of meningocerebral adhesions and as an adjunct to the radical surgery necessary to prevent posttraumatic and postoperative epilepsy."

The studies on amnioplastic have been continued by Odom (1940). Despite a rigid adherence to the method of preparation of the membrane outlined in the report of Chao et al., Odom's results have been unsatisfactory. Meningocerebral adhesions occurred in the greater number of his experiments. After an analysis of his preliminary data, Odom believed that the occurrence of meningocerebral adhesions was due to the presence of fat in the membranes. In view of this, he used lipoid solvents in the preparation of the membranes. The complete extraction of fat by these solvents was confirmed by histological examination. Unfortunately, this fat-free membrane has likewise failed in its purpose.

It is difficult to evaluate the discrepancies in the results with amnioplastin. The most plausible explanation is that the cerebral wounds produced by Odom were more extensive and therefore associated with a greater cellular reaction. Less likely are minor differences in the preparation of the membrane and in the operative and histological techniques. This contradiction in the experimental data led Penfield (1940) to warn against the use of amnioplastin until further studies had been carried out.

Within the past year further reports on the use of amniotic membrane have appeared in the literature. Garcin and Guillaume (1940) have used it to repair the dural defects associated with craniocerebral gunshot wounds. Their results are not stated. Rogers (1941) has recently voiced his enthusiasm for amnioplastin. He reports success with the use of this membrane following craniotomy and neurolysis. His impressions are based entirely on the clinical results. He records no observations of the tissue reaction to the membranes.

Recently reports concerning the use of fetal membranes in ophthalmological surgery have appeared in the literature. De Rötth (1941) has used grafts taken from fresh, sterile, fetal membrane in the treatment of symblepharon. At the time of operation the chorion was placed against the wound leaving the amnion as the free surface. In all of his cases the membranes healed in situ and were eventually transformed into conjunctiva. His only difficulties were attributable to shrinkage of the grafts. Law

and Philip (1941) prefer amnioplastin to viable amniotic membrane because of the availability of supply, reliability of sterilization and its amorphous character. They report one case in which the lower lid was excised and substituted by amnioplastin. A good functional result was obtained.

Allantoic Membrane.

Beef allantoic membrane, known commercially as "Insultoic Membrane", was first employed for the prevention of adhesions by Johnson (1937). He covered the traumatized peritoneal surfaces of rabbits and tendons of calves with this material. While the membrane stimulated a foreign body reaction and was eventually encapsulated, his results were excellent due to the smoothness of the inner surface of the formed connective tissue capsule. Adhesions did not occur unless the membrane slipped or was of insufficient size to cover the traumatized area (1941).

The excellent results obtained by Johnson have been confirmed by the work of Davis and Aries (1937). These observers covered denuded peritoneal surfaces and sutured nerves and tendons of dogs with allantoic membrane. Around the nerves and tendons this membrane was superior to beef and human amniotic membrane, sheet catgut, beef cecum, cellophane and rubber latex which were used as control materials. In the peritoneal cavity, however, better results were obtained with amniotic membrane, especially if its mucus surface was intact. The allantoic membrane prevented peritoneal adhesions only to the extent and

size of the patch which was used.

Chao, Humphreys and Penfield (1940) had encouraging results with allantoic membrane in the prevention of meningocerebral adhesions. The adhesions that formed were few in number and the cellular response slight. Unfortunately, their experience with this membrane was limited. Because of this, further experimentation seemed indicated.

Cargile Membrane.

In 1902, Morris reported the use of prepared ox peritoneum in the prevention of postoperative peritoneal adhesions in human cases. He named this membrane in honor of Doctor Charles H. Cargile of Bentonville, Arkansas, who suggested its use. Morris reported good clinical results but subsequent observations on the condition of the membrane were not made.

While Morris may be justly considered a pioneer in the use of membranes of peritoneal derivation, he was preceded by Baum. In 1894 Baum described his good clinical results following the use of prepared peritoneum of freshly slaughtered calves to protect traumatized peritoneal surfaces. Again no postoperative observations on the condition of the membrane or the protected tissues are recorded.

In his original article Morris mentioned the close adherence of Cargile membrane to exposed brain tissue and intimated that it may be of value as a temporary dura mater. The validity of this statement was apparently not confirmed by experimentation. Craig and Ellis (1905)

were the first to attempt dural repair with Cargile membrane. They reported experiments in which this material was employed to repair dural defects in dogs. Their results were entirely vitiated due to suppuration in the wounds.

Prime (1909) pioneered in the use of Cargile membrane for the specific purpose of preventing adhesions between the brain and its coverings. However, in his experiments the membrane was encapsulated and adhesions were invariable if the cortex was traumatized.

These early observations on Cargile membrane were followed by reports on other viable and non-viable membranes of peritoneal derivation. In practically all instances the purpose of the membrane was the closure of dural defects. Included in this group are membranes derived from hernia sacs, omentum and the parietal and visceral peritoneal reflections. The data on these materials are outlined in Tables III and IV. Satisfactory results have been obtained when these peritoneal membranes were used as dural substitutes. However, meningocerebral adhesions have occurred in those instances where the brain has been damaged.

Cargile membrane has been repeatedly recommended in the surgery of peripheral nerve injuries. In 1919, Joyce used the prepared membrane of a fine variety to protect sutured and neurolysed nerves. Four of his cases were re-explored at 3, 4, 7 and 19 months following implantation. From his observations on these cases he

concluded that the membrane is absorbed in less than 6 months. During this time it fulfills its purpose in the protection against adhesion formation.

Huber (1920) also reported satisfactory results following the use of Cargile membrane. The commercial type of membrane was absorbed in 10 days and felt to be unsatisfactory. However, if this material was placed in 70% followed by absolute alcohol and then dried, his results were better. The "alcoholized" membrane was not absorbed within 5 to 6 months and during this time protected the nerve and incited only a minimal connective tissue reaction. His results with formolized arterial sheaths, fat and fascia lata were much less satisfactory. Cairns and Young (1940) consider the fresh membrane as being superior to the "alcoholized" form. They remark that the latter type causes a greater tissue reaction.

In addition to his studies of amniotic and allantoic membranes Johnson (1937) employed Cargile membrane to prevent peritoneal adhesions in his experimental animals. In all of his experiments the membrane was treated as a foreign body and the results were uniformly poor.

Chao and his co-workers (1940) used Cargile membrane in their studies of the prevention of meningocerebral adhesions in cats. They found dense adhesions and a moderate cellular response in all of the experiments.

In summary, therefore, the experiences with Cargile membrane have been generally unsatisfactory. Nevertheless, due to the availability of large amounts

of this material, the promise it has shown in peripheral nerve surgery and the lack of an adequate study of its usefulness in the prevention of meningocerebral adhesions, a further trial seemed warranted.

Tantalum.

Surgery, and especially orthopedic surgery, has had a great need for metallic appliances which are non-irritating to tissues and resistant to the corrosive action of body fluids. Numerous metals, both in the pure state and in the form of alloys, have been used in the past. Vitallium, an alloy composed of cobalt, chromium and molybdenum, is reported to be the least irritating of the metals in use at the present time. The chief disadvantage of vitallium is its inability to be machined; all appliances made from it have to be cast.

Burke introduced the medical profession to tantalum in 1940. This metal is the seventy-third element in the periodic table. It was discovered by Ekeberg in 1802 but first obtained in the pure state by Bolton in 1905. Physically it is a bluish-gray, extremely hard but, nevertheless, a malleable and ductile metal. Chemically, it approaches glass in its resistance to acids. Only hydrofluoric, sulfuric and phosphoric acids will attack it. While resistant to weak alkalies, it is attacked and destroyed by boiling alkalies. It is completely inert when in contact with salts except those which hydrolyze to form strong alkalies.

Following a study of materials capable of resisting the corrosive action of the body fluids, Burke selected tantalum. He used it in the form of bone screws and plates in both dogs and rabbits. In none of the experiments was there any gross or microscopic evidence of tissue irritation. He also used tantalum wire as a skin suture in 34 patients. The reaction was again minimal. A few weeks after removal of the sutures it was impossible to detect where they had passed through the skin.

These observations of Burke are testimony to the inertness of tantalum. The qualities of lack of tissue irritation and the availability of the metal in the form of foil led to the use of tantalum in this study.

Polyvinyl Alcohol Compounds.

The search for materials in which the rate of resorption in the tissues could be controlled disclosed the polyvinyl alcohol compounds. These compounds are used commercially in the manufacture of shatterproof glass. Their chief attraction in the present study is the change in solubility rate obtainable by modifying their structural formulas. This may be exemplified as follows: The replacement of the hydroxyl groups of polyvinyl alcohol with acetate groups eventually changes the compound to polyvinyl acetate. The compounds formed in the stages of transition vary in their solubility. Maximum solubility is obtained when 20% of the hydroxyl groups have been replaced by acetate groups. Pure polyvinyl alcohol and polyvinyl

acetate are less soluble than this 20% compound. One therefore has a wide range of polyvinyl compounds from which to choose.

In the problem under consideration the most favored compound would be the one which would remain intact for at least one month. This length of time would permit the protected arachnoid to repair itself without invasion from the overlying structures. On the basis of "in vitro" solubility a polymerized vinyl alcohol having a 5% replacement of hydroxyl groups with acetate groups was selected.

Only one paper on polyvinyl alcohol compounds has made its appearance in the medical literature. In 1938 Dötzer reported experiments on the reactions of bacteria in contact with polyvinyl alcohol. Colon bacilli, streptococci, staphylococci, pneumococci and tubercle bacilli were inoculated in nutrient media containing either pure polyvinyl alcohol or polyvinyl alcohol with hydroxyquinoline potassium sulphate added in concentrations of 0.1% and 0.16%. Pure polyvinyl alcohol was found to be bacteriostatic but not bactericidal. However, with the addition of the small amounts of antiseptic, most of the bacteria were killed when the ratio of polyvinyl alcohol to culture media was 1:1 and all were killed when this ratio was 10:1.

In his report Dötzer mentions the animal experiments of Braun and Herrmann in which polyvinyl alcohols were used. However, no details or references are given.

A certain amount of information is obtained from the applications which have been submitted to the Patent Offices of the United Kingdom and the United States of America by Herrmann and Haehnel (1933); Herrmann, Baum and Haehnel (1937), Herrmann, Hammer, Kassell and Haehner (1937) and Herrmann, Braun and Haehnel (1939). In these reports they point out that the polymerized vinyl alcohol and polyvinyl compounds are endured by the body without causing suppuration or fistula formation. They are easily sterilized, possess great tensile strength and resistance to fracture and may be made more or less resorptive as required. The experimental background for their statements is not presented.

III. METHODS AND MATERIALS

Cats were used in all of the experiments. Anesthesia was obtained with a 10% alcoholic solution of nembutal injected intraperitoneally in doses of 0.6 cc. (3/5 grain) per kilogram of body weight. In a few instances it was necessary to increase the depth of anesthesia with ether. The animal's head was placed in a clamping device to insure immobility during the operative procedure.

Operative Technique.

After shaving the scalp, applications of green soap, 70% alcohol, ether and a 5% alcoholic solution of mercurescein, in this sequence, were used in the preparation of the skin. The scalp was draped as a sterile field and rigid aseptic precautions were observed throughout the operative procedures.

The skin and the galea were divided with a mid-line incision extending from the brow up to the occipital region, and retracted laterally. The temporal muscles were reflected by incising the fascia along the superior temporal line and separating them from the skull with a periosteal elevator. A wide exposure of the convexity of the skull was obtained in all instances.

The openings in the skull were made in the parietal region bilaterally, using a trephine and mastoid rongeurs. These bony defects were approximately square in outline and 1.5 to 2.0 cm. in diameter. Bleeding from the diploic veins was controlled with Horsley's wax.

Care was taken to remove all excess wax.

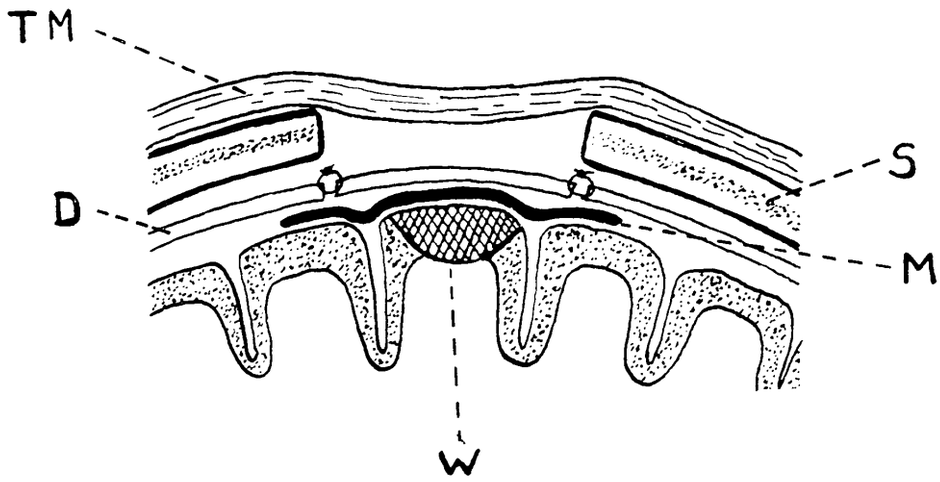
The dura was incised about 2 mm. from the anterior, medial and posterior margins of the bony defect and reflected laterally in the form of a flap. Bleeding from the larger dural vessels was controlled with light cauterization or packing.

The cerebral cortex on one side, usually the right, was wounded by electrocoagulation of the surface of one or more gyri. In many instances the area of thermal destruction was repeatedly pierced with the point of a scalpel. At times large blood vessels were involved in the cauterized zone and experience warned against the use of the scalpel. Failure to adopt this policy usually meant loss of time in the control of bleeding. In a few of the experiments some of the cauterized cerebral tissue had to be removed with the automatic suction to isolate and cauterize the bleeding vessels.

Both the wounded and the unwounded cerebral hemispheres were covered with the material of choice. The edges of these materials were tucked well under the cut edge of the overlying dura (Fig. 1). The dura was closed with two fine silk sutures, one at each corner. The tissues were then thoroughly irrigated with physiological saline solution. The temporalis muscles, galea and skin were apposed with interrupted sutures of black silk. Dry dressings were applied and fixed to the skin with liquid adhesive.

Fig. 1.

Diagrammatic cross section showing the method of covering the cerebral wound (W) with the membrane (M). Temporal muscle (TM). Dura (D). Skull (S).


TM
D
S
M
W

Materials.

1. Amniotic Membrane.*

Human amniotic membrane was used in all of the experiments. According to Keibel and Mall (1910) the amnion is a transparent, glistening membrane which is fused with the placenta and chorion, but separable from them. It consists of a connective tissue stroma and a layer of cuboidal or cylindrical epithelium. Fat granules are frequently demonstrable in these layers. Rarely the epithelium becomes many-layered and forms villi. The membrane is devoid of blood vessels (See Fig. 2).

Three different types of amniotic membrane were used. For practical purposes these may be termed:
A. Viable. B. Attenuated. C. Fixed.

