MENINGO-CEREBRAL ADHESIONS : A STUDY TO

PREVENT THEIR FORMATION BY THE USE

OF CORTISONE

by

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TABLE OF CONTENTS.

INTRODUCTION.

This study was prompted when the writer was engaged on a histological problem regarding the effect of intramuscular cortisone on glial and neuronal elements.

The relationship of meningocerebral adhesions and cerebral cicatrices to the incidence of post traumatic epilepsy is one which is often contested. In this work no attempt is made to emphasise the relationship, or otherwise. The incidence of post traumatic epilepsy is reviewed, the diverse attempts to prevent adhesions are analysed, the physio-biological properties of cortisone are presented and the results of the experimental work, contained herein, are set forth.

The study was carried out within the framework of a limited supply of cortisone. Its object and prime purpose was to suggest the lines and avenues of clinical neurological investigation which might be safely and profitably explored when supplies of cortisone become readily available. It is therefore hoped that the acceptance or rejection of the importance of scar tissue, or an "adhesion hypothesis", will in no way modify the importance of the basic conclusions.

" But I have seen s severely
    wounded brain healed "

(from Galen's commentaries on
  the Aphorisms of Hippocrates)
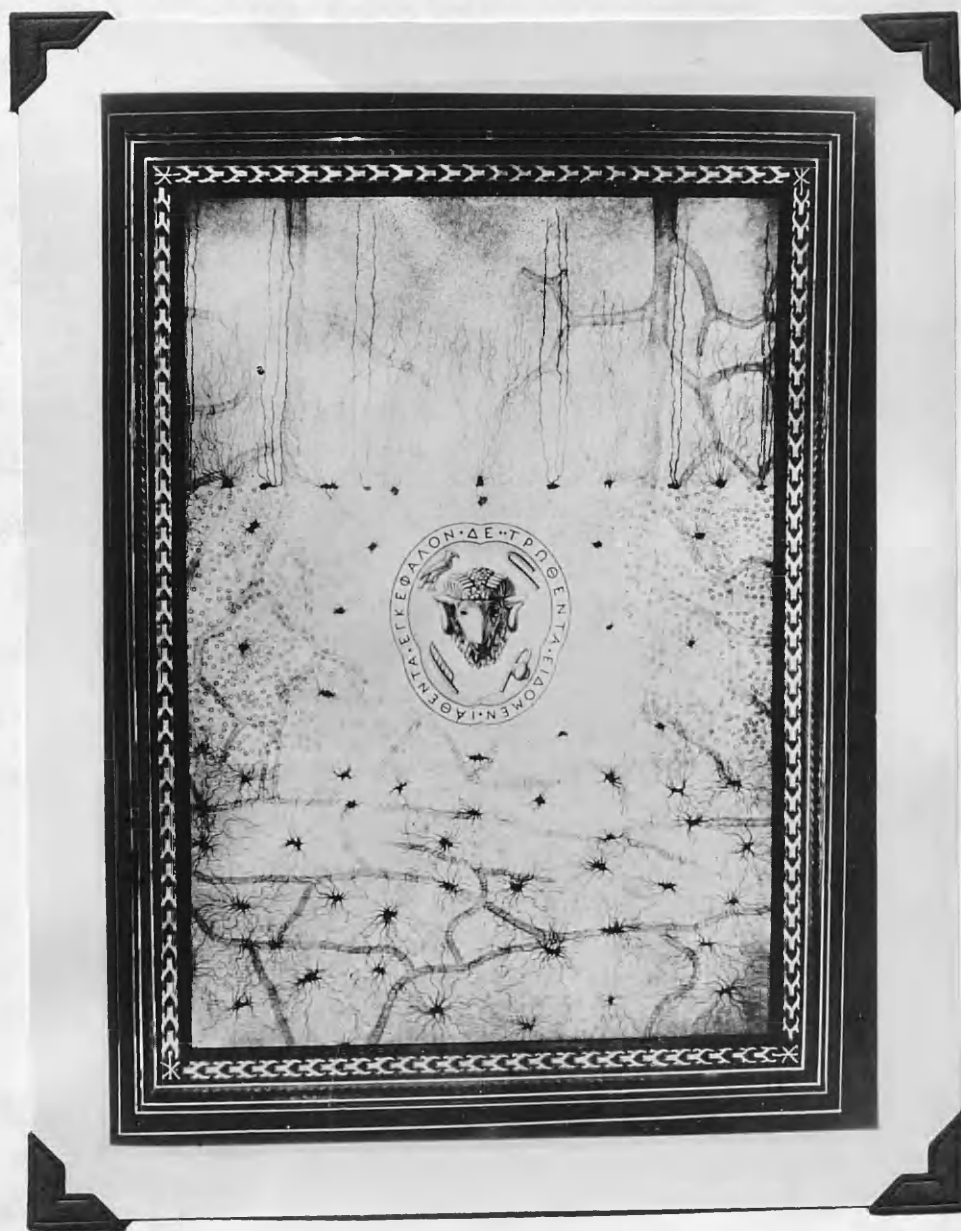
THE PREVENTION OF MENINGO-CEREBRAL ADHESIONS.

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. Richardson (1911) and Ochsner and Garside (1932), in their studies, reviewed the methods and materials which have been used for the prevention of peritoneal adhesions(Fig). It may be contended that the presentation of these reviews contributes little to the problem under discussion. They are testimony to the confusion which have existed in the prevention and treatment of peritoneal adhesions. New methods or materials will have been tried and acclaimed by one, or a number of observers, and then failed in the hard test of time and trial. The problem to this day remains unsolved.

Literature relating to methods and materials employed to prevent adhesions between the brain and its enveloping membranes is scanty in comparison to the writings on adhesion prevention in general. In fact, most of the reports concern various substances which have been utilized primarily to repair dural defects. A suitable substitute for normal human dura is highly desirable for two primary reasons: first, the dura may have to be removed because of its involvement in a disease

process; and second, the dura may^injured with or without
damage to the underlying nervous tissue. In order to meet
those needs for a protective layer which might be easily
available, numerous materials have been studied in the
laboratory, and also clinically. These methods of duraplasty
have been reviewed by Von Saar (1910), Buné (1933), de
Bernardis (1935), Caporale and de Bernardis (1936) and Glaser
and Thienes (1938).

These experiments and reports on duroplasty were
of great value since they provided a base line for the investi-
gation of other materials. For the purpose of presentation
and discussion these materials may best be classified under the
following heads:

a) Metals.

b) Viable animal membranes.

c) Non viable animal membranes.

d) Miscellaneous.

METALS. The debut of the modern period in the surgery
of post traumatic 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 meningo-cerebral
adhesions. Horsley excised the epileptogenic cicatrices, but
did not cover the area of removal with protective materials.
Beach is creadited with the first suggestion to use those sub-
stances. In 1890 he reported a case of post traumatic epilepsy

TABLE 1.

Showing the various metals which have
been used in the prevention of adhesions.

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
TANTALUM	PUDENZ	1942	CAT	CORTICAL SURFACE	"	ENCAPSULATION
TANTALUM	DELARUE	1944	DOG	CORTICAL SURFACE	"	DENSE, DENSE ADHESIONS.

treated by lysis of the meningo-cerebral adhesions. At the
same time he stated that should the seizures recur, he would
reoperate and implant gold foil between the brain and the dura.
In 1897 he reported that this plan was effected at a second
craniotomy in 1892. The patients 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
20th century. The observations of Beach on gold foil were
followed by the reports of Oliver (1896), Estes (1896), Summers
(1897), and Woolsey (1897), on the metal; those of Ray (1901),
Harris (1904) and Prime (1909). on silver foil, and Morehead(1896)
and McJosh (1898) on platinum foil. Chao, Humphreys and Penfield
(1940) reported their experiences with silver foil, aluminum foil,
nickel plate and stainless steel plate. Pudenz and Odom (1942)
reviewed the properties of tantalum and conducted an experimental
enquiry into its possible use in the prevention of meningo-
cerebral adhesions. Tantalum is an element, the seventy-third
in the periodic table. It is a bluish white metal, resembling
steel in its physical properties and glass in its chemical
characteristics. Pudenz used tantalum foil in 5 animals and
the observation period extended over 79 days. While encap-
sulation of the tantalum occured, it was very slight. He
felt the histologic evidence indicated progressive diminution
rather than increase, in the thickness of the cpsule. This

is in contradistinction to the progressive capsular proliferation
noted with other alloplastic materials eg. celluloid (Penfield
1924). The impenetrable character of tantalum foil had prevented
a direct ingrowth of connective tissue from the overlying
structures. The only point of attachment between the cerebral
wound and the dura was the capsular margin. There was a
negligible reaction of inflammatory cells to the tantalum,
The removed pieces of foil were always bright and shining,
suggesting a complete absence of corrosion by the body fluids.

Robertson (1944), reported the repair of 26 cranial
defects with tantalum over a two year period. He felt there
was a minimal reaction of tissues to the presence of tantalum.
None the less, in one case (reviewed six days after operation),
there was a thin, filmy, translucent, gelatinous membrane
enveloping the tantalum. Microscopic examination showed it to
be composed of "tangled masses of fibrous strands". In the
same year Delarue, Linell and McKenzie (1944), published an ex-
perimental study on the use of tantalum in the subdural space
in 12 dogs. In all these animals there was marked reactive
thickening of the dura overlying the tantalum and in many, a
similar, but slighter, reactive thickening of the underlying
arachnoid membrane was present. The following year Robertson
and Beacher (1945), reported the use of tantalum foil immediately
over the cortex in six patients. In each instance the findings
were invariably similar - a fine, thin, smooth, glistening,
diaphanous membrane surrounded the foil. This envelope was very
loosely adherent to the arachnoid and dura but was easily
separated.

Irrespective of these findings it must be realized that tantalum does not possess the quality of resorbability, and even although it would appear that it is relatively inert in the tissues, this is a definite disadvantage. The study of Pudenz extended over a maximum of 79 days, and it would have been better to have observed the state of affairs over a minimum period of 18 months. The metal used was 1/1,000 inch thick. The grain structure of the metal will not permit the rolling of tantalum into thinner foil. This thickness and rigidity of .001 inch foil is a most definite disadvantage since pieces of some size will not conform to the convolutional pattern of the brain and a dead space is, in consequence, likely. One feature common to all of these metals is encapsulation. The intensity of cellular reaction is variable and would seem dependant on the degree of electrolysis of the metal.

Viable Animal Membranes. At the close of the first decade of the twentieth century the metallic substances were giving way in favor of viable and non-viable animal membranes. These viable membranes have generally been employed for the closure of dural defects and not for the prevention of meningo-cerebral adhesions. This work was originated with Kirshner (1909), who 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 (Bruning 1911), periosteum (Ronde 1933, Bunè 1933),

TABLE 2.

Showing the viable animal membranes used
by various investigators.

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

and fat (Rehn 1913, Denk 1914, Chao et al 1940). Homoplastic
hernia sac was succesfully 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
Penfield (1940), presented experimental data on the use of viable
membranes to prevent meningo-cerebral adhesions specifically.
Both fat and fascia lata were used over brain wounds in cats.
Adhesions occured in all of the experiments. The materials
became incorporated in a new-formed brain covering which replaced
dura and incorporated pia without formation of seperate meningeal
linings. Fat in particular, produced a most severe cellular reaction

Examination of these facts and the data outlined in
table 2, permits of the generalisation that, from the
standpoint of dural repair, the autoplastic viable membranes
have been successful. However, when the cortex has been
damaged and subsequent examination ao the tissues was possible,
meningo cerebral adhesions have invariably been the rule.

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 his 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

TABLE 3.

A table of 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.

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), also reported
observations on this membrane. Prime noted adhesions in his
dogs in every instance when the cortex was damaged.

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
(Finster 1910, Von Saar 1910), Human amniotic membranes (Chao
et al 1940, Odom 1940), sheep peritoneum (Hanel 1909), and calf
artery (Ritter 1910).

These non-viable membranes have, from time to time in
the past, shown great promise in the prevention of meningo-
cerebral adhesions. This was especially true of amniotic and
allantoic membranes. Chao reported (1940) that of all the
animal tissue used fat produced the most severe cellular
reaction and human amniotic membrane the least. Cargile
membrane gave a poor result. When it was placed over pia that
had been slightly injured dense adhesions resulted.

Chao and al (1940), extended their observations over
intervals extending from 10-60 days after the lacerated brain
had been covered with amnioplastine. In no instance was there
evidence of gross adhesion. The amnioplastin sheet proggess-
ively disappeared. In the 10 day animals a mucoid material
which represented the membrane was to found in the space between

TABLE 4.

A compilation, without reference to worker or date showing materials primarily mechanical in action and also those thought to be primarily chemical in action.

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A compilation, without reference to worker or date
showing materials primarily mechanical in action
and also those thought to be primarily chemical in
action.

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

injured cortex and re-forming dura. At 30 days no gross or
microscopical evidence of membrane could be found. Micro-
scopically in the ten day group there was no evidence of any
foreign body reaction,and no organized adhesions. Chao
believed that the growth of fibroblasts beneath and above the
membrane was a reaction to the presence of a vanishing foreign
body. By twenty days the dural defect had completely filled
in, the pia had partially closed over the destroyed brain, and
the membrane between the two was represented by a thin amorphous
material.

Rogers(1941), reported his experiences in the treat-
ment of peripheral nerve injuries with amnioplastin. None of
the cases reported had extended over one year, and Rogers had
not had the opportunity to reopen a wound and re-examine a nerve.
trunk that had been isolated by the membrane some time previously.
It need hardly be added that a much longer time will be required
to ascertain whether the late results of these peripheral cases
are good,and for an opportunity to occur by which it may be
ascertained from the condition of the operation field whether
neural isolation persists and whether the membrane is absorbed
as completly in man as in experimental animals of Chao et al
(1940).

Pinkerton(1942) used amnioplastin in the treatment of
adherent digital flexor tendons. The membrane used was as
recommended by Chao et al (1940), and Penfield(1940). In all
cases the superficial tissues remained freely movable over the
tendon for three months after operation. In one case the

amnioplastin was examined "in situ" two months after insertion.
It was found as a thin, transparent gelatinous membrane, from
which the overlying fibrosed tissues were easily separated,
and beneath which the tendons could be seen to move freely,
Here the cases were only of four months duration when reported,
and an observation over a much longer period of time would be
of more value.

Pudenz and Odom(1942), in their experimental study
found that the amniotic membrane, prepared according to their
procedure, was completly absorbed at the end of 92 days.
They also felt that this membrane was relatively unassociated
with an inflammatory cell reaction, but that an intense
inflammatory cell response was associtated with the viable type
which contained an epithelial layer.

<u>Miscellaneous.</u> There remains for consideration a
number of materials which are best classified under the heading
of miscellaneous. It includes various substances of plant or
mineral origin as well as the newer plastic and synthetic materials.
The various substances which have been used with rather poor
results include rubber tissue(Abbe 1897), celluloid(Hantsch
1922), parchment(Oberniedermayer 1928), mica(Chao 1940),
Cellophane(Chao 1940), Olive oil(Prime 1909), polyvinyl alcohol
compounds(Pudenz and Odom 1942).

Cellophane and mica were found to promote dense
adhesions and mild cellular reactions. Less is known of the
Polyvinyl alcohol compounds. Little has been written of them.
These compounds are used commercially in the manufacture of
shatterproof glass. Their chief attraction is the change in

TABLE 5.

A miscellaneous list, including reference
to recent work on plastics.

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
POLYVINYL COMPOUNDS	PUDENZ	1942	CAT	CORTICAL SURFACE	"	DENSE ADHESIONS and INFLAMMATORY CELL REACTION.
FIBRIN FILM	INGRAHAM ET AL	1944	MONKEY	"	DUROPLASTY	MINIMAL CONNECTIVE TISSUE RESPONSE.
POLYTHENE FILM	BROWN ET AL.	1947	DOG	CORTICAL SURFACE	"	SIMILAR TO TANTALUM.

solubility rate obtained by modifying their structural formulas.
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. Theoretically the most attractive compound would
be one which would remain intact for at least a month. This
length of time would permit the protected arachnoid to repair
itself without invasion from the overlying structures. Only two
papers on the use of polyvinyl alcohol compounds can be traced
in the literature. That of Pudenz and Odom(1942), and Dötzer
(1938), who reported experiments on the reaction of bacteria
in contact with polyvinyl alcohol. The experience of Pudenz and
Odom(1942), with polyvinyl alcohol compound is extraordinarily
disappointing. In a series of five animal experiments
encapsulation was maximal and the response of inflammatory cell
types was intense. This included polymorphonuclear leucocytes,
small round cells, phagocytic cells and foreign body giant cells.
Dense adhesions occured in all cases. Review of the micro-
photographs of this work shows that in some instances the polyvinyl
alcohol film showed no evidence of resorption and cellular reaction
was most intense. Obviously, the evidence from this study would
indicate this material aggravates, rather than retards or prevents,
the formation of adhesions. None the less it would be rash to
dismiss the material on this basis alone,since if a controlled
resorption of one of the many compounds could be established, it
might well prove a useful material in clinical practice.

In 1944 Ingraham and Baily published an account of the use of fibrin films in the repair of dural defects and in the prevention of meningo-cerebral adhesions. This substance, fibrin film, was prepared by the fractionation of human blood plasma. This material was subject to wide variation by small alteration in the conditions of preparation. In order to determine the reaction of the cerebral cortex to these fibrin films, Ingraham and Baily 1944, performed craniotomies on 10 monkeys. The cerbral cortex was traumatised by multiple needle wounds (10-25) penetrating the cortex for at least 2 millimeters. These needle wounds were distributed as to cause bleeding in every instance. The animals were sacrificed after periods of observation from 24 hours to 6 months. Up to one week the film had changed its appearance but little, and there were only a few wondering cells about it. As time went on, the film became surrounded by a small amount of fibrous tissue from which it could b.e easily seperated. In monkeys allowed to survive for more than a month, parts of the films could be seen broken up with some giant cells about the small isolated fragments. But the end result was a layer of fibrous tissue about the same thickness as the original films. At the end of six month there were no adhesions, but the layer covering the cerebral cortex was found to be composed of thin transparent tissue rather than film. When the bone had been rongeured away and the skull defect pertained the overlying temporalis muscle was closely adherent to the film although the subdural space was free from adhesions. The film had been used

clinically in 44 patients and different opportunities had arisen for examination of films at intervals varying from 14 hours to 81 days after implantation. Grossly, there was no evidence of inflammatory reaction and there were no adhesions. Histological examination disclosed the same features as described in the experimental animals.

Ingraham, Bailey and Cobb (1945), set out to perfect a sterilisation technique for the fibrin film less cumbersome and more practical than the glycerol method used in the 1944 report. They decided on steam pressure sterilisation and reported animal and clinical studies using the film prepared in this fashion. The arachoid, pia and superficial cerebral fissures were lacerated several times by the use of a curved French needle and the monkeys killed at an interval of one day, two weeks, and one, two, three, five and six months after operation. Pathologic studies indicated that the fibrin films were gradually replaced by a neomembrane of fibrous tissue without the formation of meningo-cerebral adhesions. Absorption of the fibrous film was almost complete at three months, and no film remained at five and six months after operation. A further paper from their laboratories(1947) reported on the insertion of fibrin film between the sutured dura and the intact lepto-meninges. Where the fibrin films were inserted, no evidence of adhesion could be seen, whereas on the control side, adhesions were present in all the animals, and when the brain was separated from the dura small fragments of the cortex were pulled out by several of the small firm adhesions.

This experiment demonstrates that in the monkey at any rate,
small firm adhesions may form between the brain and dura where
silk sutures used to close the dura lie in contact with the
leptomeninges.

It is only to be expected that the great strides made
by the plastic industry should stimulate interest in the
possible application of many of these substances in the surgical
field. However, the number of synthetic plastics which can be
buried safely within human tissues is surprisingly small. Methyl
methacrylate and nylon (Ingraham et al 1947), have been found
to be well tolerated by the tissues. The latest material found
to fulfil most of the requirements is "Polythene". Polythene is
a long chain polymere of ethylene and has, on theoretical grounds
the simplest chemical formula of all the plastics. Each molecule
is formed of a saturated alophatic hydrocarbon chain, each
carbon atom of which carries two hydrogen atoms

$$\left(\begin{array}{c} H \\ -C- \\ H \end{array} \right)_n.$$
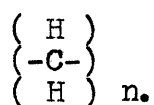
As it is now manufactured, Polythene has a molecular weight of
about eighteen thousand which is very suitable for extrusion
into tube and thin sheets. This form of plastic has a micro
crystalline structure which does not require the aid of a
plasticizer, which is generally a tissue irritant, to make it
flexible and pliable. Polythene stretches without breaking eas-
ily, but has relatively little elasticity. It can be extended
easily in the form of tubes of any conveient size, or sheets
of any desirable thickness.

Ingraham, Alexander and Matson(1947), reported results in the

implantation of polythelene directly into the cerebral cortex(1), and (2) in the replacement of an area of excised dura with polye-thelene film. Tissue reaction were studied in 65 animals sacrificed at 5, 7, 10, 14, 21, 30, 60, 90, and 150 days. None of the animals showed evidence during life of cerebral irritation or of any unusual behaviour that could be attributed to the presence of the polythelene.

Histologic section through the area of implantation up to 10 days showed no more tissue reaction than was found adjacent to a control stab wound elswhere in the cortex.. No collections of polymorphonuclear leucocytes were found in any of the sections. Sections made through the implantation sites in experiments lasting more than 10 days showed a thin layer of glial tissue and slightly compressed cerebral tissue around the cavity containing the plastic. The glial layer was one to three cells in thickness and increased gradually over the weeks, until at 90 days it was six to eight cells thick. The surrounding cerebral tissue showed no increased vascularity and no inflammatory or foreign body reaction.

In 32 cats polythelene film 0.002 inch (0.005¢m) in thickness was used to replace dura, there being no injury to the cortex. The necessity for obtaining and using only the pure product was emphasised here since in the earlier experiments where presumably an impure quality was used, there developed relatively large hematomas between the arachnoid and the film, which were very gradually absorbed and replaced by fibrous tissue.

In the last 13 cases the pure film apparently was used and no hematomas were encountered. Animals killed in less than 10 days showed no gross or microscopic reaction around the film, and the underlying cortex was plainly seen through it. After 10 days it became apparent that the film was being gradually encapsulated by a thin neomembrane on both the inner and outer surfaces. These layers were apparently derived from the dura. The inner surface was generally adherent to the underlying arachnoid by filmy adhesions. In animals allowed to survive 30-90 days, the film was found completly enclosed by a thin non-adherent fibrous envelope and there was mild thickening of the arachnoid.

In only three animals was polythene placed over damaged cortex, replacing the dura. One animal was re-explored after three days the othersafter 20 days. There was no gross reaction to the film in the animal explored after three days, but in the animals studied after 20 days there were adhesions to the neomembrane enclosing the film. Systemmatic experiments had not been performed to determine the effectiveness of polythene film in preventing meningo-cerebral adhesions over damaged cortex, but it would appear that the final stage would be comparable to the findings of Pudenz and Odom(1942) in regard to tantalum, namely, that the film would become encapsulated by a thin fibrous envelope, the undersurface of which was adherent to the cortical cicatrix. Brown, Grindlay and Craig(1948) reported the use of polythene film in duroplasty in 10 animals. In 2 animals the cortex was lacerated. The tissues were inspected at intervals of 2, 4 and

6 months. In all cases the film was entirely non-adherent to
the underlying leptomeninges and cerebral cortex. Grossly and
histologically a thin subdural neomembrane formed between the
film and the arachnoid. This neomembrane was non-adherent and
could be easily dissected of the underlying arachnoid in the
two wounded and in the unwounded animals. No foreign body
giant cells were seen. Clinically these authors had used the
film in order to prevent adhesions between the brain and the
extracerebral structures in lobotomy. No observations on the
efficacy of this procedure are recorded.

Busch, Bing and Hansen(1949), reported on the use of
gelatin and polythene film as dural substitutes. They prepared
the gelatine films from formalin hardened gelatine to which had
been added sulphonated lauryl-alcohol to make the film more
flexible and easier to stitch. Four cats were trepanned
and the dura corresponding to the trepannation orifice was
removed. A piece of gelatine film was then inserted, its
margin extending under the edge of the cranial defect. One
cat presented a favorable result whereas examination of the
others revealed broad adhesions which could not be divided
without tearing of a small tissue of cerebral tissue.
Accordingly, the gelatine film prepared by this method must be
regarded as valuless in the prevention of meningo-cerebral
adhesions and a poor dural substitute. Their experiments with
polythene film were carried out using film 0.10mm. thick and
sterelized with formaline Preliminary subcutaneous, intra-
peritoneal and intrathoracal application in rats showed that
it was unabsorbable and induced no tissue reaction. Further,

in one rat a bag of polythene was placed about one kidney and
slight hemorrhage was caused by the manipulation. Two weeks
later there were no adhesions between kidney and films, or between
film and surrounding tissues.

The practical usefulness of polythene film was verified
by experiments on 3 dogs. In two of the dogs, a small defect
was produced in the surface of the brain, as well as a piece
of dura removed, with the red hot point of a pair of forceps.
The animals were killed 6, 8, and 10 weeks after the operation.
In all cases there were adherences between bone and brain on the
control side, but in none of the animals were there any adherences
between the polythene film and the brain.

Following this experimental investigation Busch et al
(1949) used polythene film 0.06 mm. thick in 51 clinical cases
where a dural substitute was required with apparently satis-
factory immediate results, but no histological studies are
presented of re-examination of this material.

POST TRAUMATIC EPILEPSY.

HISTORICAL REFERENCES.

In the Broca museum in Paris there are trephined skulls of neolithic man which Broca argued as evidence of fanciful, ritualistic or religious proceedures. Victor Horsley believed that the trepanations were in some instances attempts to cure Jacksonian convulsions (Ballance 1922). They may well have been traumatic in origin. Hippocrates pointed out that a blow on one side of the head might be followed by contra lateral paralysis or convulsions. The evidence that he used the trephine for such conditions is not definite. Likewise, although Galen and Celsus both used the trephine, that they did so for post traumatic epilepsy is doubtful. References to trepanation for abscess and for fracture of the skull are frequent in the writings of the thirteenth, sixteenth and seventeenth centuries. Percival Pott (1713-1788) indicates clearly that the symptoms following head injury are due to brain injury, not to skull fracture. Jean Louis Petit (1674-1750) lists as indications for trephining: fracture, unconsciousness, haemorrhage from the nose, mouth and ears, paralysis and convulsions and he goes on to state that trephining should not be done to cure convulsions but to remove the particular cause of them.

Ballance quotes a detailed statement of Peter de Marchettis of a case reported in 1665 (Obs.Medico-Ciirurg. vii p.11) "I remember having a consultation with D.JULIO SALA , professor at Pavia, about a man who had been wounded in the head with a dagger. Not only was the bone injured, but the

membranes and even the brain. The external wound had been treated by certain practitioners and a cicatrix had formed. After two or three months the patient was troubled with epilepsy and had a fit twice or three times a month. When asked by Professor Sala whether he had ever had an injury to the head, he replied that he had and pointed out the place. I immediately inserted a probe beneath the crust and found a penetrating wound and proceeded at once to operation and the opening of the parts. The next day I applied the trephine; yellow pus escaped. For twenty days I applied black western bal sam with the use of which the wound granulated, and in thirty days the patient was cured of his wound and of his epilepsy."

Writing in the next century, Astley Cooper in his lectures on the Principles and Practice of Surgery relates a cure of Jacksonian epilepsy by the operative removal of a spicule of bone. The epilepsy began six months after the injury. Because of increase in the number of attacks decompression operation was done in 1822 and sixteen years later the man was still attack free (Cutter 1930). George James Guthrie (1785-1856) Surgeon in the Peninsular War, recognised that " local pain and epilepsy may follow fracture of the inner table and require operation (Ballance). Larrey (1766-1842), Napoleon's Surgeon General, makes frequent mention of traumatic epilepsy and relates one case of cure (Cutter).

Wells, writing in 1812 (Cutter) clearly describes the case of a negro who, having sustained a right parietal depression, subsequently developed fits and hemiplegia. Trephining resulted in practical disappearance of the hemiplegia but the patient

was still liable to his seizures when excited. Benjamin W. Dudley, Professor of Surgery in the Transylvanian Medical at Lexington, was the first American surgeon to give special attention to traumatic epilepsy and its cure by decompressive operation. Between 1818 and 1827 he reported five cases. All of these cases had too short follow up periods for any significance to be attached to the results. Bright (1836) should be mentioned because his is the first clear description of Jacksonian epilepsy although not due to trauma but seemingly a vascular accident.

John S.Billings, founder of the Surgeon General's Library at Washington, in his first published medical article (1861) wrote on "The surgical treatment of epilepsy" (Cutter). He lists seventy two cases of decompression with sixteen fatalities, forty two reported cures, four cases unimproved and the remaining ten were classed as improved although not entirely relieved. At least some of these cases were of traumatic epilepsy for he includes Dudleys cases (vide supra).

INCIDENCE OF POST TRAUMATIC EPILEPSY.

Peace time: Lenormant (1921) gathered together the reports of several authors upon the occurrence of traumatic epilepsy in times of peace. Brun, among 221 cranial injuries of all types, reported 18 cases - 8%. Braun in a similar group made up of 291 cases, reported 15 epileptics,- 5.2%. Of these, there were thirty gunshot wounds, one of whom developed epilepsy. Gordon and Wilson record 14 epileptics among 530 fractures of the base -2.6%. Neumann, among 108 cranial traumata on an infants

service, found 3 cases of epilepsy - about 3%. This finding is
in agreement with that of Ford (1926) that 2 or 3% of all
epilepsies seen in children are related to birth injury.
Muskins (1928) in 1000 cases of head injury seen in private
practice found only 8 epileptics. Steinhal (1929) quotes
Reichman as finding a .5% incidence among 603 peace time injuries
while he himself, among 531 cases seen in his own private
practice between 1907 and 1926, saw only one epileptic.
Later figures include those of Schou (1933), Russell (1934),
Rowbotham (1942), Feinberg (1934) and Penfield (1944).
Schou found 4.5% of epilepsy in 200 cases of head injury
reported to a Dutch insurance company. Russell 3.5% in 200
cases of head injury and Rowbotham 2.5% in 450 cases.
Feinberg found 50 cases (0.1%) of traumatic epilepsy in
47,000 cases of head injury reported to a Swiss insurance
company. In this instance, obviously, the bckground is all
types of head injury. This unusually low incidence has been
severly criticised by Garland (1942) on the ground that
idiopathic epilepsy alone occurs more frequently in the general
population. Feinberg's figures however, give the cases of
traumatic epilepsy after deduction of cases of epilepsy of
other kind (70 cases) and it should be taken into account
that idiopathic epileptics with early onset of fits would
not have been insured by the company. These figures therefore
are the largest unselected group of head injury figures we
possess at present, with regard to civil incidence.
Penfield (1944) in an analysis of 4o7 cases of head injury
followed up over a 2 - 14 year period found an incidence
of 2.7%. Penfield did not include in this "early fits" which

he considered as a symptom only. Were these included the
total incidence would be 5.2%.

Figures consequent to war injuries: The incidence of
epilepsy consequent to war wounds is much higher than that
recorded above during peace time. Allen (1906) notes that
among 167 skull injuries of the American Civil War 23 or 13.7%
were on the pension list because of epilepsy. Among 571 cases
of recovery from gunshot wounds of the skull in the Franco
Prussian War, as reported by von Bergmann for the German Army
25 or 4.3% developed epilepsy. If to these cases of epilepsy
there be added those with periodic attacks of dizziness,
numbness, trembling etc the percentage is raised to 26.7%.
In the Russo Japanese War, Eguchi found 35 cases among 1,000
skull injuries (3.5%), but two years later Holbeck succeeded
in tracing 65 cases which he had treated in the same war. Of
these 19 or 29.2% had become epileptic (Lenormant).

The first World War provided abundand material for the
study of this problem, yet the results recorded are very
discordant.
Sargent and Holmes (1916), reporting on 610 cases, only 15%
of which had been followed for more than a year, found 37
epileptics, 6%. Eight of these cases, however, had had only
one seizure; in 11 only were convulsions frequent.
Behaque (1919) in a comprehensive study of the cases in
P.Marie's clinic, numbering 3,623 head injuries, found an in-
cidence of 12.1% of epilepsy. Two thirds of the cases were
generalised, the remaining third were Jacksonian. Lenormant

Lenormant (1921) produced the following figures:

French:

    Souques, 9 in 33, 18%

    Chiray, 57 in 276, 20.8%.

    H. Claude, 24 in 247, 10%.

    Villaret, 53 in 256, 20.7%.

    Babinski, F. Netter, 34 in 150, 22.6%.

    Carriere, in a collection of one thousand wounded, 6%.

    Sollier, 15%.

    Tuffier and Gullain, 676 in 6,664, 10.4%.

    Billet (Statistique de l'Autochir. 6) 26 in 167, 5%.

Belgian:

    Derache, 2 in 24, 8.3%.

    Janssen-Denot, more than 10%.

American:

    H. Neuhof, 3 in 175, 1.8%.

English:

    W.W. Wagstaffe, 9 in 710, 1.3%. (See text)

German:

    Roper, 16 in 134, 11.9%.

    Tilman, 15-20%.

    Amelung, 74 in 520, 14.2%.

This compilation must be taken in conjunction with the figures presented in later studies.

Rawlings (1922) among 452 British cases found an incidence of 25%. These results were based upon a questionnaire sent out to 750 men. The results cannot therefore be regarded as entirely reliable but they are of value because a slightly longer time had elapsed since injury than in most of the studies mentioned above.

Turner (1923) in a review of 18,000 cases of gunshot wound of the head among British troops found that only 800 or 4.5% had become epileptic.

Falling between the percentages of Rawlings and Turner is that of Wagstaffe (1928). This was a thorough study with an eleven year survey period. Of a total of 377 cases of all kinds (penetrating dura, fractured skull but dura not penetrated, scalp wound only, concussion and fractured bone), 37 or 9.8% developed seizures.

Schönbauer (1929) cites 95 cases of Bouskin, of gunshot wound of the head, 32 of which developed late epilepsy. He refers also to 43 cases of Bychovsky reported in 1925. Of these 16 or 37% were suffering from Jacksonian attacks.

Steinthal (1929) on the basis of the 639 surviving gunshot wounds studied so carefully with Nagel two years previously arrived arrived at a figure of 28.9% or 185 cases of epilepsy. If von Bergmans inclusion of cases of dizziness, numbness etc are included the percentage is raised to 35.5%. If one compares the figures of Wagstaff with those of Steinhal there appear great differences.. The German incidence (28.9%) is three times that of the British (9.8%). Steinhal maintains that wounding of the dura plays little part whereas Wagstaffe finds epilepsy ten times more common after penetrating

wounds of the dura than after non penetrating. These
striking differences can only mean lack of a common basis
for classification and interpretation.

The last reported follow up study of wounds resulting from
World War 1 is that of Ascroft (1941) who investigated 317
cases. The material did not include those who died within the
first few years as a result of head injury. It is not easy,
as a rule, to determine from questionaires or perhaps records
whether or not a patient has had fits, but it is reasonably
safe to assume the fits to be genuine when they are accepted
as an attributable disability by medical boards. The majority
of the men in this series of Ascroft had been admitted to
Ministry of Pension Hospitals for observation, often for
long periods. Of these 317 cases 107 or 34% had fits. Ascroft
is confident this is not an overestimate. He goes on to demonst-
rate quite clearly that fits are twice as frequent when the
dura is penetrated. Nearly half (45%) of such cases were
affected. The relation between sepsis and the incidence of
fits is also stressed by Ascroft. In his series fits developed
twice as often in cases of severe and prolonged sepsis as in
those healing by first intention. This fact he convincingly
demonstrates by analysis of his figures. Since both fits
and sepsis are commonest when the wounds are deep and severe
the apparent relation between sepsis and fits might be
fictitious. He therefore grouped the cases according to the
integrity of the dura mater and showed that the same
relationship held.