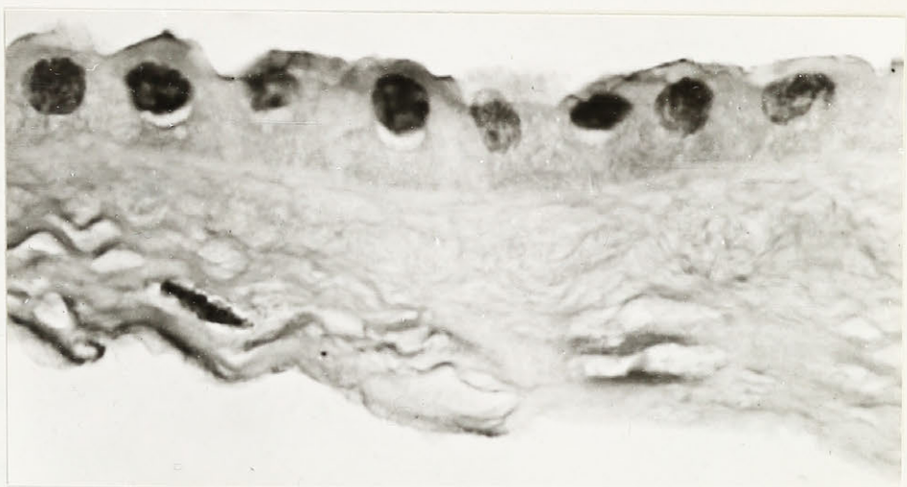
A. Viable Amniotic Membrane.

Human fetal membranes obtained at Caesarian section were placed immediately in a sterile container and kept in an incubator at 37° Centigrade until ready for use. The amnion was separated from the chorion at the time of operation by means of blunt dissection with the finger. The elapsed time between receipt and placement of the membrane on the cerebral cortex did not exceed three hours. The membrane was washed in physiological saline solution but no attempt was made to remove the mucus covering the epithelial layer.

*The fetal membranes were supplied through the generosity of the staff of the Royal Victoria Montreal Maternity Hospital.

Fig. 2.

Amniotic membrane after fixation in formalin. The epithelial and connective tissue layers are shown. Hematoxylin and Van Gieson stain.



B. Attenuated Amniotic Membrane.

In the preparation of this membrane selected pieces of the viable membrane were placed in sterilized tubes of liquid petrolatum. These tubes were refrigerated at 3° Centigrade until required for the experimental procedures.

This method of attenuation was suggested by the observations of Huber (1920) on the storage of nerve trunks for subsequent use as grafts. He notes that Dujarier and François (1918) had success with the use of grafts stored in white vaseline at low temperatures. Huber modified this technique by employing liquid petrolatum. He preserved the sciatic nerves of rabbits, removed under aseptic precautions, at a temperature of 3° Centigrade for periods varying from 7 to 39 days. At this low temperature he believes that a certain amount of viability of the connective tissue elements is preserved. In his experiments good results were obtained with homografts but not with heterografts.

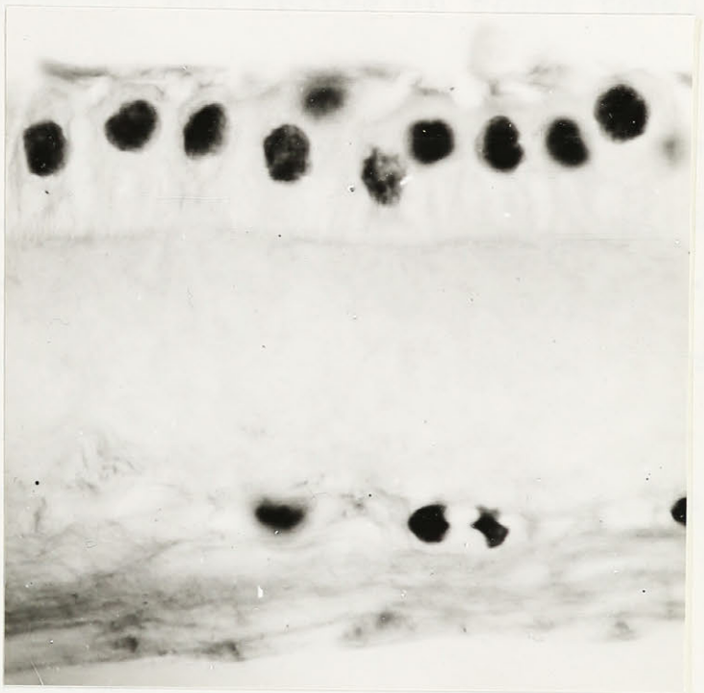
A cross section of amniotic membrane treated by Huber's method is seen in figure 3.

C. Fixed Amniotic Membrane.

This membrane was prepared according to the procedure outlined by LeVann (1941). The purpose of this method is a complete extraction of the lipoids from the cells. It is as follows:

Fig. 3.

Amniotic membrane after refrigeration for 30 days in sterile liquid petrolatum. Note similarity to viable membrane shown in Fig. 2. Formalin fixation. Hematoxylin and van Gieson stain.



Human fetal membranes are obtained at the time of delivery. The amnion is separated from the chorion by blunt dissection with the finger, and placed in acetone for 15 hours. It is then rinsed in 70% alcohol and dried on rough toweling for 24 hours. When thoroughly dry, pieces of a convenient size are cut and immersed in ether for an additional 12 hours. This is followed by another rinse in 70% alcohol and drying on rough toweling for 24 hours.

The crisp, translucent sheets are now ready for sterilization. The pieces are interleaved with filter paper, placed between two glass plates to prevent curling and wrapped in muslin. These packets are sterilized in the autoclave. The membrane is now ready for use. Figure 4 shows the histological changes in the membrane after subjection to this treatment.

2. Cargile Membrane.*

The commercial, unchromicized Cargile membrane was employed. This membrane is derived from the submucous layer of the ox cecum. It is prepared according to the method used for catgut, namely, washing, drying and sterilization by heating in a light hydrocarbon oil. The resulting material is thin, translucent and handled with ease. Histologically, the membrane shows an irregularity of contour due to tissue shrinkage with pyknosis of the mesothelial cell nuclei. It stains poorly (Fig. 5).

*Courtesy of Johnson and Johnson, New Brunswick, N.J.

Fig. 4.

Amniotic membrane after treatment by LeVann's method. Note the shrinkage of the epithelial and connective tissue layers. Formalin fixation. Hematoxylin and van Gieson stain.

Fig. 5.

Cargile membrane. The irregularity of contour and the pyknotic mesothelial nuclei are shown. Formalin fixation. Hematoxylin and van Gieson stain.

3. Allantoic Membrane.

This material is known commercially as "Insultoic Membrane"*. It is prepared from the allantois of the gravid bovine uterus. Cattle and other ungulate (hoofed) mammals are an excellent source of this material. In these animals the allantois reaches a large size and serves as an embryonic organ of respiration, nutrition and excretion. It is composed of a mesenchymal layer, containing a large number of blood vessels, and has an entodermal lining. For surgical use the membrane is prepared as follows:

After a careful dissection of the membrane from the uterus it is cleaned by repeated washing in water. The membrane is then chromicized, stretched on gauze-covered boards and dried. Pieces of a desirable size are cut, placed in open tubes and dehydrated in ovens. The method of sterilization is that employed for catgut, namely, immersion in a light hydrocarbon oil for one hour at 155° Centigrade. Following this stage of the process the oil is drained off and the tubes filled with 100% ethanol containing 0.1% of potassium mercuric iodide. Finally, the glass tubes are sealed and the membrane is ready for use. A cross section of the membrane prepared according to this method is shown in figure 6. It stains poorly and there is no cellular differentiation.

Both the single and the double thickness chromicized membranes were used in the present series of experiments. They were thoroughly washed in physiological saline

*Courtesy of Lewis Mfg. Co. - Bauer and Black
Divisions of the Kendall Co.
Chicago, Ill.

Fig. 6.

Allantoic membrane. Note the lack of cellular differentiation and the irregularity of contour. Formalin fixation. Hematoxylin and van Gieson stain.

prior to emplacement on the cerebral cortex.

4. Tantalum.*

Tantalum foil of 0.001 in. thickness was used. A thinner foil is preferable but impossible to obtain. Due to the physical characteristics of the grain structure of this metal, fully-annealed, homogeneous sheets less than 0.001 in. in thickness cannot be rolled.

The pieces of foil, cut to a desired size, were sterilized either by boiling or autoclaving. Before applying the sheets to the brain surface they were bent to conform to the cortical contour and all sharp corners were rounded off.

5. Polyvinyl Alcohol Compounds.**

The polyvinyl alcohol compound selected for the present study was one in which 5% of the hydroxyl groups had been replaced with acetate groups. The basis of selection was a series of solubility tests on polyvinyl alcohol films having 1.7%, 24%, 36%, 54% and 80% acetate group content. In carrying out these tests small pieces of each film were placed in glass jars containing 10 cc. of human cerebrospinal fluid. The jars were sealed and placed in an incubator at 37° Centigrade. The solubility rate was determined by frequent gross inspection during a 35-day period. The results are shown in the following table:

*Courtesy of Fansteel Metallurgical Co.
North Chicago,
Ill.

**Courtesy of Shawinigan Chemicals Ltd.,
Shawinigan Falls,
Que.

1.7%	Compound	-	Intact after 35 days.
24%	Compound	-	Complete dissolution at the end of 18 hours.
36%	Compound	-	Completely dissolved within 18 hours.
54%	Compound	-	Fragmentation and almost complete dissolution in 3 days.
80%	Compound	-	Converted into a soft gel in 18 hours. Little change at end of 35 days.

An examination of this table indicates that the only compound which remained intact during the period of observation was the 1.7% polyvinyl acetate. The other materials were dissolved or converted into soft gels. In view of the extension of the solubility rate of the 1.7% compound beyond the desired period of one month, a more soluble polyvinyl alcohol was selected. This compound had a 5% acetate substitution and a viscosity of 15 centiposes.

The material was made into extremely thin, transparent films resembling a fine grade of cellophane. These films were inserted between sheets of filter paper, placed over a water bath, and sterilized in an electric oven at 100° Centigrade for 45 minutes. Prior to their use on the cerebral cortex, the sheets were moistened in physiological saline solution.

Pathological Studies.

The animals were killed at appropriate intervals varying from 4 to 97 days. Following the induction of deep anesthesia with ether both carotid arteries were isolated, cannulated and the head perfused with physiological saline followed by 10% formalin.

Painstaking care was exercised in the removal of the brain. The temporalis muscle which was always tightly adherent to the dura through the bony defect was trimmed with a sharp scalpel until flush with the surface of the calvarium. The attachments of the muscle to the bone edge were divided by blunt and sharp dissection. The calvarium and part of the base of the skull were removed with rongeurs. The removed brain, well-covered with dura over both the base and convexity, was placed in 10% formalin until ready for gross section (Fig. 7 A).

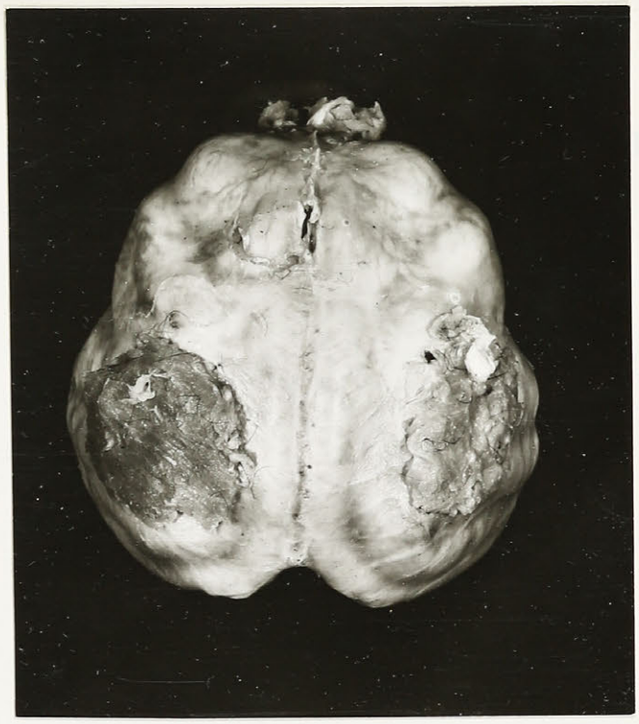
When properly hardened the brain was cut in coronal section with a sharp knife (Fig. 7 B). In doing so the greatest of care was taken to avoid rupturing any of the adhesions which may have developed.

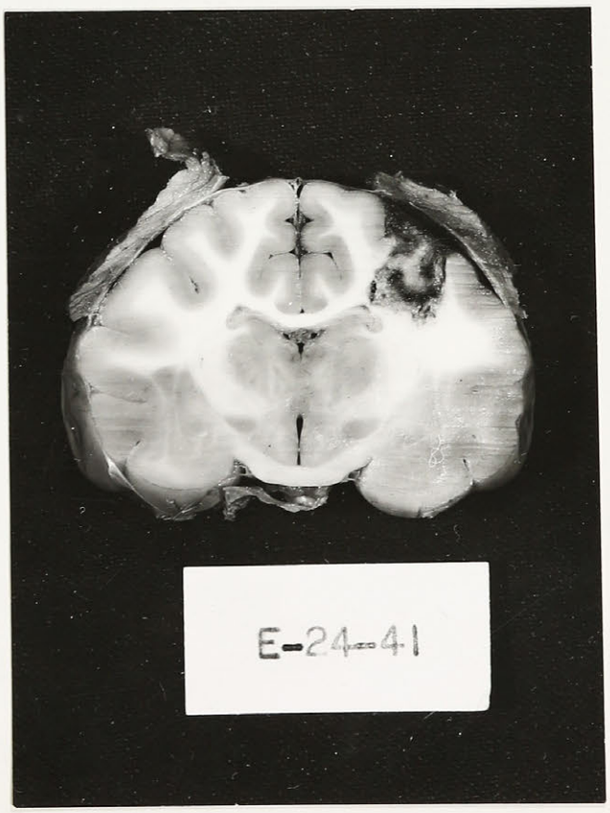
In these experiments where tantalum was used the first coronal section was made at the anterior edge of the metal sheet. This edge was then grasped with forceps and the entire sheet extracted from its bed.

One of the coronal sections was designed to pass through the center of the brain wound. The posterior block resulting from this section was examined for adhesions and preserved as a gross specimen. The anterior block, wounded face downwards, was embedded in paraffin for microscopic study. To avoid distortion of the tissue relationships during the washing, dehydrating, clearing and embedding processes the dura was fastened to the brain and leptomeninges with black silk sutures. These sutures were always placed on the side of the block opposite to the

Fig. 7.

A. Photograph of the convexity of a brain following removal. The plaques of temporal muscle are firmly adherent to the underlying dura mater.
B. Coronal section of a brain showing a large wound in the left cerebral hemisphere.




E-24-41

wound. The sections were cut at 8 to 10 micra and stained with the hematoxylin and van Gieson, the Mallory phosphotungstic acid hematoxylin and the Mallory aniline blue methods.

IV. EXPERIMENTAL DATA

In this chapter each experimental procedure is outlined in detail. Unless recorded otherwise the procedures followed were as outlined in the preceding chapter. Each group of materials is considered separately and the results tabulated at the end of the experimental protocols.

Viable Amniotic Membrane.

This material was employed in three of the experiments.

1. Cat #E-18-41.

Operation: The cortex was wounded on the right side with the automatic sucker. The electrocautery was not used. The brain on the left side was not damaged. In this instance the amniotic membrane was approximately two hours old at the time of emplacement.

Length of Survival: 10 days.

Gross Findings: On the right side there are tenacious adhesions between the cerebral wound and the overlying structures. There are no meningocerebral adhesions on the left side.

Microscopic Findings: The membrane is generally intact although some of its epithelial cells are vacuolated. It is undergoing encapsulation by fibroblasts which are continuous with those traversing the cerebral wound. A similar capsule formation is noted on the unwounded side. On both sides large collections of polymorphonuclear

leukocytes are found adjacent to the membrane. They are particularly numerous in the folds. No adhesions have formed on the unwounded side.

2. Cat #E-23-41.

Operation: The wound was made in the right cerebral hemisphere with the suction tip. The left side was not wounded. Amniotic membrane, which had been kept in the incubator for one hour following Caesarian section, was used to cover both sides.

Length of Survival: 30 days.

Gross Findings: Dense adhesions have formed between the cerebral wound and the overlying structures. There are no adhesions on the unwounded side.

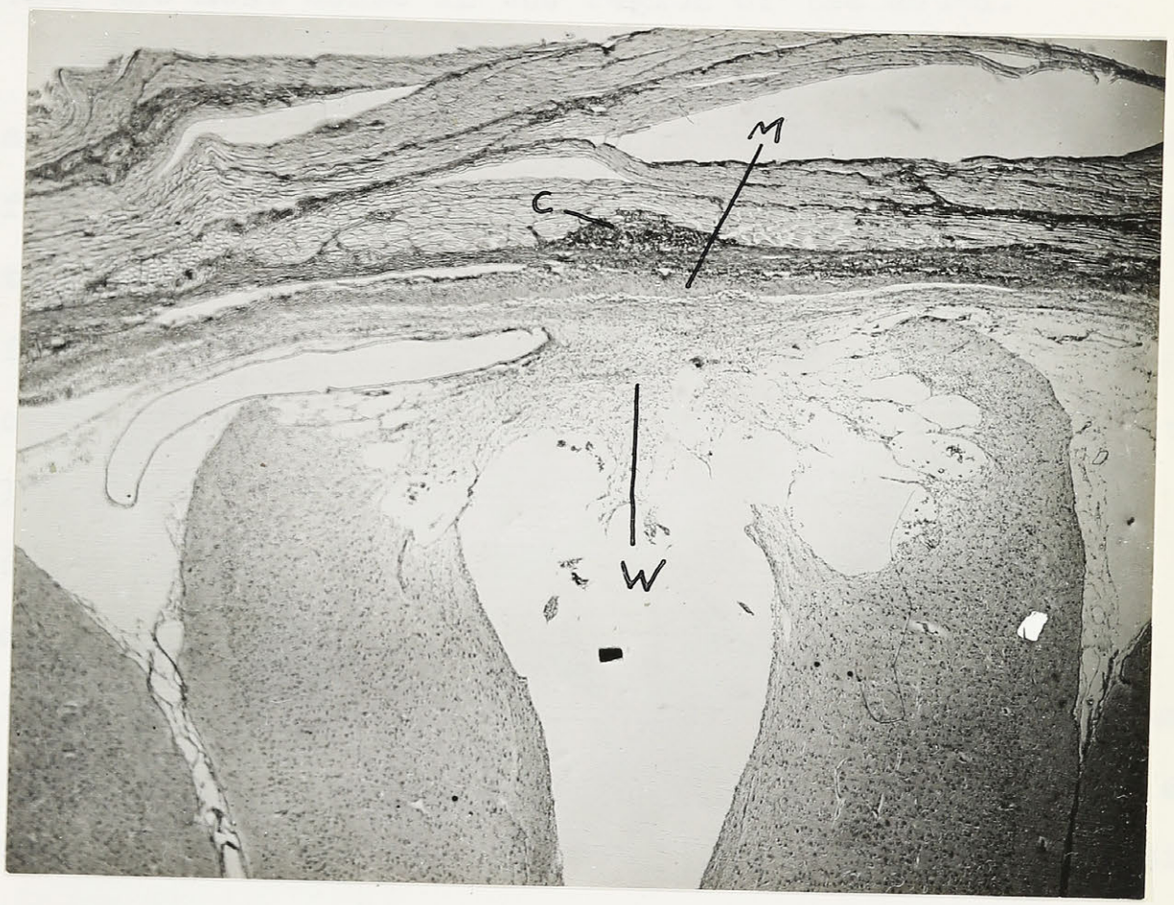
Microscopic Findings: The membrane has been encapsulated by collagenous connective tissue on both sides. The inner face of the capsule is intimately adherent to the cerebral cicatrix (Fig. 8). The epithelial layer of the membrane has in large measure disappeared and moderate-sized aggregations of small round cells have replaced it. The connective tissue layer is histologically a living structure. The fibers stain a brilliant red with acid fuchsin, and the nuclei which lie among them are large, oval, and vesicular.

3. Cat #E-53-41.

Operation: A gyrus on the right side was wounded with the electrocautery followed by scalpel puncture. The left side was not injured. Both cerebral surfaces were covered

Fig. 8.

Result 30 days after implantation of viable amniotic membrane (M). The connective tissue capsule is adherent to the cerebral cicatrix (W). An aggregation of small round cells is shown (C). Hematoxylin and van Gieson stain.


M
C
W

fresh, sterile amniotic membrane obtained at Caesarian section 3 hours previously and kept in an incubator at 37° Centigrade until needed.

Length of Survival: 97 days.

Gross Findings: Thick, tenacious adhesions have formed between the brain and its coverings on both sides. They are most dense in the region of the wound.

Microscopic Findings: The membrane is surrounded by an intense connective tissue and cellular reaction. The former is adherent to both the cerebral wound and the intact arachnoid (Fig. 9). The cells consist of a few foreign body giant cells and aggregations of small round cells. The mesodermal layer of the amnion appears histologically intact. The connective tissue fibers are distinct and stain well. The nuclei lying among the connective tissue bands are vesicular. The epithelial layer of the membrane is not recognizable as such. There are a few masses of poorly-stained, ill-defined material which may be epithelial remnants. The dural contribution to the capsule formation is nicely shown in this case (Fig. 10).

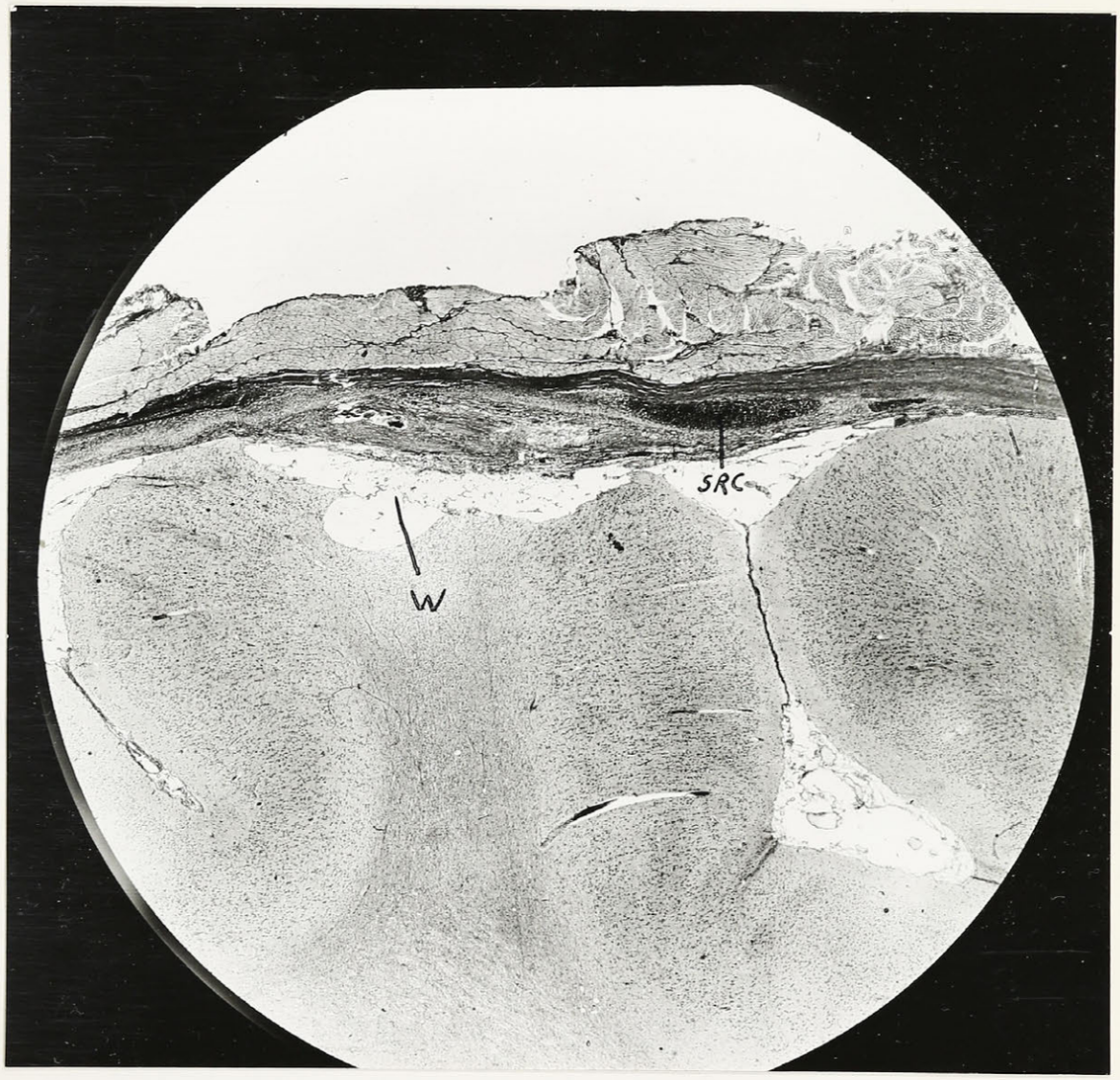
Living Amniotic Membrane.

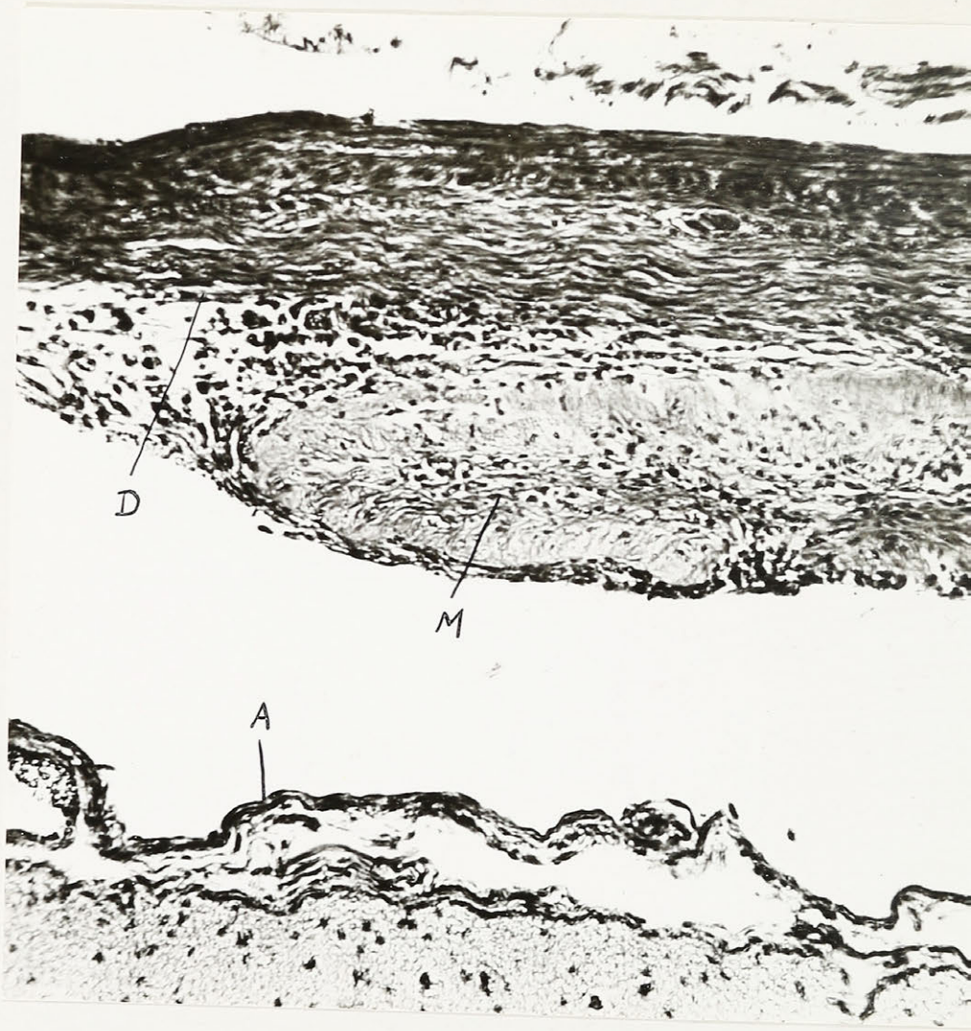
	Days Postop.	Adhesions.	Encapsulation.	Cellular* Reaction.	Remarks.
E-18-41	10	2 plus	2 plus	2 plus	Poor Result
E-23-41	30	2 plus	2 plus	3 plus	Poor Result
E-53-41	97	3 plus	3 plus	3 plus	Poor Result

* Includes polymorphonuclear leukocytes, small round cells, phagocytic cells and foreign body giant cells.

Fig. 9.

Viable amniotic membrane after 97 days. The capsule is adherent to the cerebral wound (W). A large mass of small round cells is shown (SRC). Hematoxylin and van Gieson stain.


SRC
W


D
M

A

Fig. 10.

Viable amniotic membrane (M) 97 days after implantation. Note the encapsulation by fibroblasts, continuous with the inner aspect of the dura (D). Arachnoid (A). Hematoxylin and van Gieson stain.

Abstract: The results with the living form of amniotic membrane have been uniformly poor. In all of the experiments it has been treated as a foreign body and encapsulated. Furthermore, the mobilization of polymorphonuclear leukocytes, small round cells and foreign body giant cells and the formation of adhesions between the capsule and the intact leptomeninges evidence irritation of the adjacent tissues.

Attenuated Amniotic Membrane.

This material was placed over the wounded and intact cerebral cortex of five animals.

1. Cat #E-29-41.

Operation: The cortex was wounded on the right side with the electrocautery followed by scalpel puncture. The left cerebral hemisphere was not injured.

Length of Survival: 10 days.

Gross Findings: Adhesions have formed between the brain and dura on both sides. These are delicate and filamentous except in the region of the wound where they are thick and tenacious.

Microscopic Findings: The cerebral wound is in the early stages of repair. Histologically, the mesodermal stratum of the membrane is a living structure. The connective tissue fibers are distinct and stain brilliantly. Large, vesicular nuclei are dispersed among these fibers. The epithelial layer has disappeared excepting a few small islands on the unwounded side. Encapsulation is

minimal and on the inner aspect does not exceed two to three cells in thickness. A few collagen strands have affixed the inner layer of the capsule to the intact arachnoid. There is no reaction of small round cells, giant cells or phagocytes.