Relationship between epilepsy and wound sepsis (Ascroft)

Dura intact	Healed in 15 days	12%	
	Unhealed in 60 days	32%	
			% with fits.
Dura penetrated	Healed in 15 days	36%	
	Unhealed in 60 days	57%	

The importance of injury to the dura had been appreciated by Sargent (1921) and by Foerster and Penfield (1930) and was clearly demonstrated in an analysis of gunshot wound material from the 1914-18 War by Credner (1930). This series numbered 1980 cases, with at least five years follow up,331 for more than ten years. Credner states implicitly that they are all serious head injuries and excludes those with loss of consciousness of brief duration and without neurological findings. Of the whole group, 755 or 38.2% became epileptic. Open brain injuries (dural wound) - 1234 cases - 49.5% fits. Skull injuries without brain damage - 417 cases-20.3% fits. The statistics of Credner closely parallel those of Ascroft (1941) and the material from which they are drawn is very similar.

Reviews of the results of cranio cerebral injuries sustained in World War II have made their appearance during the past few years but it is as yet too early to make a final assessment. Malty (1946) found 17% of 250 penetrating wounds to the head had had convulsions, but his cases were only followed for a short time. Watson (1947) summarised the results of a study dealing with the incidence of "late" epilepsy among 279 penetrating head injuries resulting from the 1939-45 war. The follow up period was two years. In all of the cases seizures continued and they were not included

in the analysis if they did not have recurrent paroxysmal
disorders of the same type. Of the 279 cases followed 36.2%
developed seizures within the first two years following
injury. In a review of 100 cases with surgically proved
dural penetration and injury to the brain due to shell
fragments or gunshot Aita (1948) reported that 34% had
had at least one convulsive seizure since injury.
Ritchie Russell (1951) reviewed 820 cases of brain
wounds, and found that 43% had had one or more fits
within the first five years after wounding. All of
these wounds were'penetrators'. Russell himself suggests
that this information cannot be considered too accurate
as many of the cases had to be assessed from questionaire
or 'fit form',but he believes that the incidence he presents
is an underestimate, as all the doubtful cases went into the
"no epilepsy" group. He further states that these figures
show no striking change from the published records following
the first world war, and this in spite of the vastly reduced
incidence of infection in his series.

It will be easily seen, therefore, that of all the difficult
questions surrounding the problem of traumatic epilepsy, the
most difficult is the simple statistical estimate of its
frequency. As shown above , the published figures vary
from 49% to I in I000 cases of head injury. The wide
variation is in part only due to selection. Much depends
on what one means by head injury and probably much more
on what cases are counted as remaining free from epilepsy.

At one extreme is the objection that the experience of
an operating military surgeon would include only severe
head injury with much brain damage; at the other extreme
is the fact that an investigator can hardly scrutinise,
with a reasonable degree of accuracy, such a large mass
of material as 17,000 or 18,000 cases.

THE PHYSIOLOGY OF THE ADRENAL CORTEX AND THE
BIOLOGIC PROPERTIES OF CORTISONE

Cortisone is the name given to a compound which has

previously been referred to as 17 - hydroxy - 11 - dehydro-

corticosterone or as "Kendall's compound E".   The iso-

lation and characterisation of its general physical and

chemical properties was accomplished independently by Mason,

Meyers and Kendall, Wintersteiner and Pfiffner, and Reichstein

(1936).   Partial synthesis of cortisone has been accomplished
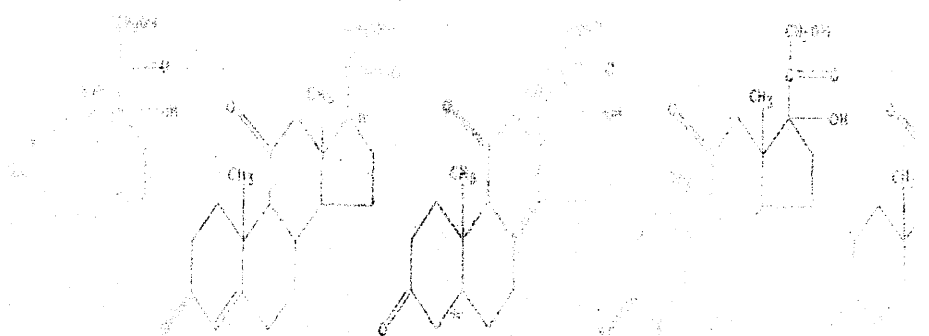
by Sarett (1946).

The physiological effects of cortisone and its use in

the treatment of diseases are closely interwoven with our

knowledge of the pituitary-adrenal system.   It is possible

as a result of the advances of the past 20 years to present

a satisfactory although incomplete account of the secretory

activities of the pituitary and the adrenal cortex.   In

contrast, there is glaring deficiency in our knowledge con-

cerning the mechanism of action of the cortical hormone on

the target cells.   Two fundamental principles of adreno-

cortical physiology have been emphasised by Ingle (1950):-

1) No fixed amount of cortical hormone represents a physio-

logical dose; the needs of the organism vary widely, depending

upon the activity and the environment of the organism.   A

dose which is pharmacological under optimal conditions may be

less than adequate for the needs of the tissues during stress

and may not prevent the development of hypocorticism.
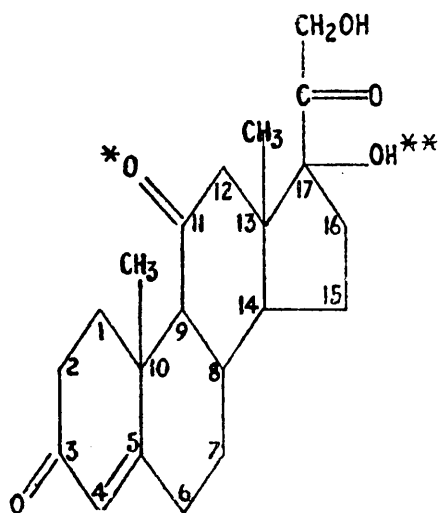
TABLE   9.
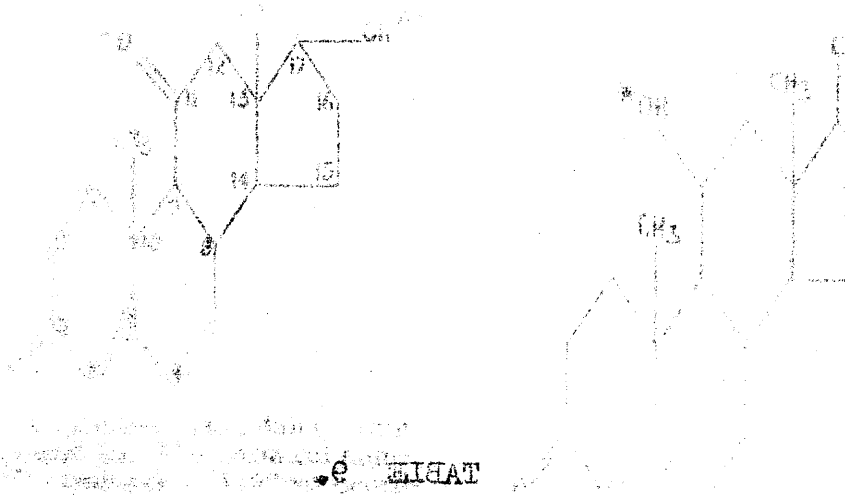
The structure of cortisone and

related compounds.

Cortisone (Kendall's compound E). The chemical name, 17 - hydroxy - 11-dehydrocorticosterone, is based upon points of difference and similarity between the molecular structures of cortisone and corticosterone (Kendall's compound B).
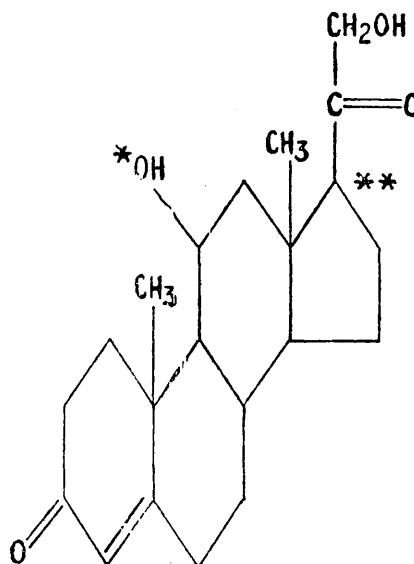
Corticosterone (Kendall's compound B)
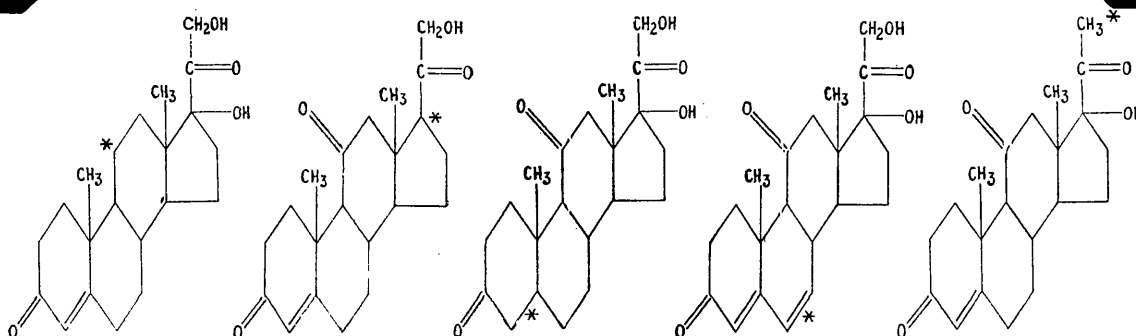
Reichstein's compound S (11-desoxy-17-hydroxycorticosterone, or "desoxycortisone"). *Molecule differs from cortisone only by the absence of an oxygen atom at position 11.

Kendall's compound A (11-dehydrocorticosterone). *Molecule differs from cortisone only by the absence of a hydroxyl group at position 17.

Dihydrocortisone. *Molecule differs from cortisone only by absence of a double bond at position 4, 5 (presence of an extra hydrogen atom).

6, 7 - Dehydrocortisone. *Molecule differs from cortisone only by presence of a double bond at position 6, 7 (absence of a hydrogen atom).

21 - Desoxycortisone. *Molecule differs from cortisone only by the absence of an oxygen atom at position 21.

2) The actions of the cortical hormone are determined in no small measure by the functional status of the tissue cells themselves.

It should be realised that the cortical hormone plays a general supportive rather than an initiating role in bodily processes.   The adrenal medulla initiates cellular and metabolic changes in response to an emergency, whereas the adrenal cortex plays a passive role and makes it possible for the various regulatory systems to expend the additional effort necessary for homeostatic adjustment.

The secretion of the adrenal cortex.

The exact nature of the secretion of the adrenal cortex is unknown.   Present estimates regarding the number and character of steroids elaborated by the gland are purely conjectural and are mainly based on indirect evidence. Twenty eight crystalline steroids have been isolated from adrenal tissue, but this contributes little to the knowledge of the nature of the actual secretion of the gland.   Many of the steriods isolated from the gland may represent inter- mediates in the synthesis of the cortical hormone or artefacts arising from the manipulations of the chemist.

(1) Multisteroid concept.   Selye, in an attempt to explain the variety of metabolic patterns which the organism may assume under different environmental conditions, has postulated

the secretion of a "glucocorticoid", a "mineralocorticoid",
a "lipocorticoid" and a testocorticoid". This concept implies
that the secretion of the adrenal cortex may vary in composi-
tion according to the requirements of the organism.

(2) "N and "S" hormone concept. Albright (1947) has
presented good evidence to support the view that the adrenal
cortex secretes an "S" hormone (cortisone like compound) and
an "N" hormone having the anabolic properties of an androgen.
He believes the "S" hormone to be secreted under the influence
of an adrenocorticotrophin and the "N" hormone under the in-
fluence of pituitary luteinizing hormone.

(3) Autonomy concept. It is known that following hypo-
physectomy the glomerulosa zone of the adrenal cortex thickens,
whereas the fasciculata shrinks markedly and the reticularis
disappears almost entirely (Deane 1946); phosphatase disappears
from the zona fasciculata but persists in the zona glomerulosa.
These observations have led Greep and Deane (1947) to assign
to the glomerulosa zone the specific function of autonomously
elaborating hormone regulating electrolyte balance; ACTH is
limited in its action to the fasciculata from which is
secreted hormone influencing carbohydrate metabolism. This
concept implies that the character of a metabolic disturbance
can determine the nature of the secretion of the adrenal cortex.

(4) Unitarian concept. This point of view regards the
secretion of the adrenal cortex as relatively fixed in

composition but varying in rate.   Furthermore, the
possibility is entertained, without conclusive evidence,
that a single steroid can account for all the metabolic
activities of the gland.   At first it is tempting to
divide the various metabolic actions of the adrenal cortex
among the 11,17-oxysteroids, D.C.A. like steroids and
androgens.   The conclusion has been reached by many that
at least two major types of steroids 11, 17-oxysteroids and
D.C.S. like steroids must be secreted by the gland in order
to explain the diabetogenic as well as the sodium-retaining
properties of ACTH in man.   However, Forsham has shown
(1949) that cortisone can induce sodium retention in patients
with Addison's disease.   Among clinical investigators, the
impression seems prevalent that the normal adrenal cortex
secretes androgen.   None the less, the experimental and
clinical data presented in support of this view may be ex-
plained just as reasonably on the basis of conversion of
cortical hormone to androgens by the liver or other tissues.

The nature of the secretion of the adrenal cortex,
therefore, remains in doubt.   Analysis of adrenal effluent
blood may help solve the problem and Nelson et al (1950)
have already found only 17-hydroxy-corticosterone and possibly
a small amount of cortisone in adrenal vein blood of the dog.

Regulation of the rate of secretion of adrenocortical hormone.

PITUITARY-ADRENAL RELATIONSHIP

TABLE 10.

Schematic representation of the
pituitary adrenal relationships
as commonly accepted. See text
for discussion and analysis.

Aldosterone
Progesterone (?)
Cortexone (?)
adrenal sex hormones

11β, 21 dihydroxy-
pregnan-3,20-dione
(hormones affecting
electrolyte balance)

Cortisone (compound E)
and
17-hydroxycorticosterone (compound F)
(hormones having therapeutic effects described
herein, and affecting carbohydrate, protein, and
electrolyte metabolism)
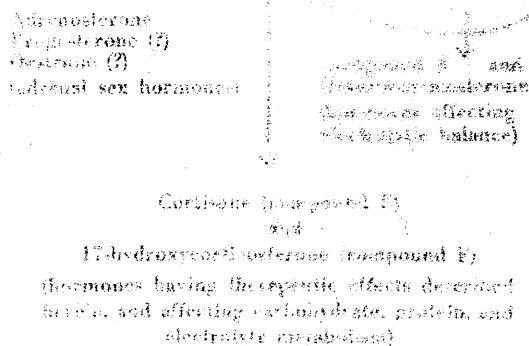
TABLE 10.

Schematic representation of the
pituitary adrenal relationships
as commonly accepted. See text
for discussion and analysis.

PITUITARY—ADRENAL RELATIONSHIPS

Higher
brain
centres

Hypothalamus

Direct or indirect
humoral pathway

Anterior
pituitary

Adrenaline

Stress

Adrenocorticotropic hormone
(humoral pathway)

Adrenal cortex

Medulla

Adrenosterone
Progesterone (?)
Oestrone (?)
(adrenal sex hormones)

Compound S and
Desoxycorticosterone
(hormones affecting
electrolytic balance)

Cortisone (compound E)
and
17-hydroxycorticosterone (compound F)
(hormones having therapeutic effects described
herein, and affecting carbohydrate, protein, and
electrolyte metabolism)

(1) <u>Pituitary regulation of secretory activity of the</u>

<u>Adrenal Cortex</u>.

It has been firmly established that the discharge of ACTH

from the adenohypophysis is an essential link in the series

of events, initiated by stress, which activate the adrenal

cortex.(Deane 1946, Ingle 1938)

The trophic factor which stimulates the adrenal cortex

has been isolated as a homogeneous protein from sheep(Li,

1943) and hog (Sayers 1943) pituitary tissue.   No substance

other than ACTH has been demonstrated to have a direct trophic

action on the adrenal cortex.   There is no evidence from

chemical fractionation studies to support the opinion of

Selye that the pituitary elaborates a "glucocorticotrophin",

a "mineralocorticotrophin", a lipocorticotrophin" and a

"testocorticotrophin".

(2) <u>Regulation of Pituitary Adrenocorticotrophic activity</u>.

The question next arises as to the nature of the regulatory

mechanism which determines the rate of discharge of ACTH.

(1) A considerable body of indirect evidence can be

marshalled in support of the concept that the titer of

cortical hormone in the body fluids regulates the rate of

discharge of ACTH from the adenohypophysis (Sayers 1950 .

Discharge of ACTH in response to moderate stress may be

completely or partially blocked, depending on the dose of

cortical steroid administered.   Furthermore, with increasing

TABLE 11.
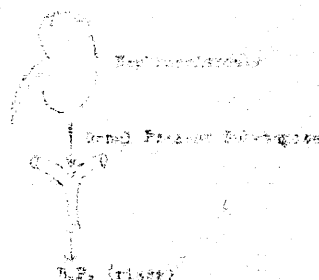
A diagrammatic representation of
Selye's concept of stress.

TABLE 11.

A diagrammatic representation of
Selye's concept of stress.

STRESSOR

Damage or Shock   ?