2. Cat #E-30-41.

Operation: The electrocautery was used to produce the wound in both the right and the left cerebral hemisphere. The left side was wounded due to difficulty in obtaining a proper closure of the unusually thin dura on the right side.

Length of Survival: 18 days.

Gross Findings: Fine, filamentous adhesions have formed on both sides. These are not increased over the cerebral wound.

Microscopic Findings: A delicate trellis of connective tissue fibers fills the crater of the cerebral wound. These fibers bind the wound to the delicate inner capsule of the membrane. The connective tissue component of the latter is tinctorially intact. Only an occasional mass of shrunken cells representing the epithelial layer is noted. There is no reaction of cells other than the fibroblasts and the endothelial-like cells lining the connective tissue capsule. The contribution of the arachnoid in the formation of the capsule is shown in figure 11.

Fig. 11.

Attenuated amniotic membrane (M) after 18 days. The participation of the arachnoid (A) in the formation of the capsule is demonstrated. Dura mater (D). Hematoxylin and van Gieson stain.


D
M
A

3. Cat #E-43-41.

Operation: The crown of a gyrus in the right cerebral hemisphere was damaged with the electrocautery. The left side of the brain was not injured.

Length of Survival: 30 days.

Gross Findings: A band of fibrous tissue binds the cerebral wound to the overlying structures on the right side. There are no meningocerebral adhesions on the unwounded side.

Microscopic Findings: The cerebral wound is a shallow crater traversed by connective tissue bands continuous with the delicate inner investment of the membrane. The mesodermal layer of the membrane is a living tissue from the histological standpoint. However, the epithelial layer is entirely wanting. A small mass of poorly-stained, amorphous material surrounded by giant cells is found in the capsule immediately overlying the cerebral cicatrix (See Fig. 12).

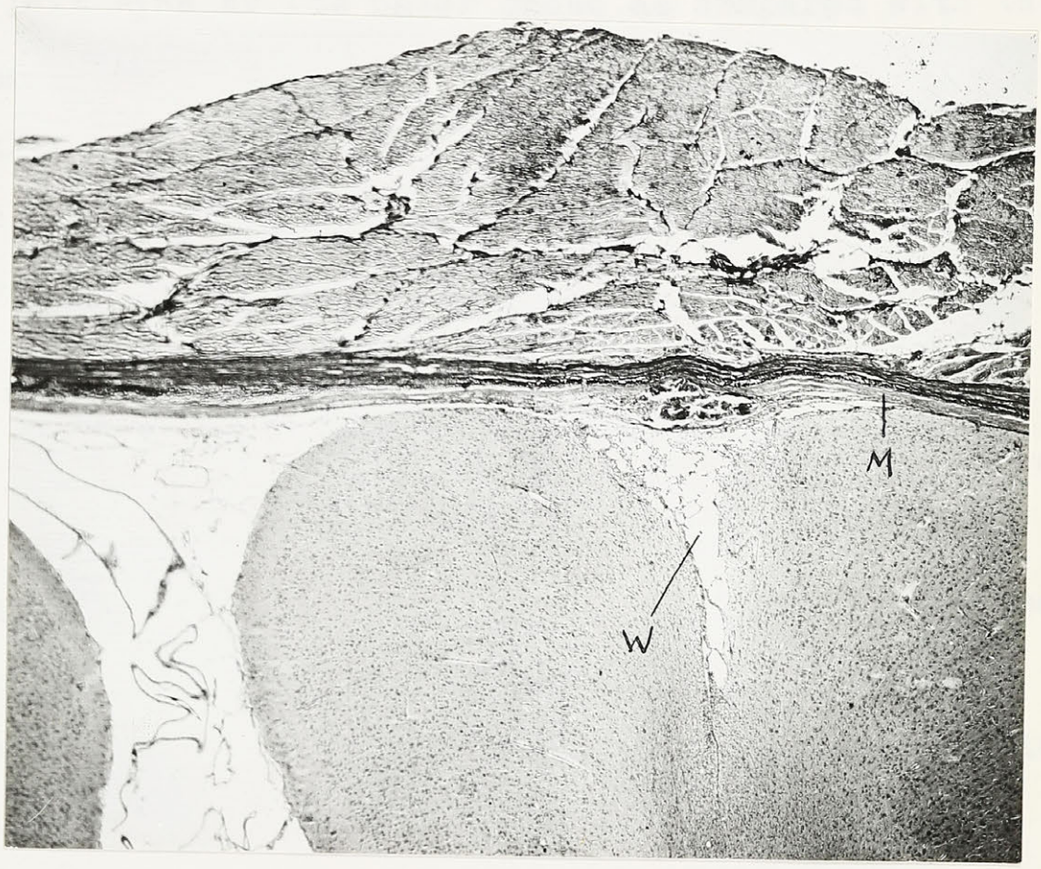
4. Cat #E-56-41.

Operation: The right cerebral hemisphere of this animal was atrophic and overlaid by a dura of at least quadruple thickness. One of these atrophic gyri was damaged with the electrocautery and scalpel puncture. The left cerebral cortex, which appeared normal, was not injured.

Length of Survival: 60 days.

Fig. 12.

Attenuated amniotic membrane (M) 30 days following implantation. Minimal encapsulation and cellular reaction. The inner layer of the capsule is adherent to the cerebral wound (W). Hematoxylin and van Gieson stain.


M
W

Gross Findings: Adhesions are confined to the region of the cerebral wound. There are no adhesions on the left side.

Microscopic Findings: The increased thickness of the dura on the right side is confirmed. Plaques of bone have formed within its layers. The membrane is identified on the left side by its paler shade as compared with the overlying dura. It is not recognized as a well-defined structure on the right side. There is no cellular reaction other than the delicate capsule formation by the connective tissue cells (Fig. 13).

5. Cat #E-66-41.

Operation: Both the electrocautery and scalpel were employed in damaging the right cerebral hemisphere. The dura was torn on this side and had to be closed loosely. The left side of the brain was not traumatized. In this experiment the membrane was not rinsed in ether prior to implantation on the cortical surface.

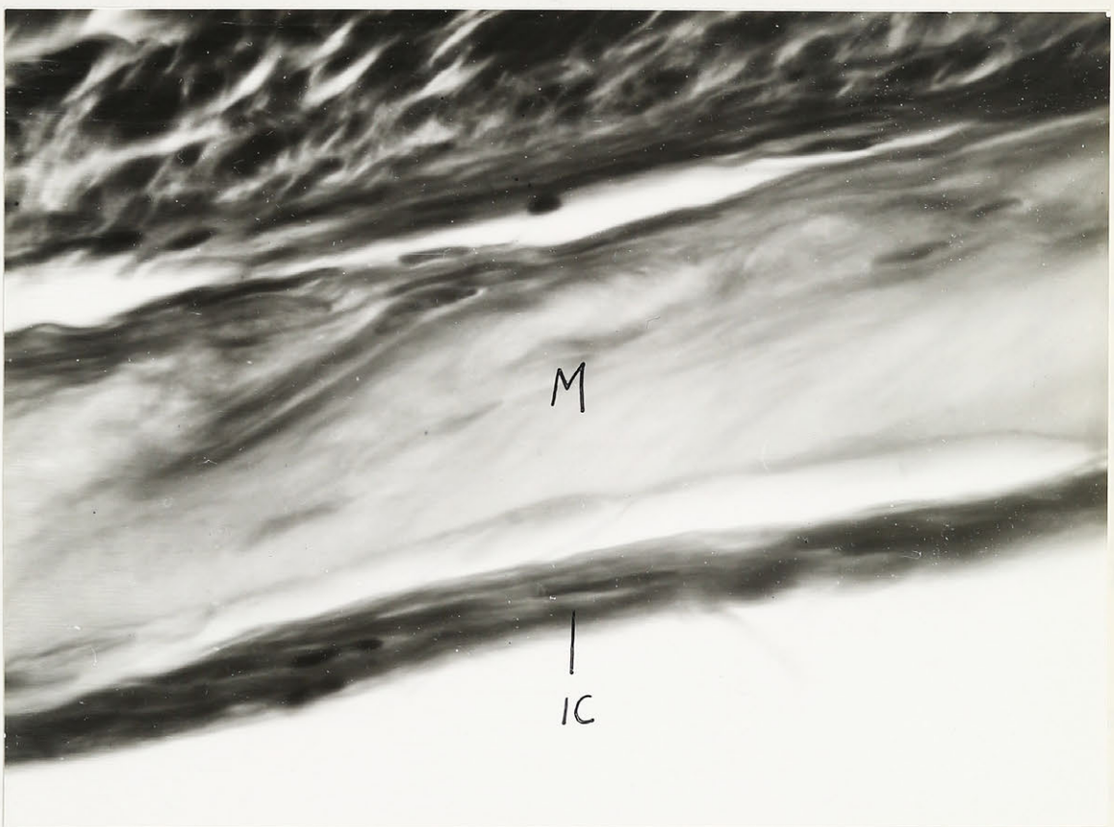
Length of Survival: 86 days.

Gross Findings: Meningocerebral adhesions have formed on the wounded side only.

Microscopic Findings: The membrane is continuous with, and indistinguishable from, the dura. The latter increases slightly in thickness reaching a maximum width over the cerebral wound. Collagen bands bind this thickened dura to the cerebral wound. Large aggregations of small round cells are found in this connective tissue layer. On

Fig. 13.

Attenuated amniotic membrane (M) after 60 days. Note the thin inner stratum of the capsule (IC). Hematoxylin and van Gieson stain.


M
IC

the left side there is minimal thickening of the arachnoid. It is non-adherent to the overlying dura.

Attenuated Amniotic Membrane.

	Days Postop.	Adhesions.	Encapsulation.	Cellular* Reaction.	Remarks.
E-29-41	10	1 plus	1 plus	0	Promising Result
E-30-41	18	2 plus	1 plus	0	Promising Result
E-43-41	30	1 plus	1 plus	0	Promising Result
E-56-41	60	1 plus	1 plus	0	Promising Result
E-66-41	86	1 plus	1 plus	2 plus	Cellular reaction probably due to oil on membrane

*Includes polymorphonuclear leukocytes, small round cells, phagocytes and foreign body giant cells.

Abstract: Despite the invariable occurrence of adhesions this material has shown promise. The fate of the epithelial layer is problematic and warrants further study. The most interesting features are the histological evidence for survival of the mesodermal layer of the membrane, the paucity of inflammatory cell types and the minimal encapsulation.

Fixed Amniotic Membrane.

Amniotic membrane prepared by the method of LeVann was implanted in five animals.

1. Cat #E-22-41.

Operation: The cortex on the right side was wounded with the electrocautery followed by scalpel puncture. The left cerebral hemisphere was not traumatized.

Length of Survival: 10 days.

Gross Findings: A large, firm clot has formed between the dura and brain on the right side. It is adherent to the cerebral wound. On the unwounded side a rare, thread-like adhesion is noted.

Microscopic Findings: The clot lies between the membrane and the dura and is in the early stages of organization. The membrane and its layers are intact. On both sides it is incompletely invested by sheets of fibroblasts derived from the dura principally, with a cellular contribution from the arachnoid to the inner layer. There is no reaction of polymorphonuclear leukocytes or small round cells. The cerebral wound is seen as a zone of coagulation necrosis which is being pervaded by elongated cells derived from the pial vessels. There are no adhesions between the cerebral wound and the overlying structures.

2. Cat #E-31-41.

Operation: The brain was wounded on the right side with the electrocautery. The cortex was not grossly damaged on the left side.

Length of Survival: 10 days.

Gross Findings: There is no adhesion formation on either side.

Microscopic Findings: The cerebral wound is covered with a thin layer of elongated cells continuous with the arachnoid. The membrane is unchanged. It is partially invested by fibroblasts which have not as yet extended to the region overlying the cerebral wound. The encapsulation on the left side is in the less advanced stage. There are no adhesions on the left side. On the right side a rare strand of collagen binds the inner layer of the capsule to the arachnoid.

3. Cat #E-27-41.

Operation: In this experiment a small mass of cerebral tissue was removed from a gyrus on the right side with the automatic suction tip. The left cerebral hemisphere was not injured.

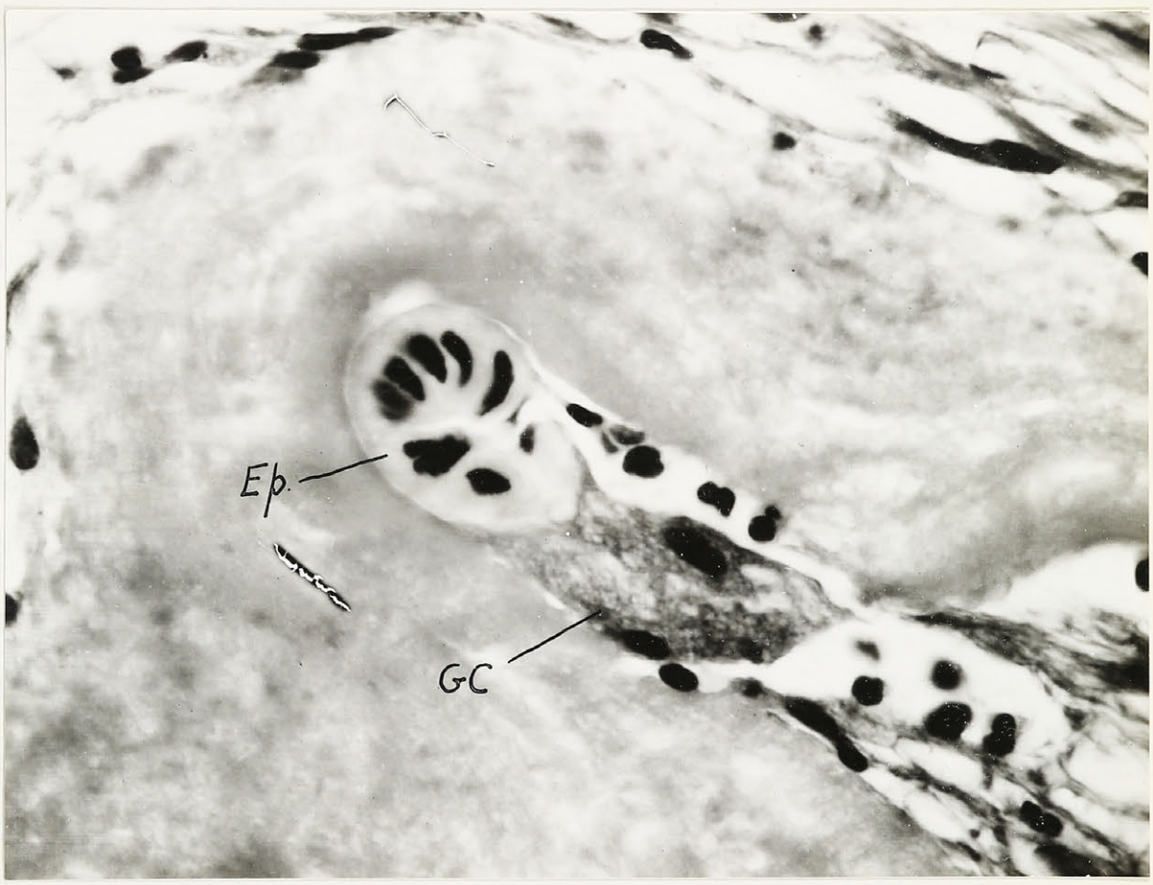
Length of Survival: 30 days.

Gross Findings: On the right side there are dense adhesions between the dura and cerebral wound. There are none on the left side.

Microscopic Findings: The membrane is intact but "woolly" in texture and stains poorly. It is surrounded by an intense cellular reaction. The amniotic epithelium is being phagocytized by giant cells (Fig. 14), and there are large collections of small round cells and polymorphonuclear leukocytes lying next to it. Some of these cellular aggregations lie in the connective tissue interstices of the capsule. The cellular reaction is most striking along the epithelial surface of the membrane.

Fig. 14.

Island of shrunken amniotic epithelium (Ep) undergoing phagocytosis by giant cell (GC). Hematoxylin and van Gieson stain.


Ep
GC

Adhesions are present between the wide inner stratum of the capsule and the cerebral wound. There is no adherence to the intact arachnoid.

4. Cat #E-44-41.

Operation: Cautery and scalpel punctures were used in the wounding of the right cerebral cortex. The left side of the brain was not injured.

Length of Survival: 60 days.

Gross Findings: Dense adhesions have formed between the brain and dura on both the wounded and unwounded sides.

Microscopic Findings: The membrane has resorbed in large part. Only a few ill-defined, poorly-stained strips remain on both sides (Fig. 15). The capsule is of moderate thickness and the cellular reaction minimal. A few foreign body giant cells are found within the space previously occupied by the membrane. On both sides the inner layer of the capsule is fused with the arachnoid and, on the right side, is densely adherent to the cerebral cicatrix (Fig. 16).

5. Cat #E-62-41.

Operation: The usual cautery and puncture wound was made in a gyrus on the right side. Due to a technical error during the reflection of the dura, the left hemisphere was also injured over an area 2 to 3 mm. in diameter.

Length of Survival: 92 days.

Gross Findings: Dense adhesions have formed between the cerebral wound and overlying structures on the right side. No adhesions are present on the left side.

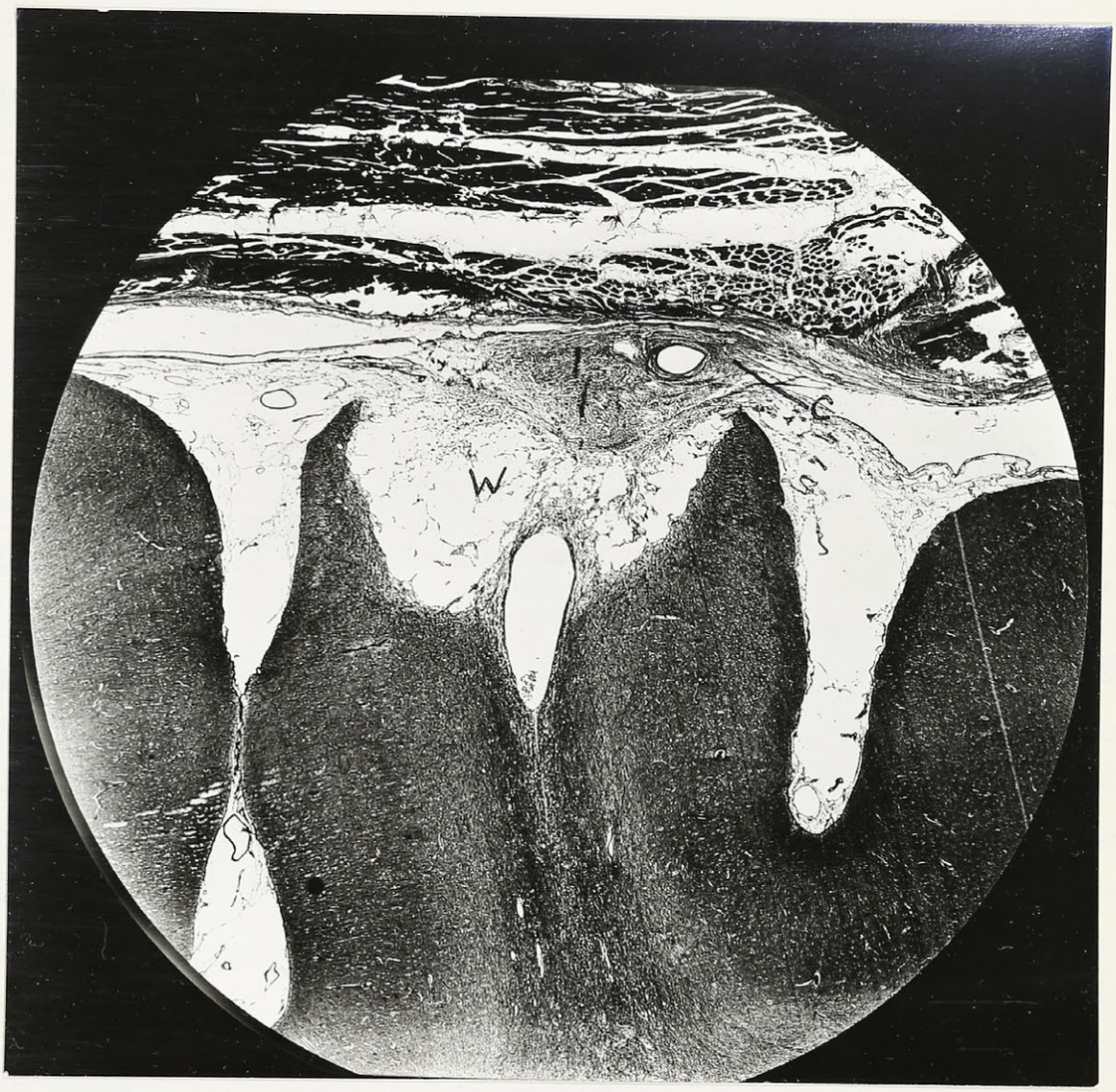
Fig. 15.

Fixed amniotic membrane after 60 days. A small strip of the membrane (M) is encapsulated and undergoing resorption. Hematoxylin and van Gieson stain.


M

Fig. 16.

Fixed amniotic membrane 60 days after emplacement. The membrane is almost completely resorbed. The adherence of the capsule (C) to the cerebral wound (W) is shown. Mallory's phosphotungstic acid - hematoxylin stain.


W

Microscopic Findings: The membrane has been entirely resorbed on both sides. Its previous existence is indicated by a stratum of connective tissue, continuous with and three to four times the thickness of, the normal dura. An occasional perivascular collection of small round cells is noted within this layer. It is adherent to the cerebral wound by connective tissue bands but there are no adhesions to the intact arachnoid on either side.

Fixed Amniotic Membrane.

	Days Postop.	Ad-hesions.	Encapsu-lation.	Cellular* Reaction.	Remarks.
E-22-41	10	0	1 plus	0	Result obviated by subdural hemorrhage
E-31-41	10	0	1 plus	0	Inconclusive result
E-27-41	30	2 plus	2 plus	3 plus	Poor result
E-44-41	60	2 plus	2 plus	1 plus	Poor result
E-62-41	92	2 plus	2 plus	1 plus	Poor result

*Includes polymorphonuclear leukocytes, small round cells, phagocytic cells and foreign body giant cells.

Abstract: The fixed amniotic membrane is treated as a foreign body and encapsulated. This capsule increases in thickness until the membrane is resorbed between the sixtieth and ninetieth days following implantation. In the ninety-two day animal, the inner and outer layers of the capsule were fused throughout their entire extent. The material is a tissue

irritant and provokes an outpouring of inflammatory cells. These cells are more prominent along the epithelial layer. In all of the experiments adhesions have formed between the inner layer of the capsule and the cerebral cicatrix.

Allantoic Membrane.

This membrane was used in five animals.

1. Cat #E-34-41.

Operation: During the reflection of the dura small cortical veins were ruptured on both sides. The bleeding points were cauterized on the right side while on the left the hemorrhage was eventually controlled by packing. A small zone in a gyrus on the right side was then cauterized. The scalpel was not used. Both surfaces were covered with the single-thickness membrane.

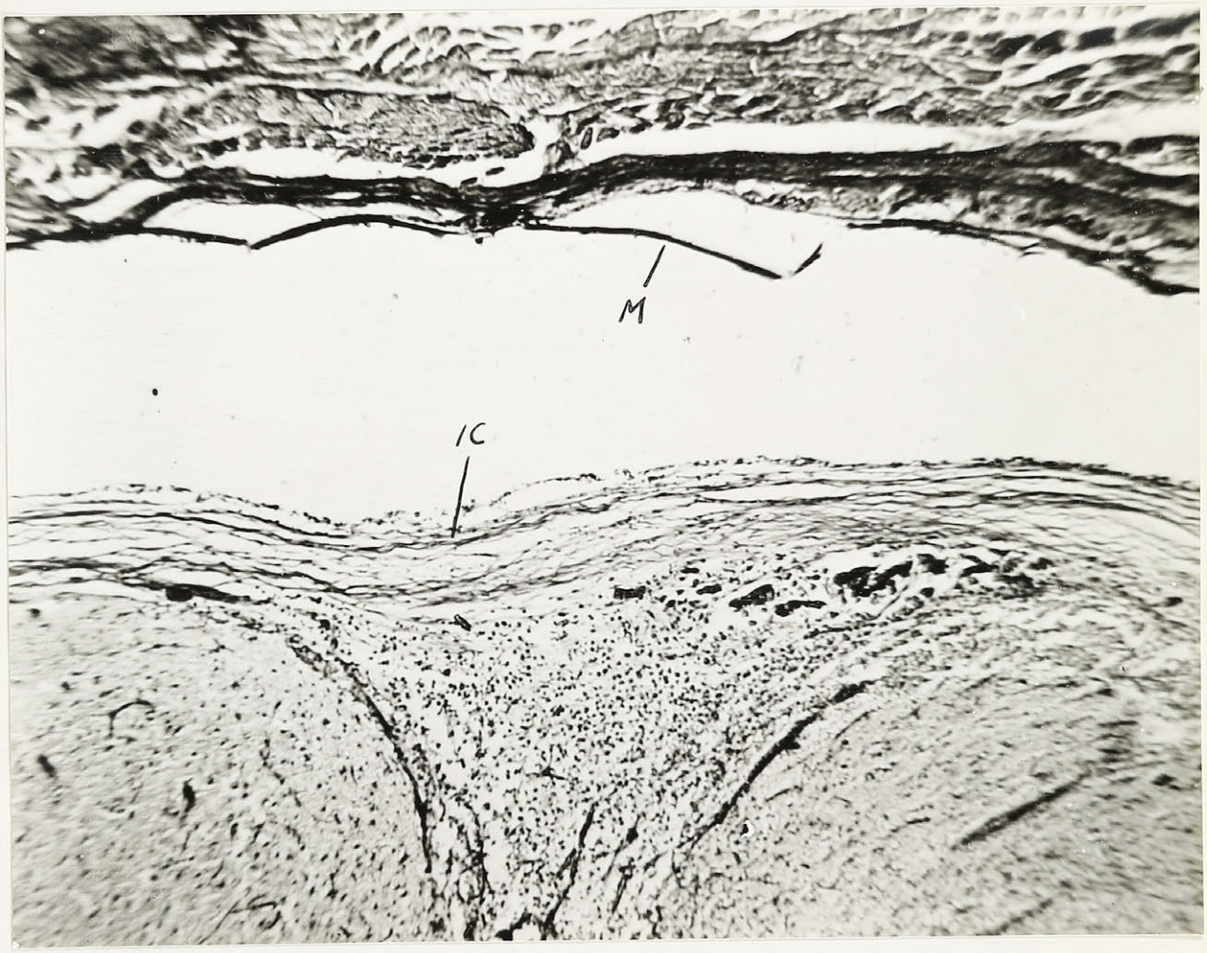
Length of Survival: 24 days.

Gross Findings: There is no evidence of adhesion formation on either side.

Microscopic Findings: The membrane is intact and surrounded by a connective tissue capsule. The latter is derived from the dura principally, although it contains cells contributed by the arachnoid. Due to the arachnoidal component there are adhesions between the capsule and the leptomeninges. There is an inflammatory reaction to the membrane consisting of foreign body giant cells and small round cells (Fig. 17).

Fig. 17.

Allantoic membrane (M) 24 days following implantation. The inner layer of the connective tissue capsule (IC) is intimately fused with the cerebral wound (W). Hematoxylin and van Gieson stain.


M
IC

2. Cat #E-59-41.

Operation: The cautery and scalpel were used to wound a gyrus of the right cerebral cortex. The left side was not traumatized. The material of double thickness was used.

Length of Survival: 30 days.

Gross Findings: There is no evidence of adhesion formation on either side.

Microscopic Findings: The membrane is unresorbed. Along its margins are pools of homogeneous material, staining a bright pink with acid fuchsin, and clusters of foreign body giant cells. A dense connective tissue capsule has formed around the membrane and is adherent to the cerebral wound and to the arachnoid on both sides.

3. Cat #E-55-41.

Operation: The application of the electrocautery to the right cerebral cortex was followed by extensive subpial bleeding. The left side of the brain was not injured. Single-thickness membrane was placed over both sides.

Length of Survival: 63 days.

Gross Findings: There are thick, tenacious adhesions to the wound on the right side. Fine, filamentous adhesions bind the brain to the overlying structures on the left.

Microscopic Findings: The membranes are intact but invested by a dense capsule of collagenous connective tissue, the inner surface of which is adherent to the

arachnoid (Fig. 18). A few foreign body giant cells are found along the margins of the membrane but there are no other inflammatory cells.

4. Cat #E-64-41.

Operation: The suction tip was used to wound the cortex on the right side. The electrocautery was not employed. There was no gross injury to the left side of the brain. Single thickness insultoic membrane was implanted.

Length of Survival: 80 days.

Gross Findings: Dense adhesions have formed on both sides and are especially prominent in the region of the cerebral cicatrix.