Lyophilized   ACTH
A.P. Extract

DCA   Cpd E (Glucocorticoids)
        Cpd F

Blood Count
(e.g. Eosinopenia)

Thymo-Lymphatic
   Involution
Reticulo-Endothelial
      System

Nephrosclerosis

Renal Pressor Substances

B.P. (rises)

COLLAGEN TISSUE
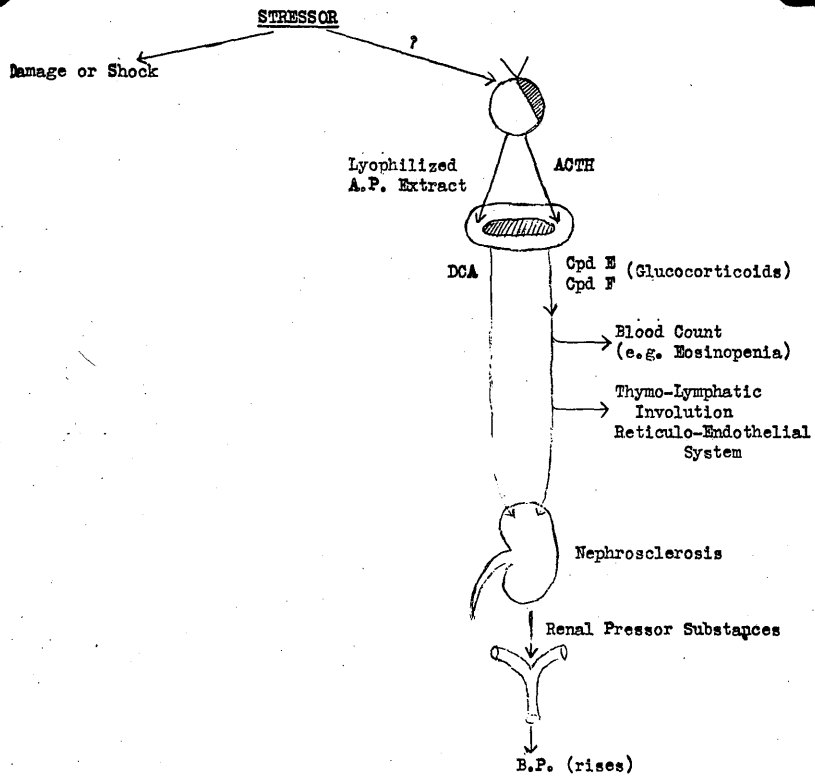
increases → Fibroplasia ← decrease
DCA   Glucocorticoids
increases → E.S.R. ← decrease
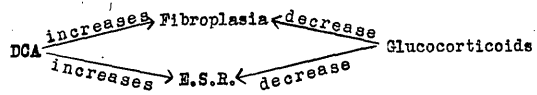
intensity of stress, the amount of cortical steroid required to suppress pituitary adrenocorticotrophic activity becomes correspondingly greater (Sayers and Sayers, 1947).

These quantitative relationships may be adequately explained if it is assumed that the rate of discharge of ACTH from the adenohypophysis fluctuates in accordance with the varying requirements of the organism for cortical hormone. This peripheral-humoral concept of regulatory control considers the activity of the adrenal cortex to be dictated by the requirements of the tissue cells of the organism for cortical hormone. The cortical hormone may act directly on the hypophysis or indirectly through some metabolite which varies in concentration as a result of the excess or a deficiency of the hormone. The multitude and complexity of changes which can occur in the blood bathing the pituitary gland forbids a ready answer to the problem. The peripheral humoral concept implies that a normal pituitary adrenocortical system does not allow an organism to be subjected to a plethora of cortical hormone, such as is suggested by the "diseases of adaptation" thesis of Selye.

(2) <u>Central-neural and Central neuro-humoral mechanism.</u>

The rapidity with which ACTH is released in response

to stress suggests the possibility that a neural or neuro-humoral factor is involved in acute situations. From the work of Cheng et al (1949), it is obvious that the integrity of neural or of neuro-vascular links between the hypothalamus and adenohypophysis is not essential for the discharge of ACTH. The experimental evidence, however, does not rule out the possibility that neural factors may modify the rate of discharge of ACTH from the pituitary.

(3) The role of the sympatho-adrenal system.

The close anatomical approximation of the adrenal medulla and cortex together with the fact that they both play important rôles in homeostasis naturally leads to some speculation regarding a possible integrative functional relation between the sympatho-adrenal and pituitary-adrenocortical systems. Vogt(1944) reached the conclusion that epinephrine has a direct stimulatory effect upon the adrenal cortex. Her experiments, however, do not rule out the possibility that epinephrine acts via the adenohypophysis to bring about a discharge of ACTH. Epinephrine may induce discharge of ACTH from the adenohypophysis by any of the following possible mechanisms:-

1) By central action on effector cells in the adenohypophysis or through the hypothalamus which in turn would activate the adenohypophysis.

2) Epinephrine may act like other non-specific
agents and stresses to increase tissue utilisation
of cortical hormone with a consequent lowering of
venous titer of the hormone.

3) Epinephrine may be the denominator common to all
types of stress and the specific agent which promotes
utilisation of cortical hormone by the tissues.

Sayers (1948) and Long (1947) have suggested that
epinephrine acts like other non-specific stresses and does
not have a direct action upon the pituitary.

The nature of the regulatory mechanism or mechanisms
which are concerned with the discharge of ACTH has an
important bearing on the treatment of collagen diseases.
The beneficial effects of cortisone or ACTH appear to be
associated with the development of hypercorticism rather
than replacement of a hormone deficiency.   The possibility
has been entertained that epinephrene, a substance more
readily obtainable than cortisone or ACTH might be of thera-
peutic benefit by stimulating the discharge of ACTH from
the pituitary.   Epinephrine may be expected to be of
therapeutic benefit if it acts centrally to bring about
discharge of ACTH without regard to the rate of utilisation
of cortical hormone by the tissues or to the titer of
hormone in venous blood.   On the other hand, if epinephrine
acts by increasing the rate of utilisation of cortical hormone
by the peripheral tissues, then it would be expected to be

of slight benefit at most; for the tissues will not

be flooded with an excess of cortisal hormone, but

rather they will receive quantities of hormone appro-

priate to the increased needs induced by epinephrine.

The titer of cortical hormones in the body fluids

appears to play a major role in the regulation of

pituitary adrenocorticotrophic activity. The exact

nature of the process by which the changing levels

of cortical hormone in the blood influence the rate

of discharge of ACTH from the adenohypophysis is un-

known; it is here that the peripheral humoral concept

is particularly vague.

Increased rate of utilisation of cortical hormone during stress.

At the present time, it is not possible to deter-

mine whether the increased rate of "utilisation" of

cortical hormone which accompanies stress is

1) shared by all cells of the organism,

2) involves only those cells affected by

the stress stimulus,

3) is participated in by both injured cells

and buffer organs attempting to restore homeo-

stasis.

Despite the lack of particulars, certain broad aspects

of the problem of cortical hormone "utilisation" in

stress are worthy of consideration. In general, it would appear that rate of cortical hormone "utilisation" parallels cellular activity and that the hormone is necessary for the mobilisation of cellular work. (Means, 1949; Ingle, 1938).

The indices of the rate of secretion of adrenocortical hormone.

It may be stated that there is no entirely satisfactory method for measuring the secretory activity of the adrenal cortex. Indices for the assessment of adrenocortical activity may be classed under four general headings, according to whether measurement is made of:-

a) alterations in the adrenal cortex.

b) alterations in the organism

c) rate of excretion of steriods in the urine.

d) titer of corticoids in the blood.

Continued hyperactivity of the adrenal cortex is associated with an increase in the size of the gland.(Tepperman,1943). Histological techniques have been employed to measure fluctuations in the secretary activity of the adrenal cortex and to differentiate the zones of the adrenal cortex in regard to functional activity. (Sayers,1948; Deane, 1948). Dougherty and White (1947) have shown that circulating lymphocytes are under the regulatory control of the adrenal cortex and this has made available

a valuable tool for the measurement of the activity of adrenal cortex. The phenomenon is initiated by the discharge of ACTH from the adenohypophysis. But this must be accepted with dertain precautions since a few agents, e.g. X-irradiation and urethane, have a direct lymphocytolytic action as shown by the lymphocytopenia they produce in adrenalectomised animals. Hills et al (1948) observed that the number of circulating eosinophils is determined by the activity of the pituitary-adrenocortical system and this has made available a very simple method for assessing adrenocortical function. Following the administration of ACTH, the drop in the number of eosinophils, expressed in percentage of the pre-injection count, is approximately twice as great as the drop in the number of lymphocytes; furthermore, the eosinophil response is believed to be less variable than the lymphocyte response (Forsham,1948). In man, absence of an eosinopenia following the administration of ACTH, is indicative of adrenocortical insufficiency (Thorn, 1948). It should be borne in mind also that eosinophils are influenced by factors other than the secretion of the adrenal cortex.

Substances are present in human urine which exhibit certain properties of the cortical hormone. Corticoids which have like biological properties and which are

determined by bioassay may be designated "biocorticoids" and those which have similar chemical properties and which are determined by chemical assay may be designated "chemocorticoids". Obviously, the two groups overlap considerably. The other index which has been much used to date is analysis of urinary 17-ketosteroid output. Sayers (1950) believes this method should be rejected as an index of adrenocortical activity, not because of the uncertainty of its physiological significance, but because of the lack of correlation between the rate of 17-keto-steroid excretion and adrenocortical activity as deter-mined by other means. Considerable confusion has arisen in the clinical literature due to misinterpreta-tion of the significance of urinary 17-ketosteroids.

BIOLOGIC ACTIONS OF CORTISONE.

Hyman and Chambers (1943) noted that adrenal cortex extracts and certain steroids reduced the rate of oedema formation in perfused frog legs. Opsahl (1949) reported effects of adrenal cortical insufficiency, adrenal cortex extracts and steriods upon the spreading action of hya-luronidase. In studies upon mice, it was found that the dermal spread of India Ink was enhanced by adrenal-ectomy, whereas the administration of adrenal cortex extracts to either normal or adrenalectomised mice inhi-bited spreading. It was also found that adrenal

cortical extracts inhibit the intradermal spreading of India Ink enhanced by hyaluronidase. (Opsahl,1949).

Seifter et al (1949) observed that hyaluronidase reversibly accelerates osmosis and abolishes the semi-permeable nature of membranes prepared from the excised bladder of rats. Adrenal cortex extract and oestrone antagonised the effect of hyaluronidase upon the permeability of bladder membrane, whereas 11-desoxycorticosterone enhanced the action of hyaluronidase. In a further study of the effects of hyaluronidase and steroids upon permeability, phenolsulphonphthalein was injected into the joint of a rabbit, and its speed of absorption through the synovial membrane was measured by determining the time and rate of its excretion in the urine. Hyaluronidase markedly increased the permeability of the synovial membrane. The compound 11-desoxycorticosterone acetate also increased permeability, but when given in addition to hyaluronidase, there was no additive effect. Cortisone acetate and, to a lesser extent, adrenal cortex extract were effective in decreasing the permeability of the synovial membrane (Seifter et al 1949). These substances are considered to affect permeability by acting upon the hyaluronate of the ground substance of the membranes.

Organic Metabolism.

Immature adrenalectomised rats treated with cortisone

TABLE 12.

Current concepts of the endocrine control

of protein metabolism.

Pyruvic Acid
Succinic Acid
or other Carbon
Skeltons

TABLE 13.

Diagrammatic representation of the role

of the adrenal cortex in the blood

sugar regulating mechanism.
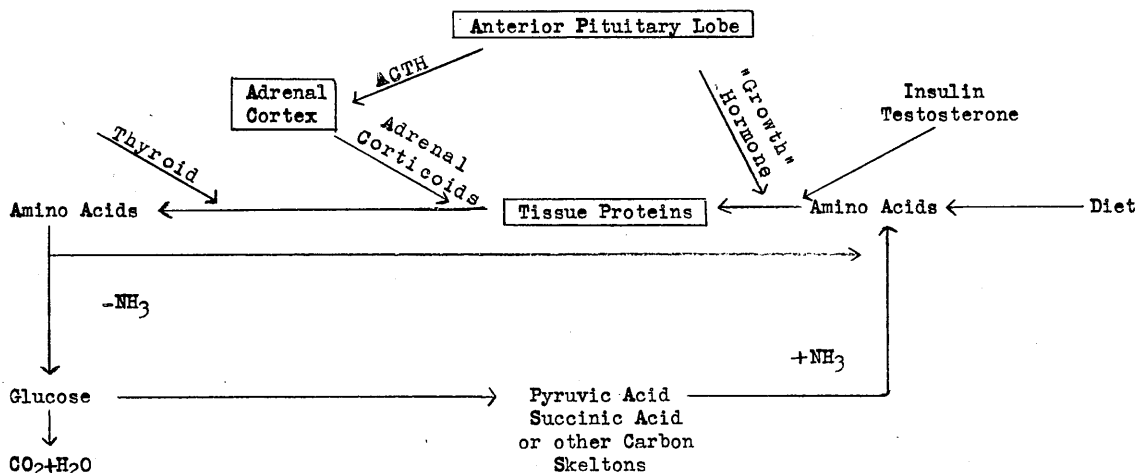
(after Thorn, 1950).

TABLE 12.

Current concepts of the endocrine control
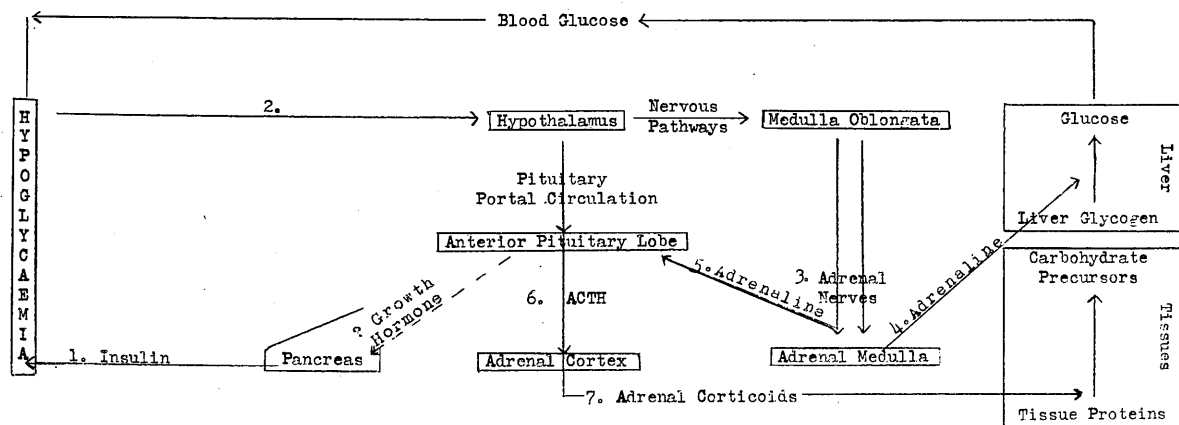of protein metabolism.

TABLE 13.

Diagrammatic representation of the role
of the adrenal cortex in the blood
sugar regulating mechanism.

(after Thorn, 1950).

B. Endocrine Control of Protein Metabolism

Anterior Pituitary Lobe

Adrenal Cortex

ACTH

Adrenal Corticoids

Thyroid

"Growth" Hormone

Insulin
Testosterone

Amino Acids ← ←— Tissue Proteins ← Amino Acids ← Diet

$-NH_3$

$+NH_3$

Glucose ——→ Pyruvic Acid
Succinic Acid
or other Carbon
Skeltons

CO_2+H_2O

C. Blood Sugar Regulating Mechanism

Blood Glucose ←

H Y P O G L Y C A E M I A

2.

Hypothalamus

Nervous Pathways

Medulla Oblongata

Glucose

Liver

Pituitary Portal Circulation

Anterior Pituitary Lobe

Liver Glycogen

Carbohydrate Precursors

? Growth Hormone

6. ACTH

5. Adrenaline

3. Adrenal Nerves

4. Adrenaline

Tissues

1. Insulin

Pancreas

Adrenal Cortex

Adrenal Medulla

7. Adrenal Corticoids

Tissue Proteins

in doses of 0.25 to 1.0 mg. daily are able to survive
and grow but at a subnormal rate (Kuizerga, 1943).
Larger doses of cortisone inhibited growth in immature
normal rats. (Wells,1940). Cortisone has been shown
to fail to sustain growth in young, sexually mature
adrenalectomised rats at any dosage level. Ingle (1941)
Winter (1951) treated young male rats for a period of
six weeks with 3 mg. of cortisone acetate daily and showed
that growth ceased during this period. When the injec-
tions were stopped, growth was resumed. Addis (1950) found
that the normal rat responds to the injection of hog renin
by developing an intense proteinuria. Karnofsky, Stock
and Rhoads (1950) injected cortisone acetate into the
yolk sac of the 4-day chick embryo. At a dose of 1 to 2
mg. per egg, there was a marked retardation of the growth
of the embryo. Karnofsky (1950) also demonstrated
that cortisone acetate and 17-hydroxycorticosterone inhibit
the growth of the young chick.

Whitaker and Baker (1948, 1949) noted that the per-
cutaneous application of cortisone had a local inhibitory
effect upon the growth of hair. Baker and Castor (1950)
made a study of the cutaneous atrophy induced by the
percutaneous application of a highly concentrated extract
of adrenal cortex in the rat. Following the cessation
of hair growth, thinning of the epidermis occurred and
there was a reduction in cellularity of the connective

TABLE 14.

The final common pathway of metabolism
showing the relatioships of carbohydrate
protein and fat.