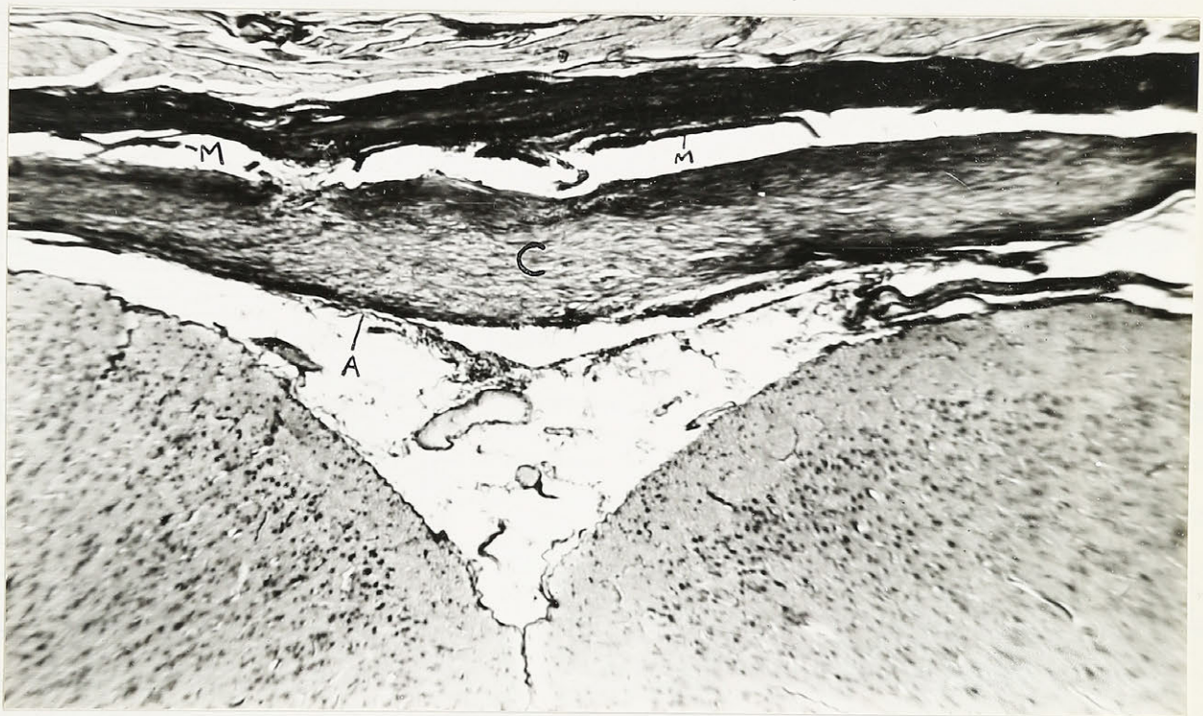
Microscopic Findings: The membrane is embedded in a mass of collagenous connective tissue. It stains poorly and is moderately swollen, suggesting early resorption. There is a reaction of giant cells and mononuclear phagocytes along both surfaces of the membrane. The inner surface of the capsule is adherent to the cerebral wound on the right side and to the arachnoid on both sides.

5. Cat #E-63-41.

Operation: A gyrus in the right cerebral hemisphere was wounded with the electrocautery followed by scalpel puncture. Following the latter procedure two pial vessels were ruptured and part of the coagulated zone was removed with the suction tip. The bleeding points were isolated and cauterized. The left cerebral cortex was not wounded.

Fig. 18.

Allantoic membrane (M) after 63 days. A dense connective tissue capsule (C) has formed and is adherent to the arachnoid (A) on the unwounded side. Hematoxylin and van Gieson stain.


M
M
C
A

The double-thickness membrane was used in this experiment.

Length of Survival: 85 days.

Gross Findings: The brain is tenaciously adherent to the overlying structures on both sides.

Microscopic Findings: On both sides there is a moderate-sized capsule which is adherent to the arachnoid and the cerebral wound. The membrane is intact and surrounded by foreign body giant cells and mononuclear phagocytes in large numbers.

Allantoic Membrane.

	Days Postop.	Adhesions.	Encapsulation.	Cellular* Reaction.	Remarks.
E-34-41	24	1 plus	2 plus	2 plus	Poor result
E-59-41	30	2 plus	3 plus	2 plus	Poor result
E-55-41	63	2 plus	3 plus	1 plus	Poor result
E-64-41	80	3 plus	3 plus	1 plus	Poor result
E-63-41	85	3 plus	2 plus	3 plus	Poor result

*Includes polymorphonuclear leukocytes, small round cells, phagocytic cells and foreign body giant cells.

Abstract: In these five experiments the membrane has been treated as a foreign body and walled off by connective tissue. The formation of adhesions to the intact arachnoid and the presence of foreign body giant cells and phagocytes are indicative of tissue irritation. There was no resorption of the membrane during the 85 days of observation.

Cargile Membrane.

1. Cat #E-20-41.

Operation: A small zone in a gyrus of the right cerebral hemisphere was cauterized and punctured several times with a scalpel. The left cerebral hemisphere was not traumatized.

Length of Survival: 4 days.

Gross Findings: No adhesions are present on either side.

Microscopic Findings: The membrane is intact on both sides. There is no encapsulation or reaction of inflammatory cells. Adhesions between the brain and the overlying structures are lacking.

2. Cat #E-35-41.

Operation: A gyrus on the right side was damaged with the electrocautery. There was no gross damage to the left cerebral hemisphere.

Length of Survival: 10 days.

Gross Findings: Dense meningocerebral adhesions have formed in the region of the cerebral wound. Numerous fine, tenuous adhesions are found on the left side.

Microscopic Findings: The membrane is intact and invested in thin connective tissue capsule. This capsule is derived chiefly from the dura with the arachnoid fused to the inner layer. Connective tissue bands bind the capsule to the cerebral wound. The capsule is lined with flattened cells resembling endothelium. There are no giant cells, small round cells or phagocytes.

3. Cat #E-25-41.

Operation: A cautery and puncture wound was inflicted on the right side. The left side was not traumatized.

Length of Survival: 30 days.

Gross Findings: There is tenacious adherence of the cerebral wound to its coverings on the right side. A maze of fine, tenuous adhesions has formed on the unwounded side.

Microscopic Findings: The membrane is embedded in a thick connective tissue capsule. Large aggregations of small round cells are found within its folds. Giant cells are likewise numerous. On both sides the inner aspect of the capsule is adherent to the pia-arachnoid.

4. Cat #E-41-41.

Operation: A gyrus on the right side was wounded with the electrocautery and the point of a scalpel. A small subpial hemorrhage occurred, forming a halo around the wounded zone. The left cerebral hemisphere was not injured.

Length of Survival: 60 days.

Gross Findings: Tenacious adhesions have formed between the cerebral wound and the enveloping structures. There are fine, tenuous adhesions to the pia-arachnoid on both the wounded and unwounded sides.

Microscopic Findings: An unusually thick connective tissue investment has formed around the membrane on both sides. The membrane is fragmented and many of the pieces show evidence of resorption. Pools of homogeneous material, staining a pinkish-yellow in the van Gieson

technique, have formed around these fragments. Within the right capsular space small round cells, mononuclear cells and giant cells are found but are not numerous. The cellular reaction is even more intense on the left side. There are adhesions between the capsule and the leptomeninges on both sides (Fig. 19).

5. Cat #E-60-41.

Operation: The brain on the right side was injured with the electrocautery. The small area of coagulation necrosis was repeatedly punctured with a scalpel. The left cerebral hemisphere was not damaged.

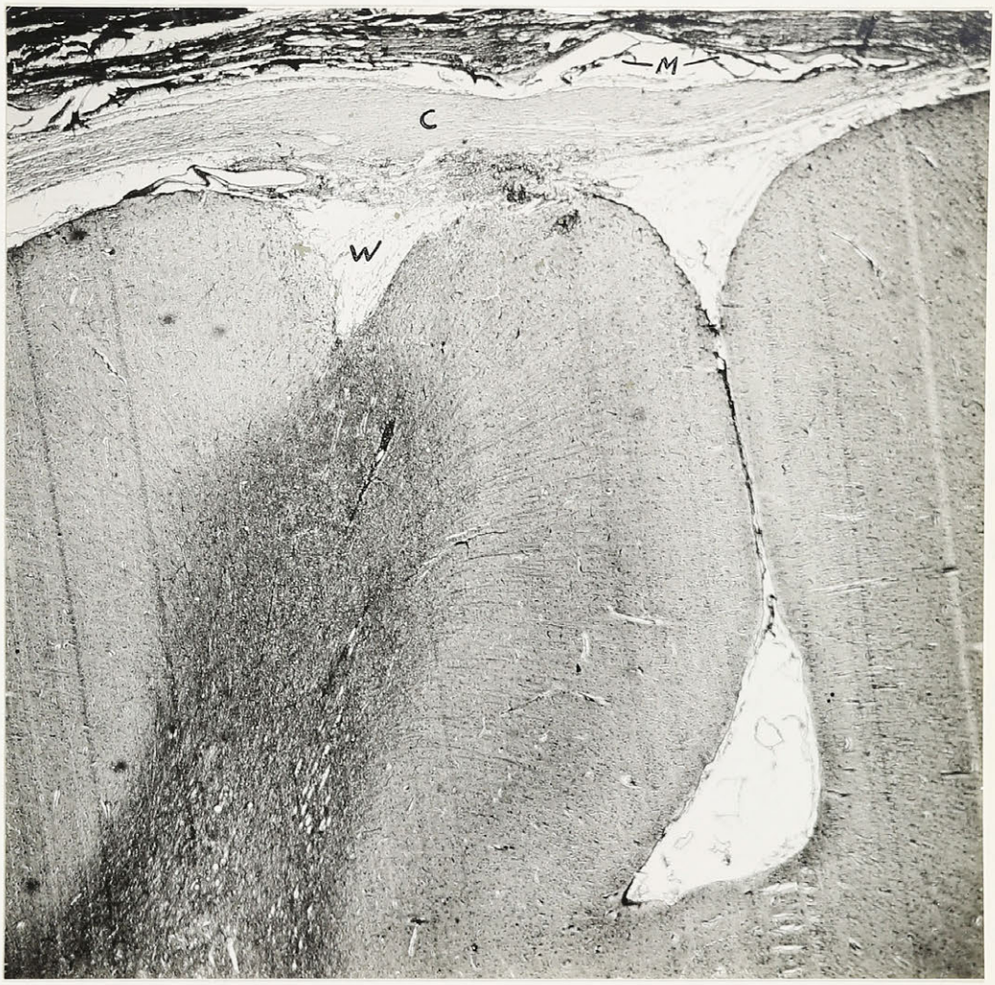
Length of Survival: 90 days.

Gross Findings: There are tenacious adhesions between the brain and its envelopes on both sides.

Microscopic Findings: The connective tissue capsule investing the membrane is unusually thick and adherent to the cerebral wound and the leptomeninges on both sides. Islands of new bone formation are found in the connective tissue immediately underlying the temporal muscle. There is no indication of resorption of the membrane and the cellular reaction to it is minimal.

Fig. 19.

Cargile membrane (M) after 60 days. The thick inner layer of the capsule (C) is intimately adherent to the cerebral wound (W). Hematoxylin and van Gieson stain.


M
C
W

Cargile Membrane.

	Days Postop.	Adhesions.	Encapsulation.	Cellular* Reaction.	Remarks.
E-20-41	4	0	0	0	Result inconclusive.
E-35-41	10	2 plus	2 plus	0	Poor Result.
E-25-41	30	2 plus	3 plus	2 plus	Poor Result.
E-41-41	60	3 plus	4 plus	2 plus	Poor Result.
E-60-41	90	3 plus	0	0	Poor Result.

*Includes polymorphonuclear leukocytes, small round cells, phagocytic cells and foreign body giant cells.

Abstract: Cargile membrane has failed in its purpose in all of these experiments. It has provoked an intense foreign body reaction. This is evidenced by the formation of a thick connective tissue capsule and the reaction of foreign body giant cells, small round cells and mononuclear phagocytes. The membrane was not resorbed within 90 days.

Tantalum.

Tantalum foil was used in five experiments.

1. Cat #E-24-41.

Operation: A large mass of cortical tissue was removed on the left side with the suction tip. The bleeding from the pial vessels was controlled with the electrocautery. A cortical vessel of fine calibre was torn in opening the dura on the right side. The hemorrhage from this vessel was controlled with packing. The right side was otherwise uninjured.

Length of Survival: 10 days.

Gross Findings: There is no evidence of corrosion of the removed foil. It has been invested by a delicate capsule. Adhesions have formed only at the margin of this capsule.

Microscopic Findings: The delicate nature of the connective tissue capsule and the presence of meningocerebral adhesions at the capsular margin only are confirmed. A layer of elongated cells covers the cerebral wound. This does not exceed one to two cells in thickness. Similar elongated endothelial-like cells line the capsule. There is no reaction of small round cells, polymorphonuclear leukocytes, giant cells or phagocytic cells.

2. Cat #E-36-41.

Operation: The right cerebral hemisphere was wounded with the electrocautery. A small subpial hemorrhage occurred in the zone surrounding the destroyed tissue. The left side of the brain was not injured.

Length of Survival: 10 days.

Gross Findings: The foil is not tarnished. There is a thin encapsulation of the metal on both sides, with meningocerebral adhesions solely at the periphery of the capsule.

Microscopic Findings: The cerebral wound is bridged by a thin layer of flattened cells. The connective tissue investment of the metal is also minimal. It is derived chiefly from the dura with an arachnoidal contribution

due to fusion of this structure with the inner capsular layer. It is this fusion which has given rise to the adhesions at the periphery of the metal. There are no giant cells.

3. Cat #E-32-41.

Operation: The cerebral wound was inflicted on the right side with the electrocautery and scalpel. The brain was not traumatized on the left side.

Length of Survival: 14 days.

Gross Findings: The tantalum foil is bright and shining. Again, meningocerebral adhesions are present at the capsular margin only.

Microscopic Findings: The connective tissue strata which invest the foil are relatively thin. The inner layer is five to six cells in thickness over the cerebral wound and tapers gradually to a thickness of two to three cells at the periphery. The capsule is derived chiefly from the dura but its inner face is adherent to the arachnoid. It is lined with flattened cells resembling endothelium. There is no reaction of inflammatory cells either within its walls or its cavity.

4. Cat #E-28-41.

Operation: The wound was inflicted on the right side with the electrocautery and scalpel. The cortex on the left side was not intentionally damaged although a small vein was torn during the reflection of the dura. The bleeding from this vessel was controlled with packing.

Length of Survival: 30 days.

Gross Findings: No change in the color or texture of the removed metal is noted. The brain is bound to the dura at the capsular margin only. The capsule is thin and translucent on the cerebral side.

Microscopic Findings: Microscopic examination confirms the thin investment of connective tissue. The capsule is derived from the dura but has an arachnoidal contribution to the inner layer. The capsular space is lined with flattened cells resembling endothelium. A rare giant cell is found within this space (Fig. 20).

5. Cat #E-54-41.

Operation: Two adjacent gyri in the right cerebral hemisphere were wounded with the electrocautery followed by scalpel puncture. The left side was not injured.

Length of Survival: 79 days.

Gross Findings: The tantalum foil is bright and shining. There is no evidence of adhesion formation even at the border of the capsule.

Microscopic Findings: The cerebral wounds are seen as shallow craters traversed by vascular bands of collagen. Both are bridged by a delicate tissue continuous with and histologically undifferentiated from the arachnoid (Fig. 21). The arachnoid is bound to the overlying thickened dura by a few wispy strands of collagen. There is no reaction of giant cells, small round cells or phagocytes in the adjacent tissues.

Fig. 20.

Result 30 days following implantation of tantalum foil. The inner layer of the capsule previously occupied by the tantalum (T) is adherent to the cerebral wound (W). Hematoxylin and van Gieson stain.