METABOLISM

A. The Final Common Pathway of Metabolism

CARBOHYDRATE   FAT

Serine ⟶

Alanine ⇌ Pyruvate

Cysteine
Cystine
Methionine

Aspartic acid ⇌ Oxal acetate ——— + ——— Aceto acetate ⟵ Leucine
Isoleucine
Tyrosine
Phenylalanine

Isocitrate

Malate α-Ketoglutarate ⇌ Glutamic acid

Fumarate   Succinate   Histidine
Proline
Hydroxyproline
Arginine
Ornithine
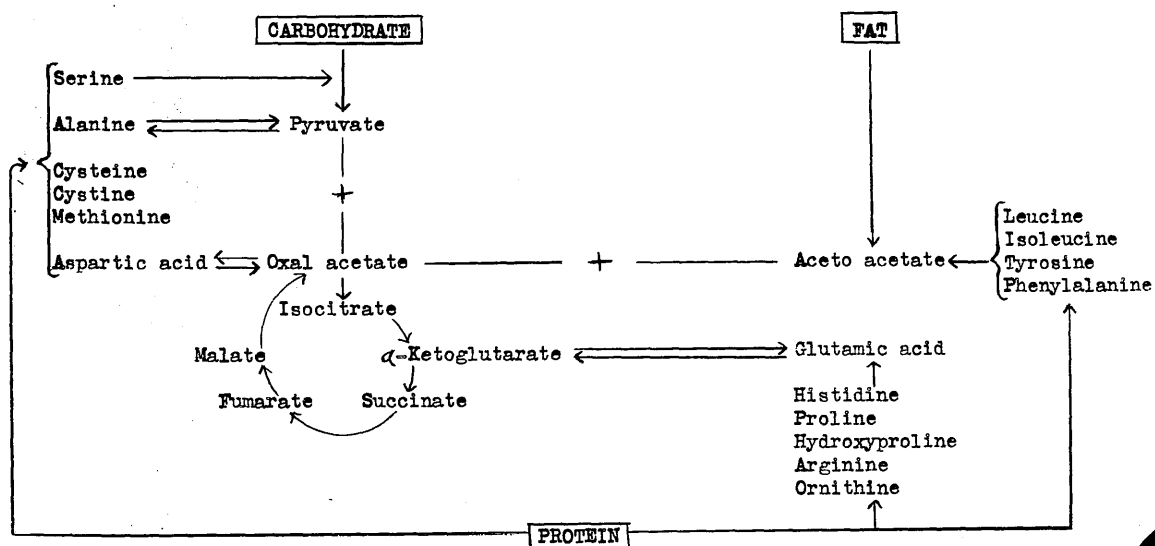
PROTEIN

tissue. However, elastic fibers were not reduced by the treatment. Baker and Castor concluded that the 11-oxygenated steroids may act directly on the protein of intercellular structures and the epithelial cells. Winter et al (1951) observed cessation of hair growth during the subcutaneous administration of 3 mg. of cortisone acetate daily in the young male rat.

Schneebeli (1950) has noted specific alterations in the fibroblasts of loose connective tissue following the administration of cortisone acetate to adrenalectomised mice. There were changes in the amorphous ground substance and striking alterations in the fibroblasts four hours after the administration of cortisone acetate. Blunt (1950) administered 25 mg. cortisone acetate daily to rabbits for 3 days prior to fracturing of the femur and thereafter until the animals were killed. Up to the fourth post-fracture day, the inflammatory and reparative responses of connective tissue were the same in both control and cortisone treated animals. After four days, however, there was retardation of all phases of healing in the cortisone treated animals. For example, new blood vessels were more numerous in the control animals.

Ragan (1949) noted that biopsy wounds failed to heal in patients with different diseases treated with

ACTH.   Howes et al (1950) investigated the healing

of skin defects in the ears of rabbits under the in-

fluence of cortisone.   These defects still had blood

vessels completely uncovered by granulations (8 days

after wounding) with doses varying from 6 - 10 mgm/kg.

body weight, daily, the cortisone having been started

three days before wounding.   Microscopically, the

tissues in the base of the wound did not increase in thick-

ness.   They contained dilated, large blood vessels sur-

rounded by an increased cell population of round cells and

fibroblasts with small nuclei.   No new blood vessels or

new reticulin fibrils were present.   Mucopolysaccharides

were diminished.   Some new granulations appeared,

however, under the epithelium that advanced slightly from

the edges of the wound.   Smaller doses 2-3-6 mgm/kg.

delayed the onset of the appearance of granulations for a

shorter length of time.   Cancellation of the Cortisone

resulted in the reappearance of granulations four or five

days later.   These same workers noted delay in the

healing of fractures in the rabbit, using the same scale

of dosages, and also that haemorrhage was more slowly

absorbed in the cortisone treated animal.

Baker and Ingle (1948) reported an increase in the

compactness of the connective tissue fibers of the dermis

following daily treatment of rats with 1 - 3 mgm. of

adrenocorticotropin for 21 days. Baker and Whitaker (1948) also demonstrated that adrenocortical steroids inhibit growth of hair and epidermis by local action.

The question which then arose was whether the retardation in growth of tissue resulted from a generalized disturbance of protein metabolism (as indicated by excess excretion of nitrogen) or by direct action of adrenocortical hormones on the peripheral tissues. Baker and Whitaker (1950) tackled this problem by applying directly hog adrenal extract dissolved in 25% alcohol to cutaneous wounds in the rat. They found some delay in closure of the wound, but the treatment did not counteract completely the stimulation to growth caused by cutting the skin. The daily doses were equivalent to 100 or 200 mg. of cortisone. Nevertheless, a definite interference in formation of granulation tissue resulted from this treatment, the effect being limited to the area of treatment. It must be noted that using cortisone itself no significant results could be obtained in this experiment.

Taubenhaus showed (1949) that in granulation tissue accumulating around abscesses induced by turpentine injections in rats, fibroblastic proliferation was profoundly stimulated by the injections of DCA but suppressed to an extreme degree by the prolonged administration of sex

hormones.   In order to determine, if possible, whether these effects might be the result of inhibition of the anterior pituitary or a direct peripheral action of steroids he attempted (1950) to analyse the separate influences of the anterior pituitary, the thyroid, the adrenal cortical hormones, and the sex steroids upon the structure of granulation tissue.

It appeared that hypophysectomised rats failed to develop significant amounts of granulation tissue.   He concluded that the thyrotropic hormone acted synergistically with the growth hormone, and that they were important factors in promoting the growth of granulation tissue. This is in agreement with the findings of Smith (1933). Cuthbertson (1941) failed to find any influence of pituitary extracts upon wound healing but he used a crude extract in which the exact content of active pituitary hormones was unknown.

Taubenbaus (1950) showed that D.C.S. when administered simultaneously with the development of the turpentine abscess, produced the stimulating effect to a much lesser degree than described before (1949), when the animals had been pretreated with D.C.S. for 3 days.   This would indicate that some mechanisms other than direct influence upon granulation tissue must be set into function which ultimately produces the stimulation.

Administration of the compound E oxysteroids produced a marked decrease in actively proliferating fibroblasts. There was also an absolute and relative increase of large phagocytes and less vascularisation was noted in these abscesses. (Taubenhaus,1950). Baker (1951) has shown that the direct application of cortisone to the wound inhibits granulation.

Cortisone has also been shown to inhibit the growth of tumour tissues under certain conditions. Heilman and Kendall (1944) found that cortisone caused rapid and complete regression of a transplantable lymphosarcoma in the mouse, but that tumors usually recurred and became refractory to treatment. Baker and Whitaker (1949) produced carcinomas of the skin by the local action of 3 - methylcholanthrene in mice. The direct application of solutions of cortisone inhibited the growth of the neoplasms. Ingle et al (1950) found that the injection of 5 mg. of cortisone acetate daily retarded but did not completely suppress the growth of the Walker carcinoma in force-fed rats. Higgins et al (1950) found that the administration of 1 mg. of cortisone acetate daily completely inhibited the growth of transplanted rhabdomyosarcomas in mice. When the administration of the steroid was stopped, the tumor implants began to grow. Re-institution of cortisone acetate therapy inhibited the growth of the tumors but did not cause regression.

Effects upon specific tissues.

Lymphoid tissue.   All of the known biologically
active 11-oxygenated steroids of the adrenal cortex cause
atrophy of the rat thymus when administered in high dosage.
This has been found to be true of cortisone (Winter,1951).
It is now also well established that the effects of the
11-oxysteroids upon lymph nodes and spleen are similar to,
but less marked than, the regressive changes induced in
the thymus. (Dougherty and White 1945).   Bogomolets
(1943), the Soviet scientist, regarded the reticulo-
endothelial system as a vital factor in nutrition and
repair and named it the physiological system of the
connective tissue.   Intent upon this, he developed an
apparently satisfactory antiserum specific for this
system which was presumed to act by stimulating or de-
pressing, according to dosage given, the function of
reticulo-endothelial tissue derivatives.   Strauss (1946)
studied the healing of experimentally produced fractures
of the radius and ulna in rabbits.   He concluded that
repair of fractures was facilitated by small stimulating
doses of anti-reticular cytotoxic serum (A.C.S.).
Rifkinson (1950) reported an attempt to influence the
healing of incised cerebral wounds by the administration
of ACS serum in 136 rats.   He felt that in this ex-
tensive series there were no significant differences in

the rate of wound healing that were outside the range

of the control material.   Timiras and Selye (1949)

noted a marked increase in the phagocytic activity of

the reticulo-endothelial system during the alarm reaction

in rats.   Histological examination showed increased

phagocytosis in the lung, kidneys, adrenals, bone marrow,

hibernating gland, thymus and lymph nodes.

Heilman (1945)a reported that in studies on cultures

of mammalian lymph node, cortisone decreased the relative

number of migrating lymphocytes and increased the rate of

lymphocytic degeneration.   Following this (1945)b, she

reported the effect of cortisone on the migration of

macrophages in tissue culture of normal rabbits' spleen.

The extent of migration of large wandering cells was in-

creased in cultures containing concentrations of cortisone.

It could not be determined whether the stimulation of

migration of macrophages was due to a primary effect on

the large wandering cell or was secondary to the action

of the test substances on other cells present in the

culture.

Tissue damage and unfavourable effects.

Following the preparation of biologically active

extracts of beef adrenal glands twenty years ago, the

erroneous concept developed that hormones of the adrenal

cortex do not damage the organism when administered in high dosage. Adrenal cortex extracts have seldom been found toxic because it is difficult to administer doses which exceed the normal secretory activity of the adrenal cortices of either animals or patients. In the case of the crystalline compounds of the adrenal cortex, however, it is easily possible to administer dosages which cause damage to tissues. Kochakian (1944) and Kendall (1945) each implanted pellets of cortisone in normal mice and noted the occurrence of cardiac and skeletal muscle lesions in these animals. Ingle et al (1945) adminis-tered 17-hydroxycorticosterone in doses of 5 mg. daily to normal rats and described deep ulcers in the pyloric portion of the stomach in 2 rats. Winter et al (1951) observed minor cellular damage in rats which received 3 mg. of cortisone acetate daily.

The most complete reports on the unfavourable effects of cortisone acetate in man are by Sprague et al (1950) and Hench et al (1950). The signs of cortisone excess are similar to and probably identical with the symptoms of Cushing' syndrome. Among the patients studied at the Mayo Clinic, a number exhibited rounding of the facial contours as an early sign of cortisone excess. Thinning of the skin with development of striae was observed in 6 patients treated with cortisone acetate. Muscular

weakness and signs of reduced gonadal activity appeared

in some of the patients   In general, the undesirable

effects were marked in those patients who received 200 mgm.

of cortisone acetate per day.

Although it is possible to cause pathologic changes

by the administration of very large amounts of cortisone

to animals (vide supra), and damage is more likely to

occur under certain abnormal conditions, it seems probable

that physiologic amounts and dosages equivalent to thera-

peutic doses in man do not cause any irreversible pathologic

changes.   It has not yet been determined whether or not

large doses of cortisone produce degenerative changes in

man.   None, so far, has been reported.

Methods and Materials.

In this study forty five cats were used, They were very carefully selected with regard to general fitness and freedom from infection. The operative procedure was carried out under nembutal anaesthesia; .6c. c/kg. body weight being the dose found most suitable, administered intraperitoneally During the operation the animal was placed in a standard head holder (Gage 1951). Strict aseptic technique was observed throughout. Following the operation the animal was returned to its cage, placed on a clean sheet of paper to avoid insufflation of foreign bodies and watched periodically Normal feeding was resumed as soon as consciousness returned but in some instances it was necessary to give the animals 20-30 c. c of glucose saline intraperitoneally else they deteriorated rapidly.

Operative technique.

The head was shaved and the skin prepared with application of green soap, alcohol and 'metaphen' in that order. The scalp was dressed as a sterile field. The skin and galea were divided by a longtitudinal incision about 1 cm. to one or other side of the midline. The temporal muscles were reflected by incising the fascia along the superior temporal line and separating them from the skull with a periosteal elevator.

Openings in the skull were made on one side only, usually the left, and as a rule, this was achieved by the use of

perforator and burr followed by a rongeur. The bony

defect was rectangular and averaged $2\frac{1}{2}$ cms by 1 cm. Diploic

bleeding was easily controlled by gentle suction and a minimum

of Horsley's wax. The dura was picked up, incised

longtitudinally and gently parted. In all the animals

except five, the pia-arachnoid and brain were then incised,

to the depth of 1 cm by a sharp scalpel, one incision

only being made. The length of the incision averaged

2 cms. A small piece of gelsponge which had previously

been moistened by soaking in the serebro-spinal fluid, and

corresponding to the dimensions of the incision, was placed

carefully and gently on the brain wound. Great care was

taken to see that no haemorrhage persisted. The dura was

closed using very fine sutures and eye needles, on the

average two or three sutures being used. The muscle and

fascia were approximated and the skin closed. In five

animals the wounds which were made were lacerated in type

and the cortex greatly disturbed, about $1\frac{1}{2}$ cm diameter and

some bleeding caused. A minimum of gelsponge was used

and then only to control the haemorrhage. In the series

of experiments where cortisone was applied locally to the brain

the gelatin sponge was soaked directly in the cortisone acetate

in saline, in others the acetate tablet was ground into

powder and placed sandwich fashiom between the slit layers

of the piece of gelsponge and then inserted into the wound.

In the series using the polythene film between the dura and

the brain, the incised brain wound was carried out as above and when the bleeding had been controlled and the plain piece of gelatin sponge inserted, the film was gently placed between the dura and the arachnoid, without damage to the arachnoid. The dura was sutured and in some instances when this was found to be impossible a small fascial graft was used to close the defect. In order to prevent skin infection the sutures were tied loosely in all wounds and the wound smeared with 'Nueskin', a proprietary preparation.

The animals were weighed daily. Where the cortisone was given intra muscularly or orally the dose was 10 mgm/kg body wt. Cortisone acetate (Merck brand of cortisone) was used in the form of the injectable saline suspension or in the form of tablets which contained 10 mgm per tablet. Eosinophil counts were performed periodically on all the animals. Electroencephalograms were carried out on certain animals from time to time, pre and post operatively.

Pathological Studies and Techniques.

The animals under observation were sacrificed at intervals of 5 to 43 days. Deep anaesthesia was obtained by the use of nembutal, .65 cc/kg body weight, intraperitoneally. Following this one or other carotid artery was isolated, cannulated and the head perfused with physiological saline followed by 10% formalin. Next the skin was reflected from the head. The muscle and fascia

were removed and the skull defect exposed. This

presentation was photographed. The skull was perforated,

well away from the midline, on the opposite side from

the brain wound. The top of the skull was rongeured right

the way round, slowly and deliberately, without damage to

the dura. Great care was then exercised in the removal

of the brain.

It will be evident that by this method the brain

was removed from the skull with the dura relatively

intact and with the convexity of the skull and dura

'in situ' over the brain wound. It was then a simple

matter to nibble the bone away carefully up to the linear

margin of the wound. The dura was then perfectly free

and by raising it gently the presence or absence of

adhesions could be ascertained and appropriate photographs

taken. This method was decided upon and adopted since

it was felt that by its use the least possible damage

was done to existing structures amd moreover it allowed

control over every stage of the uncovering of any adhesions

and prevented many of the little strains and tugs which

can so easily give rise to a false picture.

The brain was usually found to be sufficiently

hard and was sectioned coronally, four pieces of tissue

being obtained.

1.   Placed in 10% formalin and this block later

embedded in paraffin: H.V.G.,H.E.,P.T.A.,L.C.T.

and Weil stains were made on these sections.

2. Placed in F.A.B. with cobalte nitrate. Silver carbonate stain for oligodendroglia and microglia made.

3. In a few specimens where the cut could be made a very short time after sacrifice a piece of the tissue was placed straightaway into potassium bichromate solution and stained by modifications of the Golgi method.

4. In order to maintain the wound structures intact it was decided to embed the main block in celloidin and stain the sections thereby obtained by the Cresyl violet method.

TABLE OF ANIMALS USED.   Sept 50- Aug 51.

CONTROL.

44.51	8 days
43.51	15
28.51	24
29.51	31
22.51	40

CORTISONE by MOUTH.

132.51	8 days.
136.51	14
133.51	22
134.51	28.
137.51	36.

Intra Musc. CORTISONE.

36.51	5 days
48.51	7
46.51	15
49.51	24
35.51	35
52.51	25
51.51	37
34.51	43
83.51	50
84.51	30

LACERATED Wound with CORTISONE.

442.50	9 days	
443.50	20	
459.50	14	cortisone inj.
460.50	28	through scalp.
461.50	36	

7.51	8 days	
8.51	15	intra musc. inj.
21.51	28	of cortisone.

INTRA MUSC. CORTISONE in conjunction with polythene film.

149.51	3 days
150.51	5
246.51	8
247.51	14
248.51	21
249.51	33
250.51	45

CORTISONE LOCALLY.

120.51	7 day acetate.
125.51	14 " acetate.
124.51	28 " acetate.
126.51	21 " tablet.
127.51	14 " tablet.

EXPERIMENTAL RESULTS.

Cat. P. 44.51   Wt. 2.6 kg   Control.

Survival time - 8 days.

Gross. In this case a small fascial graft was required to help close the dura. Very soft looking adhesions were present along the entire extent of the wound between the brain and the dura.

Microscopic. There is a very considerable thickening of the meninges adjacent to the wound and extending some distance from it. There is intense phagocytosis throughout the whole wound and gitter cells are numerous. The gelatin sponge is present and is not yet invaded by phagocytes or inflammatory cells but numerous red blood cells are trapped in it. The wound is poorly demarcated from the adjacent brain tissue (fig. 5.). New capillaries are numerous, especially in the white matter. No reticulin or collagen is present.

Cat. P. 48.51   Wt. 3.6 kg.   Intra musc. cortisone.

Survival time - 7 days.

Gross. This animal had an uneventful course. A very soft adhesion was present only at the centre of the wound between the brain and overlying dura.

Microscopic. The wound is well demarcated from the surrounding brain. (fig. 6.). There is no thickening or inflammatory reaction of the meninges. Phagocytosis is present and is well marked. Inflammatory cells can be seen. The gelatin sponge is in place but appears to have been invaded by macrophages and is undergoing phagocytosis

Fig. 1.

Cat 44.51   8 day control.

This shows the histological appearance of
the incised wounds used in this study.
The gelatin sponge is easily recognised
lying in the wound.

HVG,   x 42.
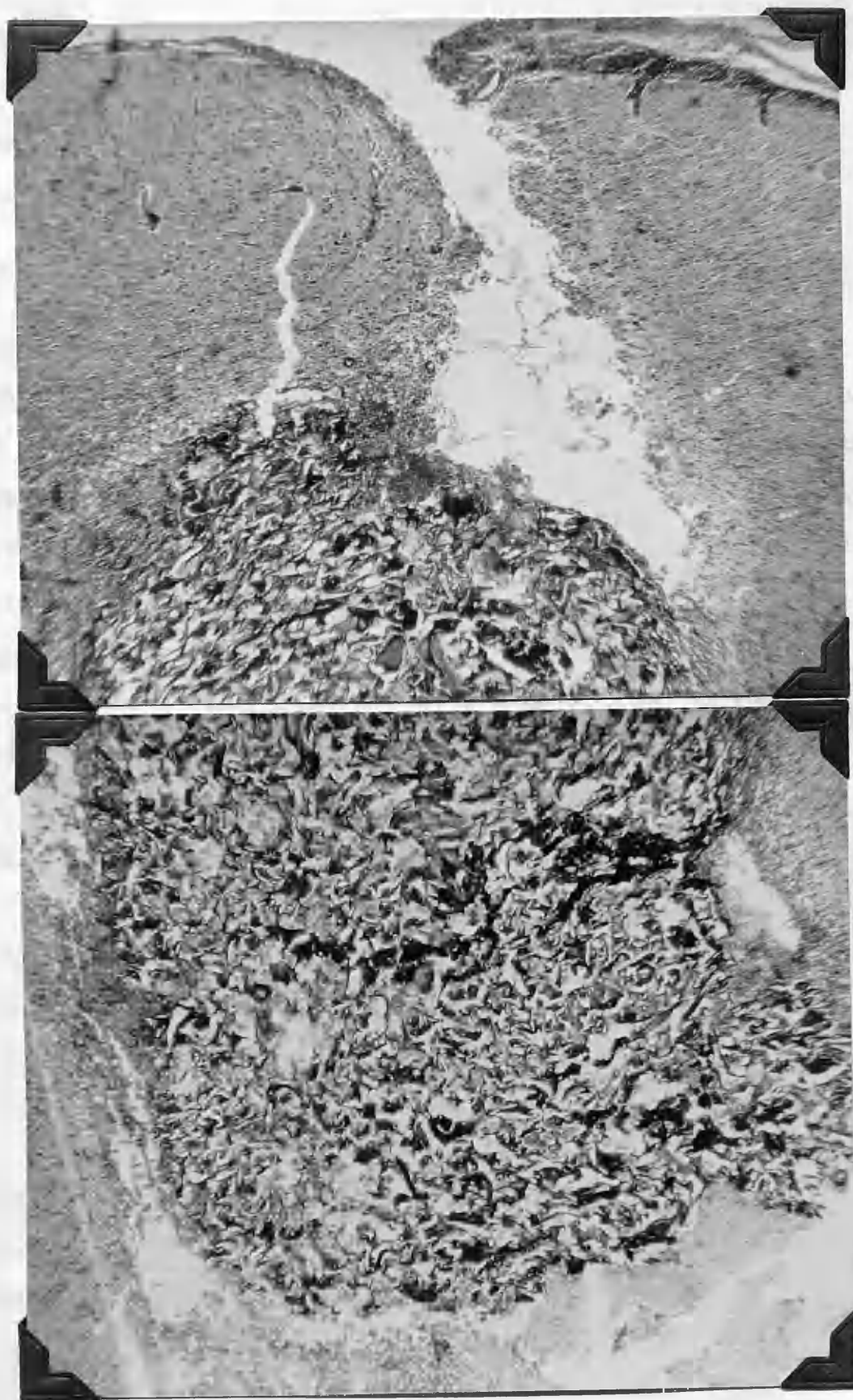
(fig. 13).   No general effect of cortisone can be recognised
on the brain tissue.   There is not reticulin to be seen.
New capillaries can be seen around the base of the wound
 but they are not numerous.

Cat. P. 43. 51.   Wt. 2.9kg.   Control.

Survival time - 15 days.

Gross. A small fascial graft was required to assist closure
of the dura.   A small superficial infection occurred at the
site of one stitch but cleared quickly on its removal.   An
adhesion was present, along the entire extent of the wound
between brain and dura.

Microscopic.   The wound is quite well demarcated from
surrounding brain.   The meninges show minimal thickening.
There is active phagocytosis present in the base of the
wound.   Plasma cells and occasional giant cells can be
seen.   Gelatin sponge has been well invaded by phagocytes.
Only very occasional fine strands of reticulin can be seen.
Collagen has made its appearance.   It is pale staining, very
fibery and runs in streams.   The gold sections show
hypertrophy of the astrocytes and a tendency to tangential
arrangement.

Cat. P. 46. 51   Wt. 4kg.   Intra musc. cortisone.
Survival time - 15 days.

Gross. The animal had an uneventful course. At sacrifice
a soft adhesion was found between brain and dura extending

Fig. 5.

Cat 44.51   8 day control.

This shows poor demarcation of the wound

with brain oedema and gitter cell zone

around the lesion.

HVG.   x   576.

Fig. 6.

Cat 48.51   7 day intra musc. cortisone inj.

Showing relatively good demarcation of wound

and lack of brain oedema.

HVG.   x   576.
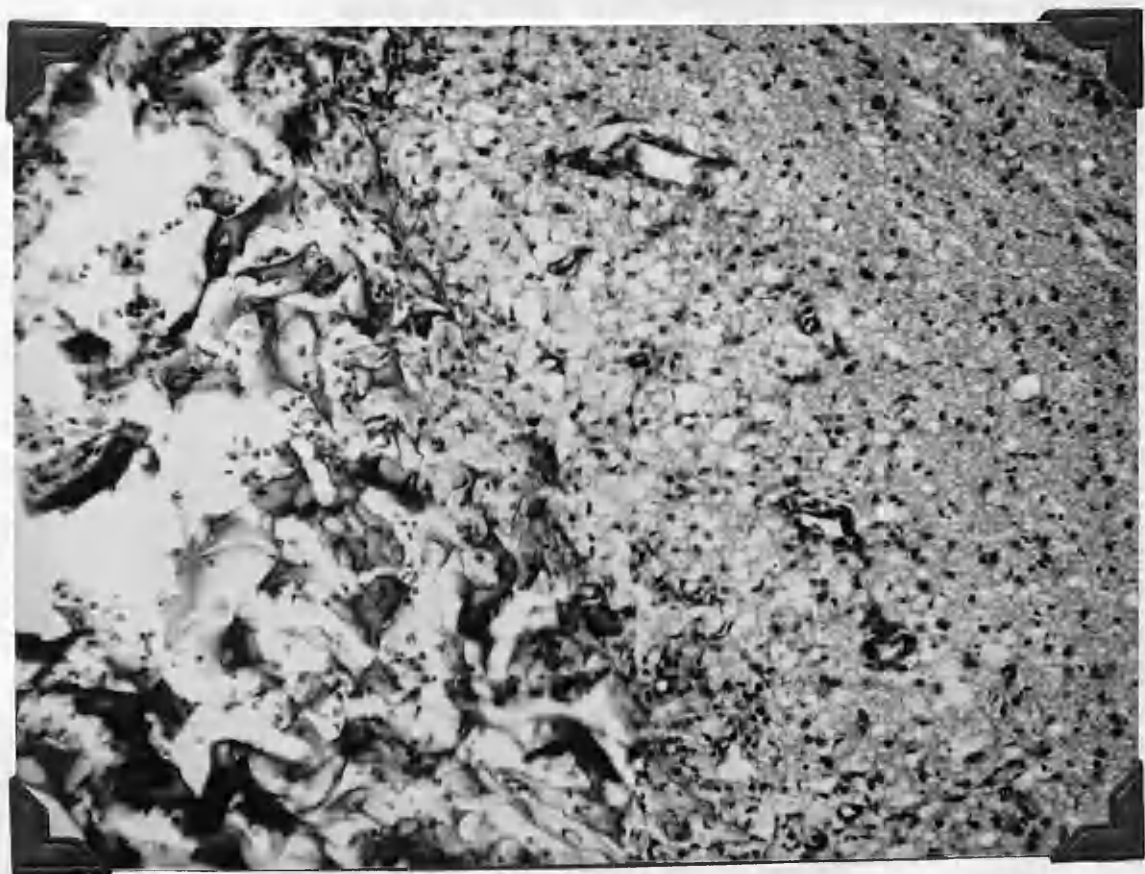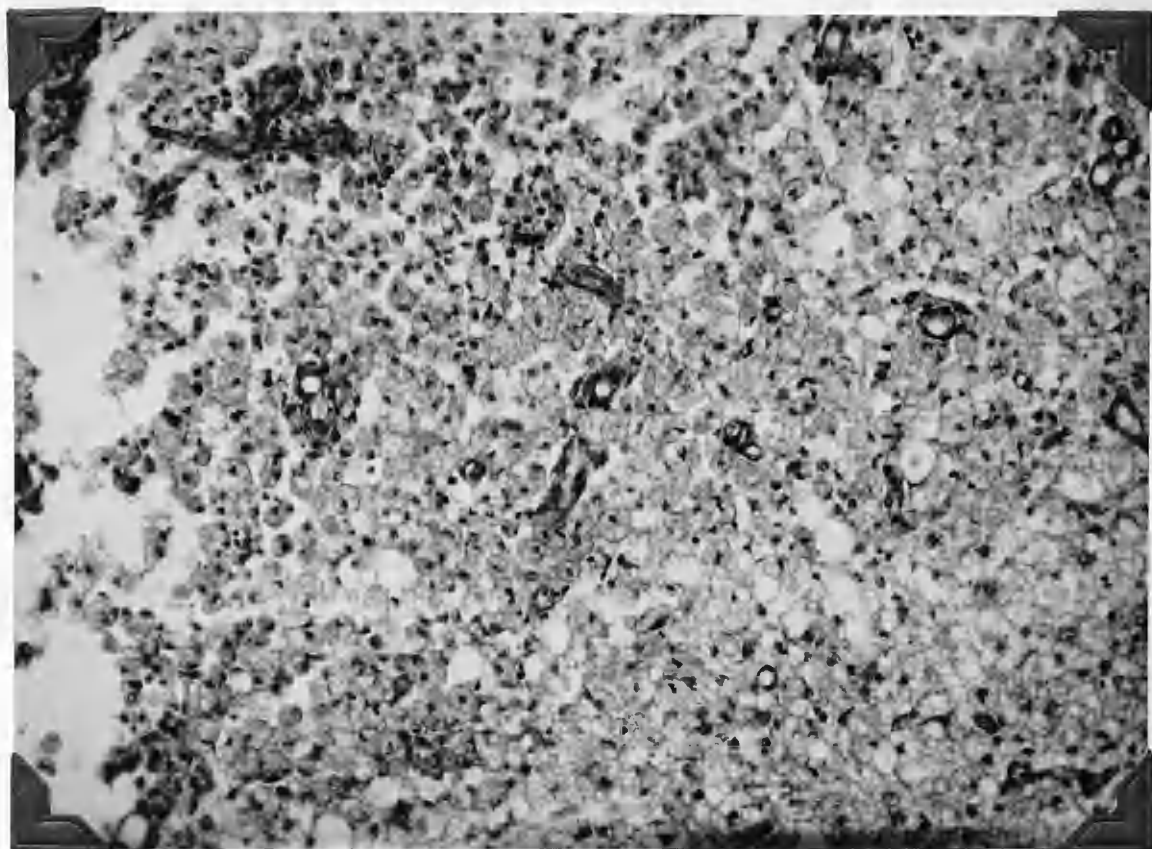
Fig. 2.

Cat 28.51   24 day control.

Showing the bony defect presenting at
sacrifice. Muscle and fascia well
bound at defect.

Photo 51-0454.

Fig. 3.

As above - Cat 28.51   24 day control.

This picture shows the dura raised at
sacrifice and a well marked meningo-
cerebral adhesion presenting.

Photo 51-0455

Fig. 4.

Cat 43.51   15 day control.

This demonstrates again a definite
meningo-cerebral adhesion at
sacrifice.

Photo 51-0427.

89
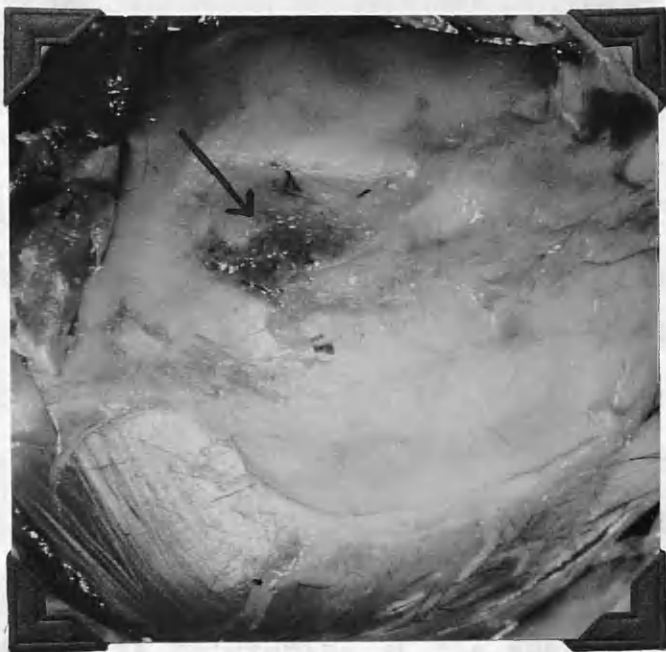
along entire length of wound.

Microscopic.   The wound is reasonably well demarcated.
There is no thickening whatsoever of the meninges.   Active
phagocytosis is taking place throughout.   Reticulin is
present, but is not plentiful.   Along the wound edges
fibroblasts can be recognised.   Collagen is present, mostly
of a fibery nature but sometimes appearing rather homogeneous.
There is no recognisable effect of cortisone.   Gelatin sponge
present.   There is thickening of the ependyma closest to the
lesion and moderate hypertrophy of the astrocytes.

Cat. P. 28. 51   Wt. 3 kg.   Control.
Survival time - 24 days.
Gross.   There were no complications in this case.   An
adhesion was present between the brain and the dura, throughout
the extent of the wound.
Microscopic.   In the chromatic sections an intense cellular
reaction about the wound can be seen.   Many new capillaries
are visible.   The meninges show only a minimal degree of
thickening over the wound.   There is active phagocytosis
and many inflammatory cells can be seen.   The gelatin sponge
is present.   Examination of the P. T. A. stain shows some
orientation of the glia fibrils towards the wound, and the
gold stains show a thick zone of gliosis in the white matter.
There is no reticulin present to speak of.

Fig. 7.

Cat 28.51   24 day control.

This is a high power view, Golgi stain, at

the base of the wound. Large proliferating

astrocytes are seen. It was intended to stain

a representative set of sections by the

Golgi method to assess the reactions of the

astrocytes according to the different methods

of administering cortisone to the animals.

Unfortunately the staining results, using

the fixed material, were inconstant and

disappointing.