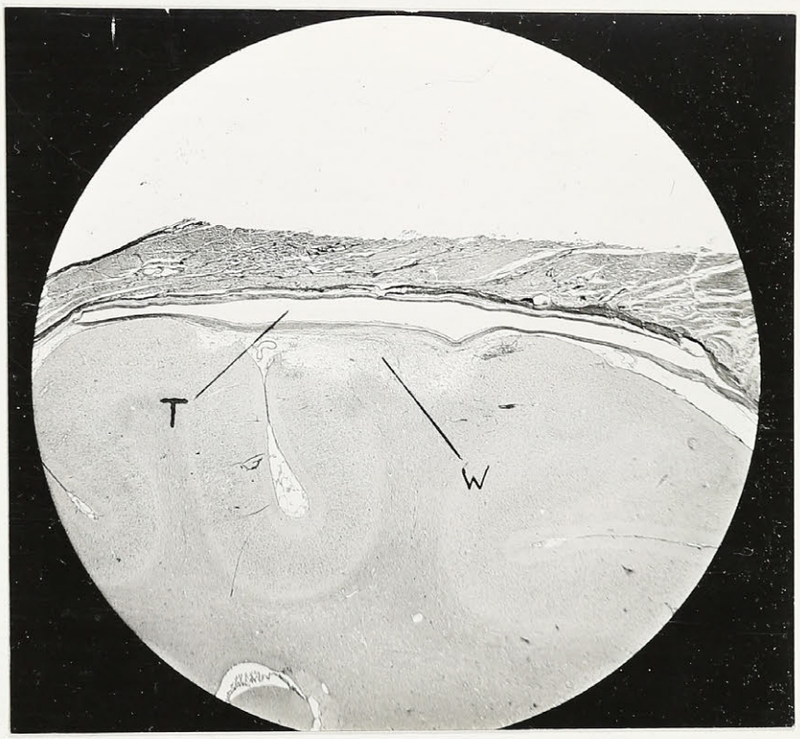
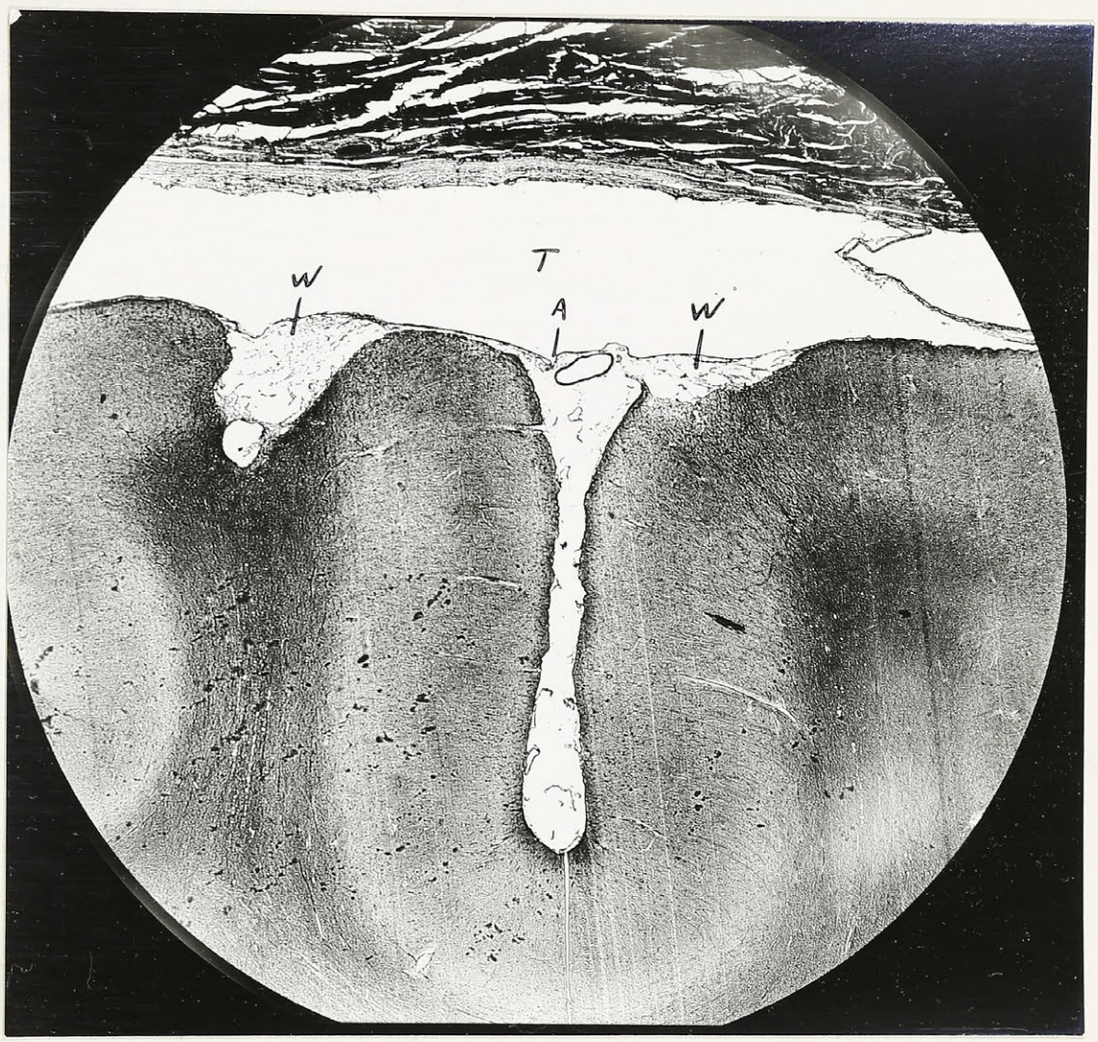

T
W

Fig. 21.

After 79 days of protection by the tantalum foil the cerebral wounds (W) are bridged by a delicate membrane continuous with the arachnoid (A). Space occupied by tantalum (T). Mallory's phosphotungstic acid-hematoxylin stain.


W
T
A
W

Tantalum.

	Days Postop.	Adhesions.	Encapsulation.	Cellular* Reaction.	Remarks.
E-24-41	10	1 plus	1 plus	0	Good Resul
E-36-41	10	1 plus	1 plus	0	Good Resul
E-32-41	14	1 plus	1 plus	0	Good Resul
E-28-41	30	1 plus	1 plus	plus-minus	Good Resul
E-54-41	79	plus-minus	0	0	Excellent Result.

*Includes polymorphonuclear leukocytes, small round cells, phagocytic cells and foreign body giant cells.

Abstract: The tantalum foil has induced a minimal reaction of connective tissue and other cellular elements. Encapsulation has occurred but has been relatively slight. Giant cells were found in one of the experiments but were exceptionally few in number. There was no reaction involving small round cells, polymorphonuclear leukocytes, or phagocytic cells. In the animal killed at the end of 79 days there was no capsule formation and the cerebral wounds were bridged by a thin membrane identical in structure with the arachnoid.

Polyvinyl Alcohol Membrane.

Thin films made of this material were used in five animals.

1. Cat #E-42-41.

Operation: A gyrus in the right cerebral cortex was wounded with the electrocautery followed by scalpel

puncture. The left side of the brain was not injured.

Length of Survival: 10 days.

Gross Findings: A large subdural hemorrhage has occurred on the right side. It reaches a maximum thickness of 6 mm. directly over the cerebral wound. There is a widespread compression of the underlying convolutions. Fine, tenuous adhesions are present between the brain and dura on the left side.

Microscopic Findings: The hemorrhage is continuous with the clot filling the cerebral wound and has displaced the membrane peripherally. On the right side the membrane is intact. It is covered on its dural surface with a broad layer of polymorphonuclear leukocytes. A few small round cells are interspersed among these cells. On the left side the membrane has been walled off by collagenous connective tissue and is surrounded by an exudate of polymorphonuclear leukocytes and small round cells. The inner layer of the capsule is adherent to the arachnoid. No bacteria are demonstrated in the Gram stain.

2. Cat #E-57-41.

Operation: The right cerebral cortex was destroyed over a small area with the electrocautery. The left side was not injured.

Length of Survival: 30 days.

Gross Findings: On the right side the membrane is surrounded by a thin capsule which is adherent to the cerebral wound. There is no evidence of capsule formation on the left.

Microscopic Findings: The observations on the gross specimen are confirmed. The membrane is invested by a dense connective tissue capsule and surrounded by large masses of giant cells and mononuclear phagocytes. The inner face of the capsule is adherent to the cerebral wound. The membrane is not present in the sections through the left side. Furthermore, there are no meningo-cerebral adhesions on this side.

3. Cat #E-58-41.

Operation: The electrocautery and scalpel were used in the wounding of the right side. The left cerebrum was not wounded.

Length of Survival: 30 days.

Gross Findings: Thick, tenuous adhesions have formed between the brain and dura on both sides.

Microscopic Findings: The capsule of the membrane is extremely thick and adherent to the wound on the right side and to the arachnoid on both sides. A few foreign body giant cells lie along the membrane. Other than this cellular reaction is minimal. On the left side the encapsulation is less striking but there is a greater reaction of small round cells, large mononuclear phagocytes and giant cells. The endothelial-like cells

which have formed along the membrane are shown in figure 22.

4. Cat #E-65-41.

Operation: Only the right side of the brain was wounded. The electrocautery and the scalpel were used.

Length of Survival: 62 days.

Gross Findings: There are dense adhesions between the brain and its envelopes on both the wounded and unwounded sides.

Microscopic Findings: The membrane is densely encapsulated and bathed in an extensive exudate of polymorphonuclear leukocytes. Giant cells are found along the margins of the membrane and mononuclear phagocytes and small round cells are scattered throughout the capsule. Pools of homogeneous material, which stain pinkish with acid fuchsin, are found in the capsular interstices. On the unwounded side the cellular reaction is similar in pattern but less intense. On both sides the inner surface of the capsule is adherent to the brain.

5. Cat #E-67-41.

Operation: The application of the electrocautery to a gyrus on the right side was accompanied by profuse subpial hemorrhage. The bleeding vessel was isolated by means of the suction tip, and cauterized. There was no gross cortical injury on the left side.

Length of Survival: 66 days.

Fig. 22.

Polyvinyl alcohol membrane after 30 days. There is no evidence of resorption. A layer of flattened cells resembling endothelium (End. C) covers one surface. Hematoxylin and van Gieson stain.


End. C.

Gross Findings: A capsule has formed around the membrane on both sides. It is intimately adherent to the wound on the right side and to the arachnoid bilaterally.

Microscopic Findings: The reaction is intense and similar in nature to that described in the previous experiment (E-65-41). The giant cells are particularly numerous (Fig. 23). In some areas the film is swollen. The adherence of the inner surface of the capsules to the cerebral wound and the leptomeninges is confirmed (Fig. 24).

Polyvinyl Alcohol.

	Days Postop.	Adhesions.	Encapsulation.	Cellular* Reaction.	Remarks.
E-42-41	10	2 plus	2 plus	4 plus	Poor Resul
E-57-41	30	3 plus	3 plus	3 plus	Poor Resul
E-58-41	30	3 plus	3 plus	2 plus	Poor Resul
E-65-41	62	3 plus	3 plus	4 plus	Poor Resul
E-67-41	66	3 plus	3 plus	4 plus	Poor Resul

*Includes polymorphonuclear leukocytes, small round cells, phagocytic cells and foreign body giant cells.

Abstract: The results with polyvinyl alcohol membrane have been disappointing. Encapsulation has been maximal and the response of inflammatory cell types intense. Adhesions invariably occurred in all of the observations.

Fig. 23.

Intense cellular reaction surrounding polyvinyl alcohol membrane (M). Giant cells (GC) are especially prominent. Hematoxylin and van Gieson stain.

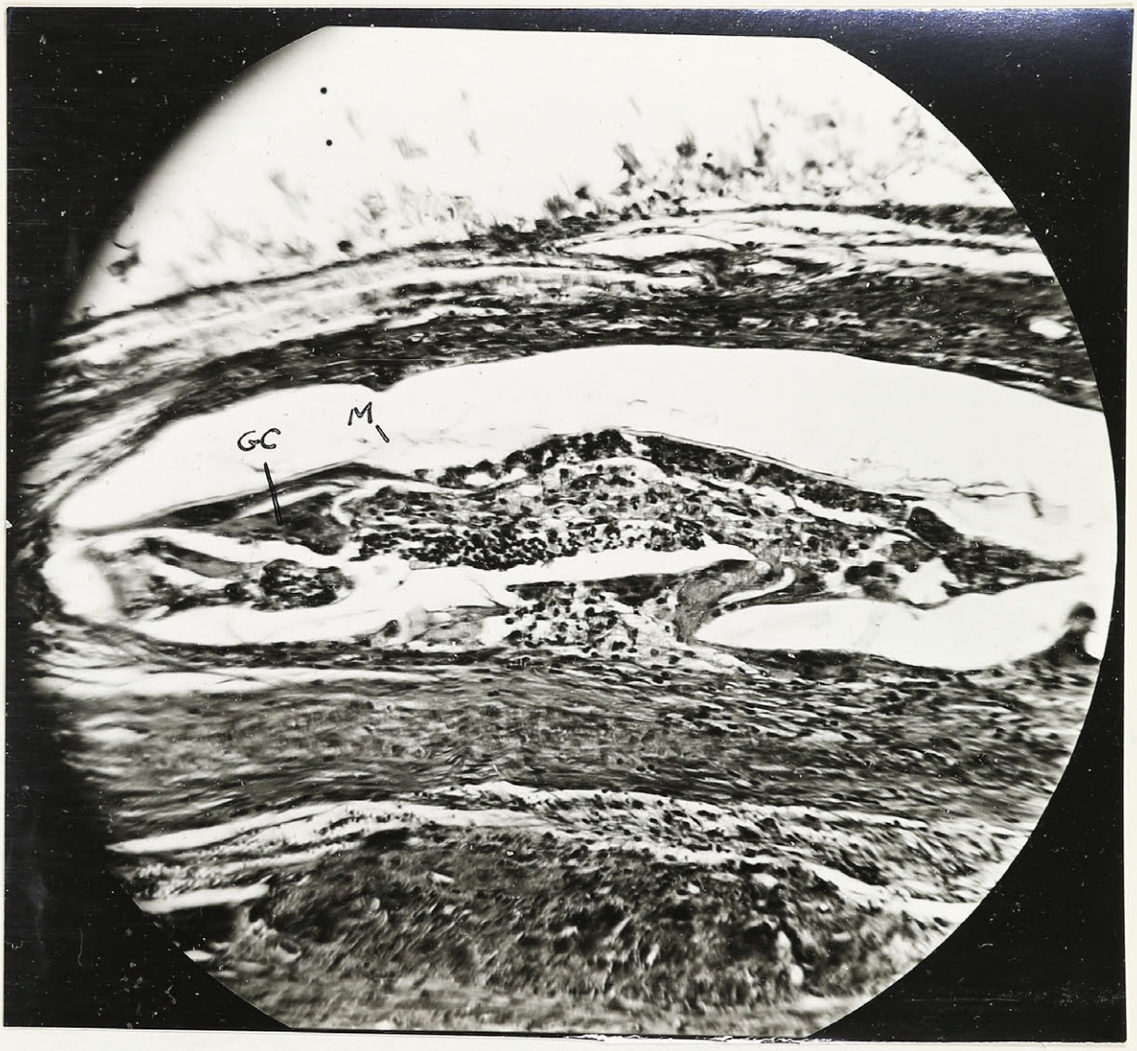
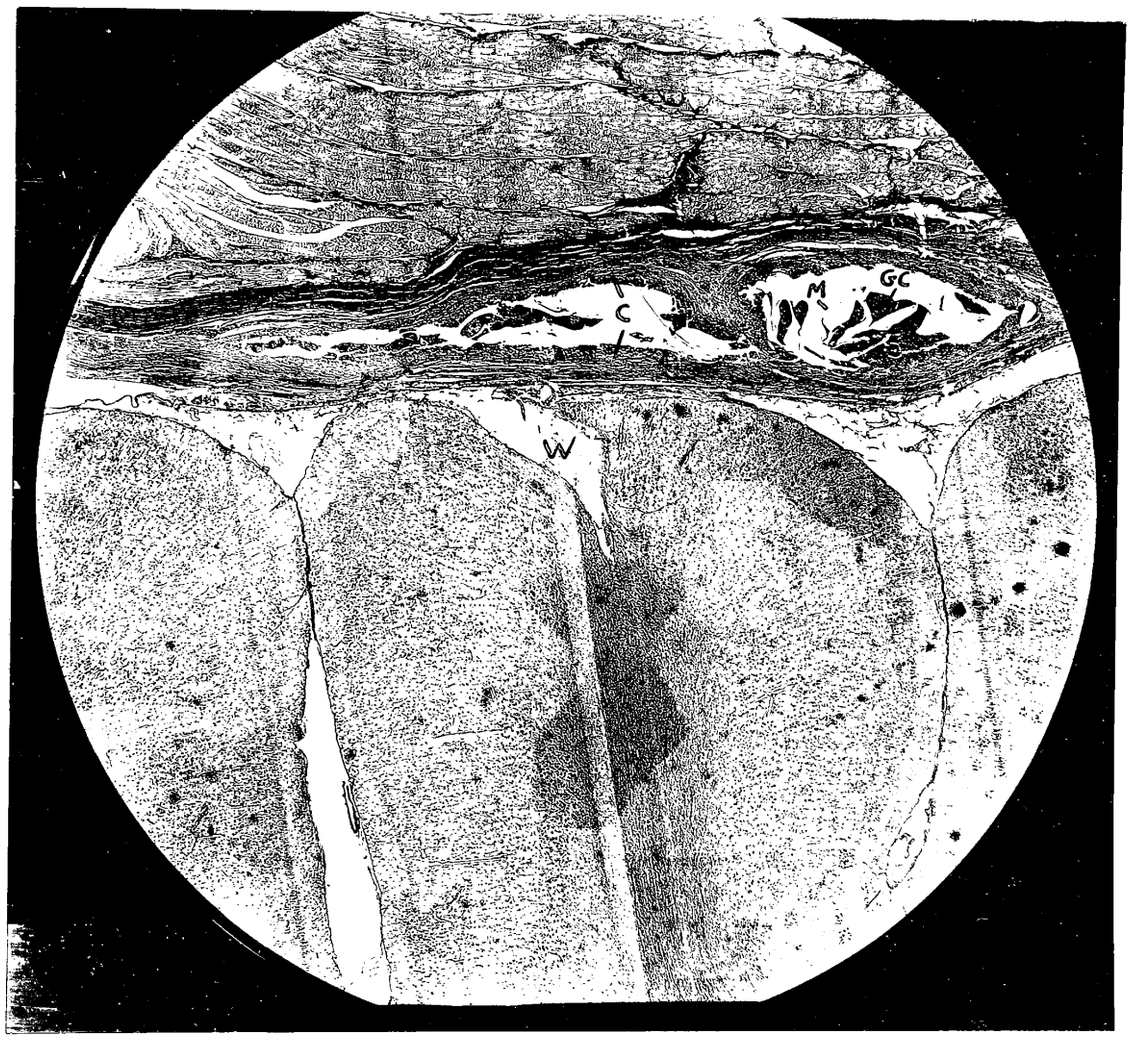