Golgi.
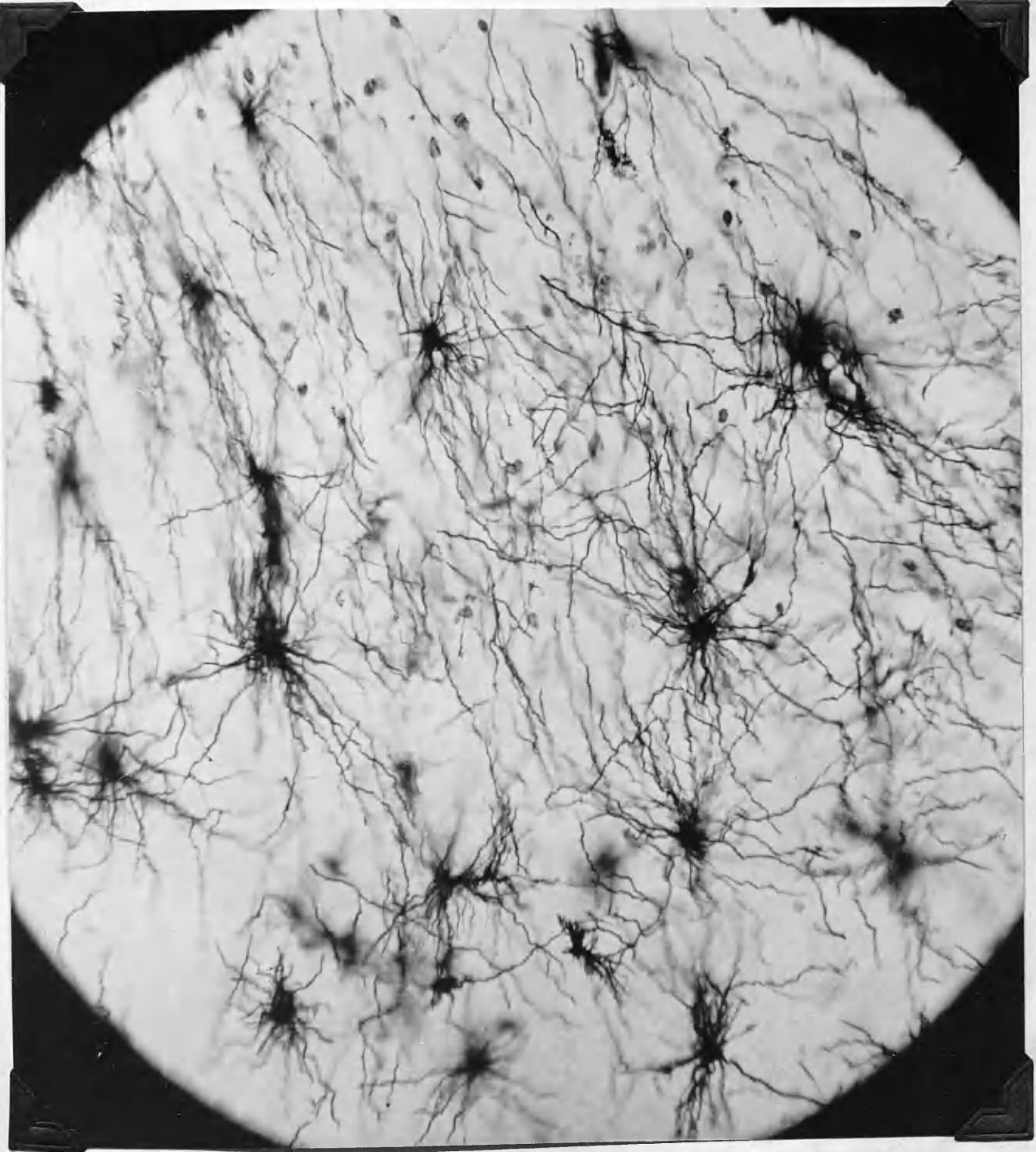
Cat.P. 49. 51   Wt. 2.65 kg.   Intra musc. cortisone.

Survival time - 24 days.

Gross.   This animal developed a head cold 4 days prior
to sacrifice, otherwise unremarkable.   Unfortunately, and
contrary to the usual practice, the brain with the overlying
meninges and skull in place had to be kept in 10% formalin
for 3 days prior to photography.

Microscopic.   This is a very well demarcated wound.   The
gelatin sponge is present.   There is no orientation of the
glia fibrils towards the wound.   Reticulin is present but
not marked.   Collagen is present and appears young.   It is
very fine and runs in strands.   No general effect of cortisone
on the brain rissue can be recognised.   The meninges are
thin and show no cellular reaction.   A little gliosis can
be recognised in the white matter.

Cat.P. 99. 51 Wt. 2.5 kg.   Control.

Survival time - 30 days.

Gross.   Following the operation this cat required intra-
peritoneal fluid, but apart from this its course was
unremarkable.   A soft adhesion was found between the brain
and the dura extending right the way along the wound.

Microscopic.   The wound is well demarcated.   The meninges
do not show any recognisable thickening.   There is still
phagocytosis going on and inflammatory cells can be seen.

Figs. 14a and 14b.

Cats 46.51 and 51.51.   Intra musc. cortisone inj.
     15 days   37 days

Showing the small but definite

adhesions found at sacrifice in

these animals treated by the intra

musc. inj. of cortisone acetate 10mgm/kg body wt.

Photo 51-1434.

Fig. 15.

Cats 46.51 and 51.51.   Intra musc. cortisone inj.

Showing the sections of the brains shown

above (figs 14a and 14b) following their

hardening in 10% formalin. The adhesion

in each case is easily seen and in both

the overlying membranes and muscle are

attached to the cicatrix.

Photo 51-1435.

a
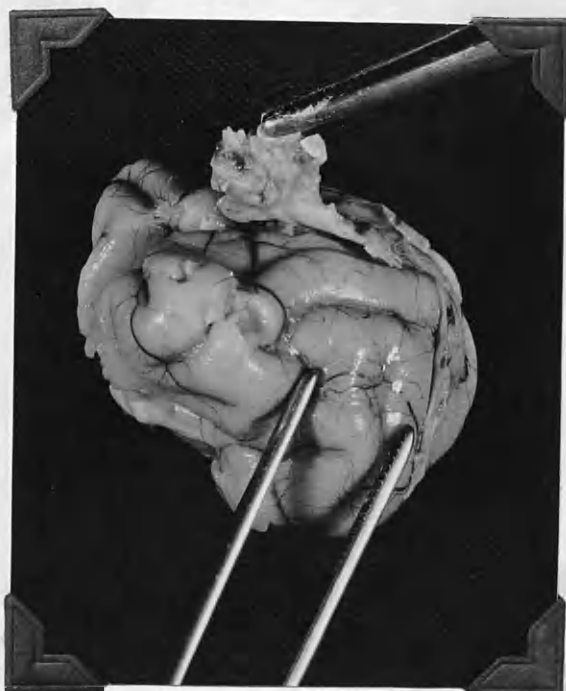
b
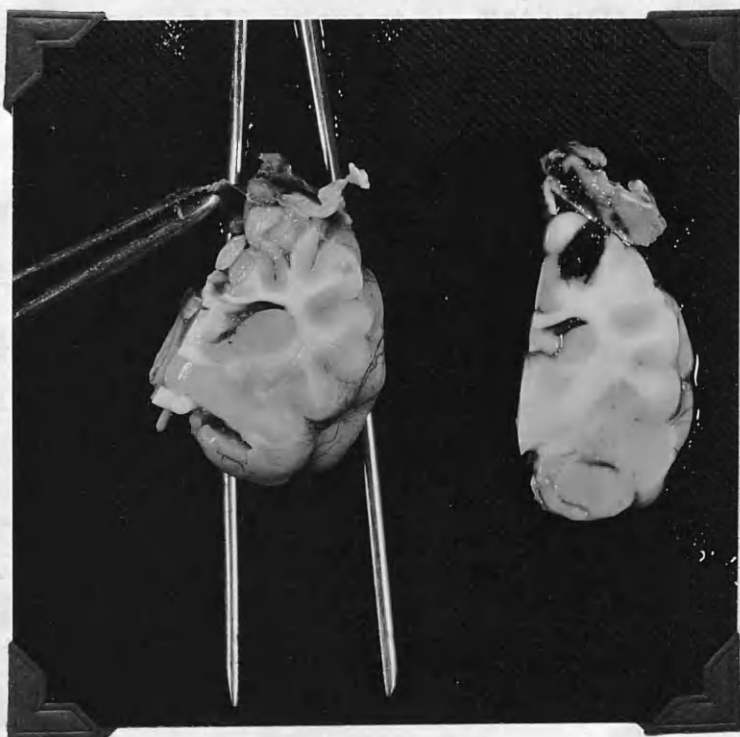
The gelatin sponge is present. No orientation of the
glia fibrils can be recognised in the P.T.A. stains. There
is a lot of reticulin present and this is well outlined.
Collagen is present, in the form of fine fibery threads,
throughout the scar. Gold stains show some astrocytic
hypertrophy.

Cat.P.35.51. Wt.3.2.kg. Intra musc. cortisone.
Survival time - 32 days.
Gross. Course unremarkable. Well marked adhesion was found
between the dura and the brain at sacrifice.
Microscopic. The demarcation of the wound from the surrounding
brain is not very good. The meninges show no thickening
and look well. There is still evidence of phagocytosis
and occasionally giant cells are seen. Remnants of the
gelatin sponge are still present. Reticulin is very
scanty. Collagen in the H.V.G. stains is plentiful. In
parts it runs in streams, in others it is a more mature,
homogeneous looking material. No general effect of cortisone
on the brain can be recognised.
Cat P.51.51 Wt.3.5. kg. Intra musc. cortisone.
Survival time - 37 days.
Gross. It was attempted in this case to obtain a coronal
section through the skull, meninges and brain with the
structures intact. This was achieved by the use of a
small electric saw. The tissue was bound intact with thread
and decalcified slowly in hydrochloric and formic acid.

Fig. 8

Cat 22.51   40 day control

   Showing the rather delicate young

   looking collagen fibres found in

   this case.

HVG.   x   312.

Fig.   9.

Cat 34.51   43 day intra musc. cortisone inj.

   This shows collagen fibres more homogeneous

   and mature than in the control wound (above)

HVG.   x   312.
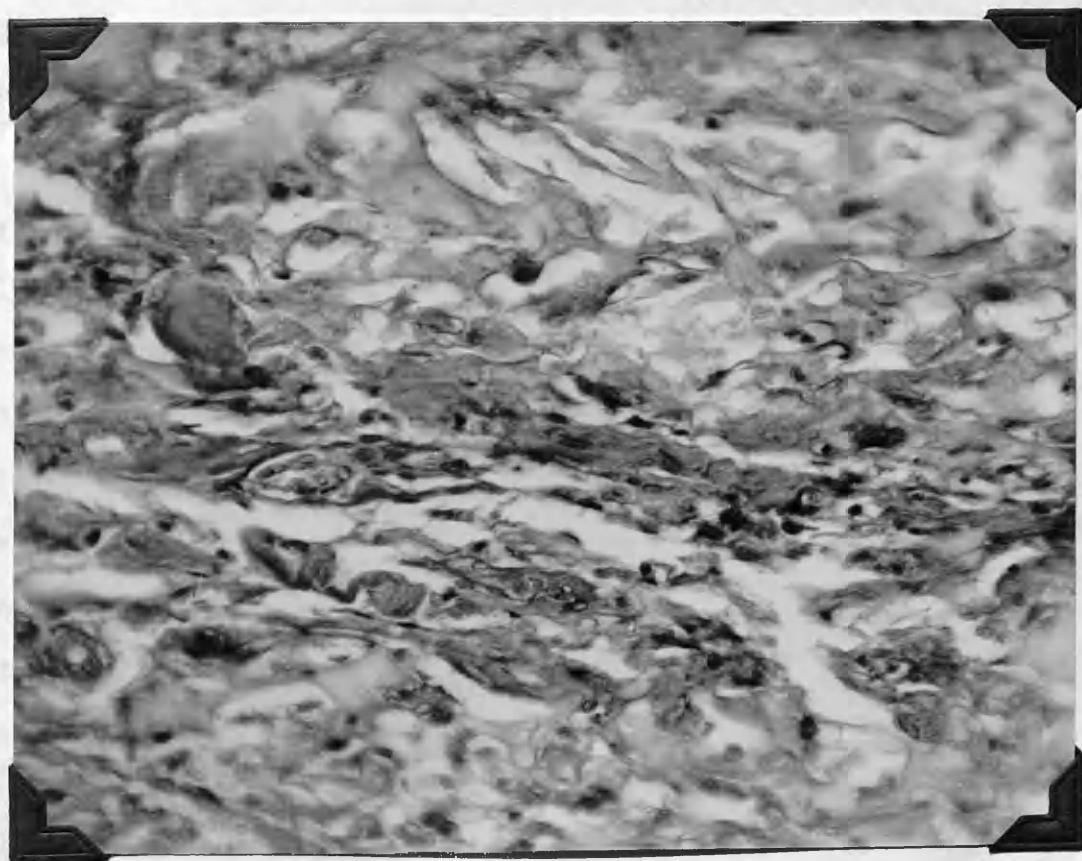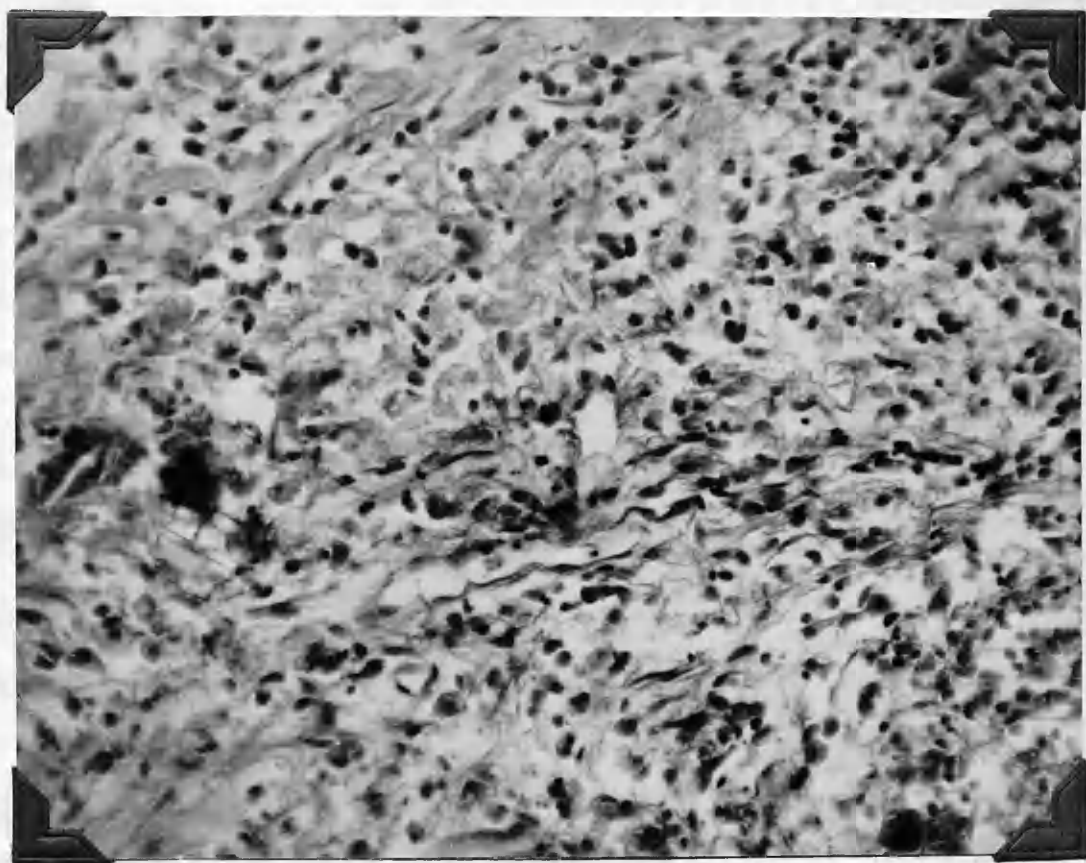
An adhesion was present.

Microscopic. The cellular elements of brain are not clearly outlined due to the decalcifying process. However, collagen is plentiful and is well formed and condensed. The gelatin sponge is present and undergoing phagocytosis. Fibroblasts are present in number.

Cat P. 22. 51.   Wt. 3. 25 kg.   Control.
Survival time - 40 days.

Gross. Course was unremarkable, remained well during the whole period. Well established adhesions between entire extent of wound and the dura were found at sacrifice.

Microscopic. The meninges show minimal thickening. The wound is not too well demarcated from adjacent tissue. There is still a great deal of phagocytosis going on in the wound. There are numerous inflammatory cells, polymorphs and plasma cells, at one edge of the wound. There is evidence of remnants of the gelatin sponge, although this is slight. In the P. T. A. and gold stains the fibrils of the glia are orientated towards the wound quite markedly and in the gold stains the astrocytes can be seen showing this change at quite a distance from the wound (fig. 10). Many capillaries are visible around the margins of the wound. There is abundant reticulin present. Collagen is very plentiful and is young looking, appearing very fibery and running in streams (fig. 8).

Fig. 10.

This is to demonstrate pictorially with
hypertrophy of surfaces and orientation
of their processes towards the wound.
Vacuoles that can occasionally be
seen.

600. x 18c.

Fig. 11.

A table giving a comparison of the
histological features of the animals
treated with intra musc. cortisone
with the controls.

Fig. 10.

Cat 22.51   40 day control

This is to demonstrate gliosis with
hypertrophy of astrocytes and orientation
of their processes towards the wound.
Vascular feet can occasionally be
seen.

GCS.   x   156.

Fig. 11.