GC
M

Fig. 24.

Dense encapsulation (C) and cellular reaction surrounding polyvinyl alcohol membrane (M). The capsule is adherent to the cerebral wound (W). Giant cells (GC) are prominent. 66 days. Hematoxylin and van Gieson stain.


M
GC
C
W

V. DISCUSSION

This series of experiments on the prevention of meningocerebral adhesions cannot be considered as other than a preliminary study. Due to the variety of materials employed and the brevity of the observational period, an exhaustive study of any one membrane was impossible. The hypotheses and conclusions which are drawn in this discussion are, therefore, based on incomplete data.

Experimental Considerations.

The findings are in general agreement with those of previous workers on this problem. The membranes, without exception, were treated as foreign bodies and enveloped in a connective tissue capsule of varying thickness. The histogenesis of this capsule has been a fascinating component of the study. In the early stages of its formation, fibroblasts from the periphery stream over the cerebral and dural surfaces of the membrane and eventually unite centrally to form the inner and outer capsular layers. In the later stages collagen is laid down with the ultimate formation of a mature connective tissue investment of the membrane.

The dura is the principal source of the connective tissue elements forming the capsule (Fig. 10). The fibroblastic proliferation from this structure in the vicinity of the membrane is frequently vigorous. In a few of the experiments there has been an active participation of the arachnoid in the walling-off process. The

edge of the protective substance has been enveloped by thin cellular layers continuous with the arachnoid (Fig. 11). More commonly, the arachnoid has been intimately adherent to the inner layer of the capsule. It is this fusion which has accounted for the frequent adherence of the overlying structures to the brain on the unwounded side. On the wounded side strands of connective tissue join the inner layer of the capsule to the marginal brushwork of piloid glia in the cerebral cicatrix.

In the greater number of instances the capsule has been lined by flattened cells resembling endothelium or mesothelium. The origin of these cells was not ascertained but in view of Clarke's (1916) investigations, one might hypothesize that they are derived from fibroblasts. A second consideration is that they originated from the endothelium of neighboring blood vessels. Whether this cellular lining would prevent adherence between the inner and outer capsular layers following resorption of the membrane is a matter undecided by this investigation.

In addition to the process of encapsulation, the membranes not infrequently provoked a response of cell types common to acute and chronic inflammatory processes. The nature and intensity of the cellular reaction varied according to the material employed and will be discussed with the individual materials.

Tantalum has invariably been the least irritating of the materials employed. While encapsulation has occurred, it has been either slight or negligible. Furthermore, there is histological evidence for progressive diminution, rather than increase, in the thickness of the capsule. This is in contradistinction to the progressive capsular proliferation noted with other alloplastic materials, e.g. celluloid (Penfield 1924).

The impenetrable character of tantalum foil has prevented a direct ingrowth of connective tissue from the overlying structures. The only point of attachment between the cerebral wound and the dura is the capsular margin. The nature of this attachment renders traction on the cerebral cicatrix due to connective tissue contraction as unlikely. Furthermore, in view of the fine quality of the capsule, vascularization of the cerebral scar by an extracerebral blood supply must be minimal.

The reaction of inflammatory cells to tantalum has been negligible. In one experiment (E-28-41) a few giant cells lay within the cavity of the capsule. There has been no exudation of polymorphonuclear leukocytes, small round cells or phagocytes. Finally, the removed pieces of foil were always bright and shining suggesting a complete absence of corrosion by the body fluids.

A comparison of the similarities and differences of the viable and attenuated forms of amniotic

membrane has been an interesting feature of this study. Common to both is the histological evidence for survival of the connective tissue layer of the membrane. The individual fibers are sharply demarcated and stain a brilliant red with acid fuchsin. In contrast to this the collagen strands of the dura and connective tissue capsule are more deeply stained. Scattered among the amniotic connective tissue fibers are the large, oval, vesicular nuclei. It is possible that these nuclei are not native to the amnion but belong to fibroblasts which have infiltrated from the adjacent tissues. Proof for this origin is wanting.

The principal difference between these two types of amniotic membrane lies in the reaction of inflammatory cells. In the experiments with the viable membrane large aggregations of polymorphonuclear leukocytes or small round cells have been consistently found. These cellular aggregations have been particularly pronounced along the epithelial layer. In contrast to this the attenuated membrane has been unassociated with this type of reaction except in one instance in which foci of small round cells were present. In this experiment the liquid petrolatum was not removed with ether prior to application of the membrane to the cortical surface.

It is difficult to account for the difference in the cellular reaction to the two types of amniotic membrane. Two possibilities must be considered. The

first is that the method of attenuation inactivates the irritating substance in the membrane. The second consideration is that the epithelial layer, which is the histological site of the irritation, is destroyed by the rinse in ether. The difficulty in demonstrating the epithelial layer of the attenuated membrane in the microscopic sections is strongly in favor of the second assumption. Confirmation of either hypothesis pends a further investigation.

The non-viable amniotic, allantoic and Cargile membranes incite an intense fibroblastic activity leading eventually to investment in dense collagenous connective tissue. In addition, a reaction of small round cells, polymorphonuclear leukocytes and foreign body giant cells has frequently occurred. The giant cell reaction to the non-viable amniotic epithelium is particularly striking (Fig. 14).

The fixed amniotic membrane was completely absorbed at the end of 92 days. The allantoic and Cargile membranes were only partially resorbed at the end of 85 and 90 days respectively. The pools of homogeneous material lying next to these membranes and their "woolly" appearance are considered as evidence for beginning resorption.

The polyvinyl alcohol films provoked a more intense reaction than any other of the membranes. Envelopment in dense connective tissue was the invariable consequence after implantation of this material. Giant

cells were prominent in the histological picture and in two instances there were sizable aggregations of polymorphonuclear leukocytes. In view of the possibility that bacterial contamination of the films accounted for the inflammatory reaction, they were subjected to a routine bacteriological examination. There was an absence of bacterial growth both aerobically and anerobically. The polyvinyl alcohol films used in these experiments were originally selected on the basis of an "in vitro" determination of solubility in human cerebrospinal fluid. The unreliability of this test has been shown in the animal experiments. At the end of 66 days there was a complete lack of evidence for even partial resorption of these films. In view of this a compound containing a higher percentage of acetate groups is desirable. It is likely that this more resorbable form would incite a less pronounced cellular reaction and capsule formation. Verification of this assumption necessitates a further study of these compounds.

Practical Considerations.

In the discussion of the qualifications of the ideal membrane for the prevention of meningocerebral adhesions, lack of tissue irritation is stressed as being of greatest importance. On this basis tantalum is superior to any other of the materials used in this investigation.

Despite the brief period of observation the author believes that the inertness of tantalum is a permanent quality. This belief is largely based on the

lack of progressive encapsulation of the metal. Burke's (1940) results with bone screws and plates and with skin sutures add further weight to this assumption. However, confirmation of this statement depends on a study of the tissue reaction to this metal at intervals over a minimum period of one year. The author plans to carry out these studies in the near future.

Tantalum does not fulfill the second requirement for the ideal membrane, namely, resorbability. However, in view of its inertness in the tissues this qualification would seem dispensable.

It is unfortunate that the physical characteristics of the grain structure will not permit the rolling of tantalum into a thinner foil. The thickness and rigidity of the .001-inch foil is a definite disadvantage because it will not conform to the convolutional pattern of the brain. The creation of a "dead" space is, therefore, not unlikely.

The potential usefulness of tantalum in neurosurgery, and especially in the treatment of craniocerebral injuries, is not limited to the prevention of adhesions. It is possible that the metal may prove invaluable for the closure of defects in the skull and dura. The replacement of the silver ribbon in Cushing's clips with a tantalum ribbon of similar calibre is highly desirable. The intensity of the cellular reaction to silver clips had led to their disfavor in the hands of many neurosurgeons.

In view of the uniform unsuccess of heteroplasty in the past, the author was skeptical of the value of the viable and attenuated forms of amniotic membrane from the very beginning. Despite this skepticism the use of these membranes may eventually become practical. The intensity of the cellular reaction to the epithelial layer of the viable type would forbid the use of this material over the wounded brain. However, the absence of this cellular reaction to the attenuated form and the histological evidence for survival of its connective tissue layer allow the assumption that it may be of practical value in neurosurgery, for example, to close dural defects. The use of amniotic membrane for this purpose would require a method for removal of the epithelium without disturbing the viability of the connective tissue. In addition, it would be necessary to find a practical method for conserving this viability under sterile conditions and for a long period of time.

Polyvinyl alcohol and allantoic, fixed amniotic and Cargile membranes cannot be recommended for the prevention of meningocerebral adhesions. The evidence gathered from this study would indicate that these materials aggravate, rather than retard or prevent, the formation of adhesions. However, if controlled resorption of polyvinyl alcohol is established it may find a niche in neurosurgical practice.

In closing the writer wishes to reiterate what has already been pointed out in the introduction to this thesis. The role of meningocerebral adhesions in determining the epileptogenic nature of a cerebral cicatrix lies in the realm of hypothesis. The value of materials to prevent the formation of meningocerebral adhesions is therefore dependent on the establishment of this hypothesis as factual. The present war offers a valuable opportunity to do this. It would require the use of a suitable material to protect the cerebral wound after debridement with a view to prevention of adhesions to the overlying structures. In later years the incidence of posttraumatic epilepsy in cases so treated could be compared with the statistics of the Great War era. It is hoped that this study will provide some additional data toward the ultimate solution of the problem.

VI. SUMMARY AND CONCLUSIONS

The data presented in this thesis concern methods for the prevention of adhesions between the wounded brain and its coverings. The investigation was stimulated by the high incidence of epilepsy following open craniocerebral wounds, particularly gunshot wounds. The theoretical significance of meningocerebral adhesions in the causation of posttraumatic epilepsy is discussed. The literature related to the problem is reviewed.

Seven types of materials, namely, human amniotic membrane in viable, attenuated and fixed forms, Cargile membrane, allantoic membrane, tantalum foil and films of a polyvinyl alcohol compound in which 5% of the hydroxyl groups had been substituted by acetate groups, were used in this study. These materials were selected on the basis of one or more of the following criteria:

1. Inertness in the surrounding tissues.
2. Delayed resorption.
3. Availability of supply.
4. Successful employment in past studies.

These materials were placed over both the wounded and unwounded cerebral hemispheres of cats. The animals were sacrificed at appropriate intervals varying from 4 to 97 days. Gross and microscopic observations of the reaction of the surrounding tissues and the condition of the membrane have been carried out.

The following conclusions are drawn:

1. Tantalum is superior to the other materials from the standpoint of both minimal tissue irritation and the prevention of adhesions. While encapsulation occurs it is minimal and, questionably, regressive. Indirect meningocerebral adhesions form via the edge of the connective tissue capsule. The writer suggests a further experimental trial before recommending the use of tantalum in humans.

2. There is histological evidence for survival of the connective tissue layer of both the viable and attenuated amniotic membranes. The epithelial layer of the viable form provokes an intense cellular reaction. This is not noted with the attenuated form. The possible use of the attenuated amniotic membrane for the closure of dural defects is suggested.

3. Cargile, allantoic and fixed amniotic membranes increase, rather than retard or prevent, the formation of meningocerebral adhesions.

4. The 5% polyvinyl alcohol films cause an intense fibroblastic and inflammatory cell reaction. The clinical use of this material is, therefore, not recommended. The possible value of a more resorbable form of this material is discussed.

VII. ACKNOWLEDGEMENTS

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