A table giving a comparison of the
histological features of the animals
treated with intra musc. cortisone
with the controls.
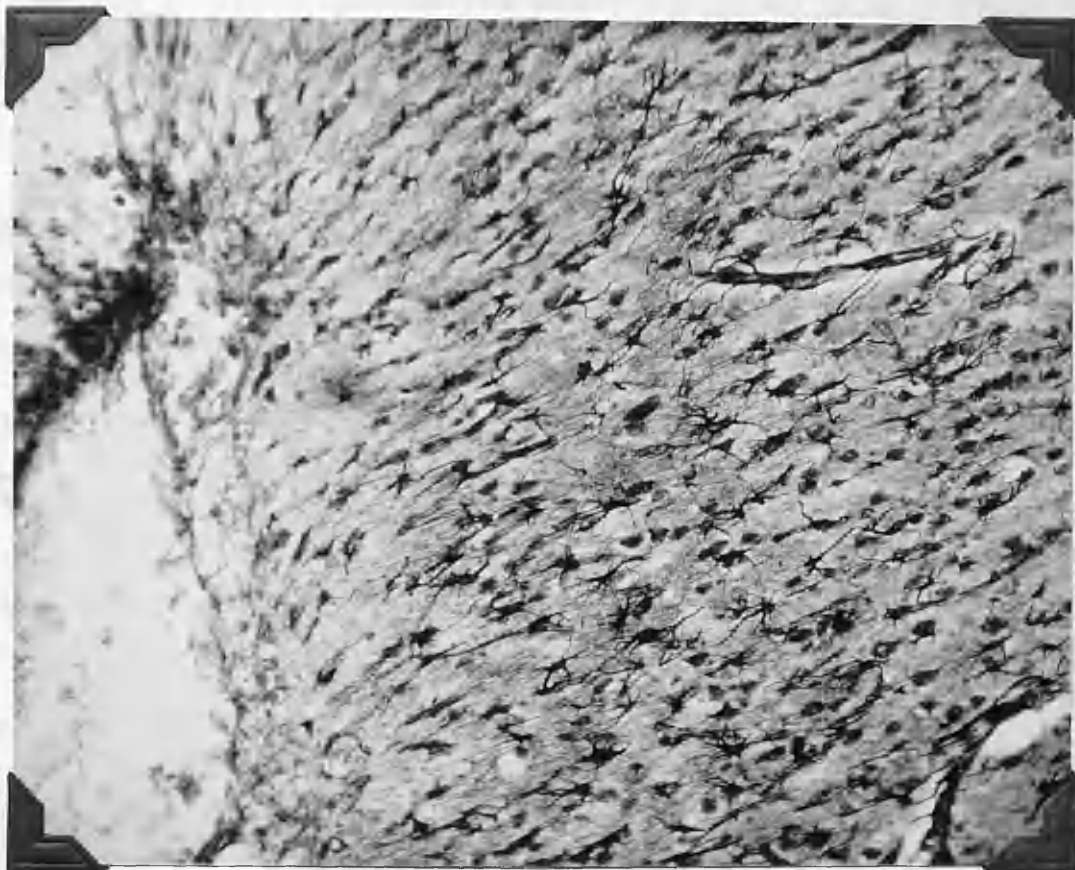
TABLE I

Histological Features of Cortisone and Control Animals

No. of cat	No. of days	Meningo-cerebral adhesion	Meningeal thickening	Zone of reaction & edema*	Phagocytosis	Gelatin sponge	Fibroblasts	Collagen	Reticulin	Vascularity	General effect of cortisone in brain
						Cortisone Animals					
51.36	5	Present	None	Minimal	Marked	Intact	Scanty	None	None	Moderate	None
51.48	7	Present	None	Minimal	Marked	Phagocytosis beginning	Scanty	None	None	Moderate	None
51.46	15	Present	None	Minimal	Marked	Fragmented	Moderate number	Appearing	Appearing	Moderate	None
51.49	24	None	None	Very minimal	Moderate	Fragmented	Numerous	Present	Present	Very slight	None
51.52	25	None	None	Moderate	Moderate	Fragmented	Numerous	Present	Present	Slight	None
51.35	32	Present	None	Moderate	Moderate	Recognizable	Plentiful	Plentiful	Present	Moderate	None
51.51	37	Present	Minimal	Minimal	Still active	Recognizable	Plentiful	Heavy and thick	Present	Moderate	None
51.34	42	Present	Minimal	Very minimal	Still active	?Recognizable	Plentiful	Thick, mature looking	Present	Very slight	None
						Control Animals					
51.44	8	Present	Considerable	Marked	Marked	Intact	Scanty	None	None	Quite marked	None
51.43	15	Present	Minimal	Minimal	Marked	Fragmenting	Moderate numbers	Appearing	None	Moderate	None
51.28	24	Present	Very minimal	Moderate	Moderate	Fragmenting	Numerous	Light-stained & wavy	None	Quite marked	None
51.29	31	Present	None	Moderate	Moderate	Recognizable	Plentiful	Plentiful	Plentiful	Very slight	None
51.22	40	Present	Minimal	Marked	Still active	Recognizable	Plentiful	Plentiful	Plentiful, thin, & light-staining	Moderate	None

* Minimal: width of less than one high power field.   Moderate: two high power fields.

Cat. P. 34. 51   Wt. 2. 5 kg.   Intra musc. cortisone.

Survival time - 43 days.

Gross.   In removing the skull in this case the bone was
nibbled right up to the edge of the wound to display the
adhesions, which extended firmly right the way along the
length of the wound.

Microscopic.   The meninges are very slightly thickened
at one side of the wound.   The demarcation from the
surrounding tissue is very good indeed and the wound appears
to have contracted well.   Gelatin sponge cannot be stated
definitely to be present but there are crystals which
probably represent elements of it.   There is no orientation
whatsoever of the glial fibrils towards the wound visible
in P. T. A. or gold stains.   The collagen which is quite
plentiful looks darker, more compact and mature than in the
control P. 22. 51 (fig. 9).   Few capillaries are noted around
the margins of the wound.   Occasional phagocytes can be
seen.   There is little reticulin.   The cicatrix is
sharply circumscribed and the adjacent architecture little
disturbed.   No general effect of cortisone on nerve cells
and glia can be seen.

Cat. 120. 51   Wt. 2. 7 kg.   Local cortisone acetate.

Survival 7 days.

Gross.   No adhesion could be seen grossly when the animal
was sacrificed.   The wound edge looked slightly irregular
when the preparation was cut after being fixed in 10% formalin.

Microscopic.   There is no thickening of the meninges what-
soever.   The wound edges have fallen together nicely and do
not gape in the   -   -   -   -   -   -   -   -

This is to illustrate a feature found
almost constantly in the sections - a
thickening of the spongeal lining in the
area nearest the wound with gradual
attenuation.

OV. x 212.

Fig. 12.

Cat 43.51   15 day control.

This is to illustrate a feature found
almost constantly in the sections - a
thickening of the ependymal lining in the
area nearest the wound with gradual
attenuation.

CV.   x   312.

Fig.   13.

Cat 48.51   7 day intra musc. inj. cortisone.

Illustrating phagocytosis of the
gelatin sponge.

HVG.   x   576.
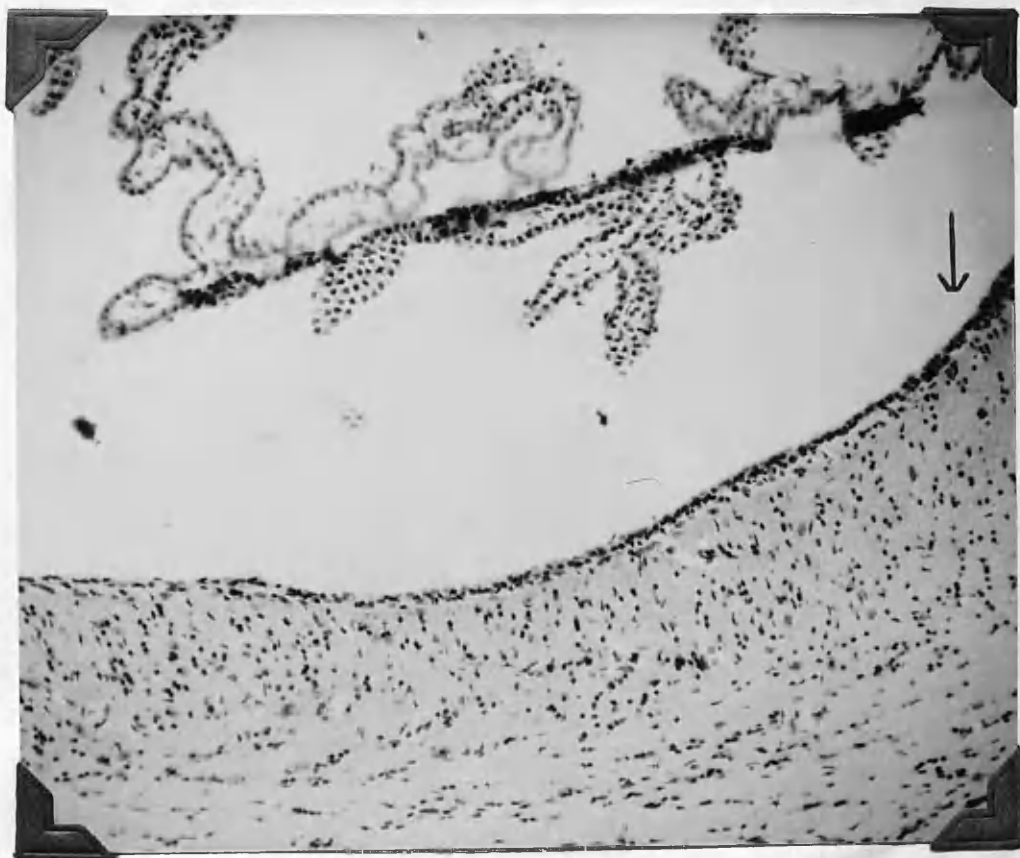
Fig. 16.

Cat 181.31   21 day   Right cortisone pellet graft.

This shows an adhesion right the

way along the surface.

Photo 21-183.

Fig. 17.

Cat 126.31   14 day   local cortisone acetate
(saline suspension)

This shows a small filmy adhesion at

the edge of the wound. No adhesion was

noted in the case of the other two

animals treated by the local

application in gelatin sponge of the

saline suspension of cortisone acetate.

Photo 21-184.

Fig.   16.

Cat 126.51   21 day   local cortisone tablet powder.

This shows an adhesion right the

way along the surface.

Photo   51-1359.

Fig.   17.

Cat 125.51   14 day   local cortisone acetate
                           (saline suspension)

This shows a small filmy adhesion at

the edge of the wound. No adhesion was

noted in the case of the other two

animals treated by the local

application in gelatin sponge of the

saline suspension of cortisone acetate.

Photo   51-1358.
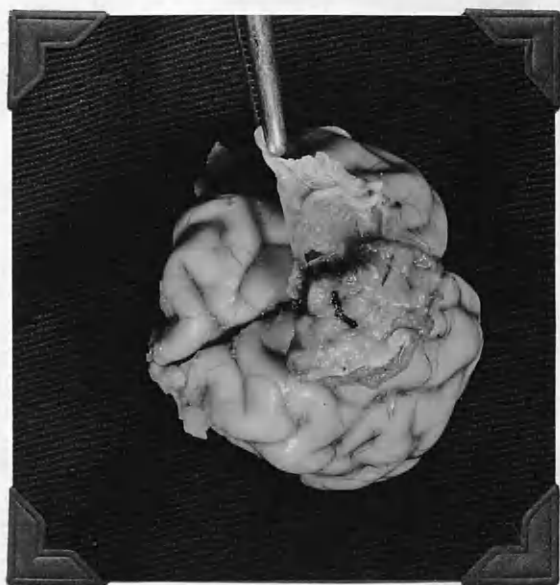
16.
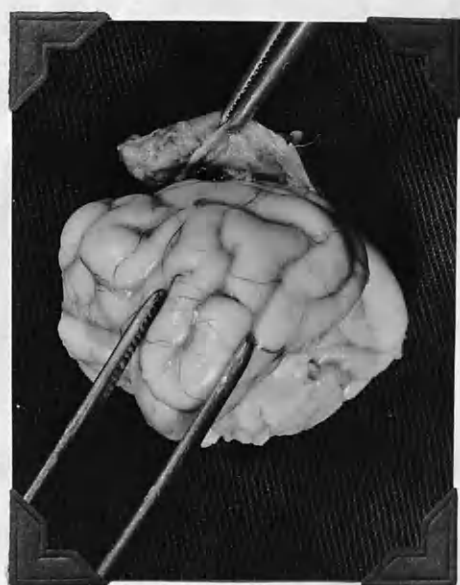
17.

Fig. 18.

Cat 120.51   7 day local cortisone acetate.
                        (saline suspensioh)

Showing a low power, general view of the

local cortisone acetate wound with

falling together of the margins and

quick disappearance of the gelatin

sponge. Haemorrhage has been perfectly

dealt with by the sponge before its

disappearance.

HVG.   x 15.

Fig. 19.

Cat 124.51   28 day local cortisone acetate
                        (saline suspension)

Low power view of the 28 day local

cortisone acetate to show good falling

together of the wound edges and no

thickening of the meninges .

HVG.   x 15.

Case 139.40

History

VESSEL
A very small thin fibro-elastic was present here and localised to the centre of the vessel. The temporalis muscle was well beaten down to the surrounding area.

MICROSCOPY
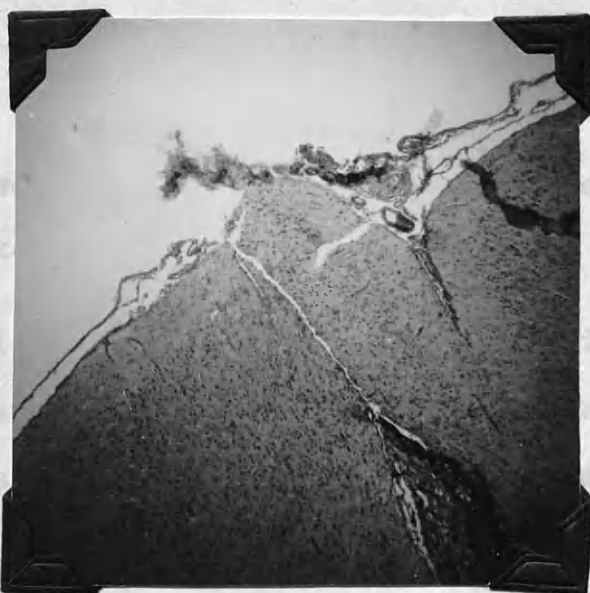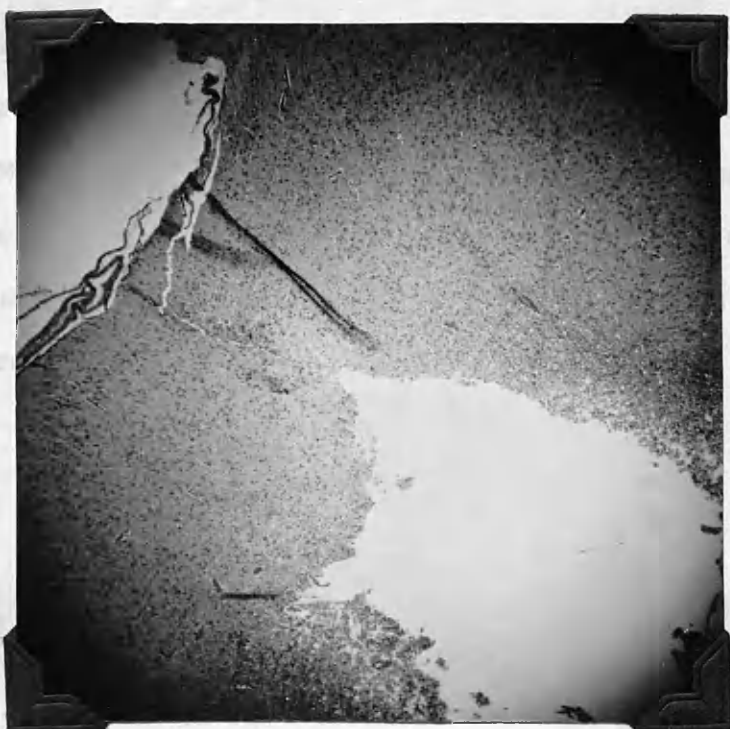
manner seen in other specimens. There is very good
demarcation, the gelatin sponge has for the most part
disappeared and the remaining appearance is that of a small
cystic space. There is no evidence of an inflammatory
reaction. Haemorrhage has been well controlled. Occasional
small vessels can be seen and these do not seem to differ
in size or number from the control series. There is no
collagen or reticulin to be seen.

Cat 125.51   wt 3 kg   Local cortisone acetate.

Survival   14 days

Gross

A very small thin filmy adhesion was present here and
localised to the centre of the wound. The temporalis muscle
was well bound down tomthe surrounding dura.

Microscopic.

Again there is a picture of a good wound with falling
together of the wound edges, similar to that seen in 120.51
There is no thickening or inflammatory reaction of the

meninges. The gelatin sponge has again largely disappeared
only small fragments of it remain and the appearance of a
small cyst persists. There is a very high degree of
phagocytosis, right the way down into the base of the wound.
There is no inflammatory reaction and haemorrhage has been

(Saline Suspension)

General appearance of the wound with
the gelatin sponge for the most part
disappeared at 14 days.

HVG. X 15.0.

Fig. 21.

Oct. M4.51   day. Local contains acetate
(saline dispersion)

This section shows excellent absorption
of the wound. This was a feature of the
wounds treated by this method in contrast

Fig. 20.

Cat 125.51   14 day   local cortisone acetate
                                 (Saline Suspension)

General appearance of the wound with

the gelatin sponge for the most part

disappeared at 14 days.

HVG.   x   15.

Fig. 21.

Cat 124.51   28 day   local cortisone acetate
                                 (saline suspension)

This section shows excellent demarcation

of the wound. This was a feature of the

wounds treated by this method in contrast

to the others.

HVG.   x   120

Fig. 22.

Cat 125.51   14 day local cortisone acetate.

Showing the excellent phagocytosis found
in the wounds treated by the local
application of cortisone acetate (saline
suspension) in gelatin sponge.

HVG. x 120.

well vascularized. Some new vessels are present but they
are not plentiful. There is a trace of collagen present;
it is fine, homogenous and light staining.

Cat 158.61   wt kg.   Local excision of tumour.
Survival time 26 days.

Gross.

There...
section...

Histology.

An inf...
very...
of ...
mass...
well...
diss...
woun...
fibrous tissue...
vessel. Collagen is present, however, and is particularly
less seen in the central portions. It is very lightly
staining. Phagocytosis is still very obvious.

Cat 157.61   wt 2.3kg.   Local breast malignancy.
Survival time 14 days.

well controlled. Some new vessels are present but they are not plentiful. There is a trace of collagen present; it is fine, homogeneous and light staining.

Cat 124.51   wt 3kg.   Local cortisone acetate.

Survival time   28 days.

Gross.

There was no adhesion noted grossly when the animal was sacrificed. The wound margins were perfectly regular.

Microscopic.

As in 120.51 and 125.51 the wound edges have come together very well. There is no inflammatory reaction or thickening of the meninges. There is excellent demarcation of the wound from the surrounding brain tissue. Haemorrhage is well controlled. The gelatin sponge has again largely disappeared and only isolated fragments remain along the wound margins. There is no instreaming of collagen and fibrous tissue from the dura as seen in the control wounds. Collagen is present, however, but is definitely less than in the control sections. It is very light staining. Phagocytosis is still very obvious.

Cat 127.51   wt 3.4kg   Local tablet application.

Survival time   14 days

Fig. 23.

Cat 126.51   21 day local cortisone tablet.

Showing cicatrix at top ,of wound and
mass of necrotic and inflammatory
material occupying wound.

HVG.   x   15.

Fig. 24.

Cat 126.51   21 day local cortisone tablet.

Large area of necrosis and necrotic
debris in centre of wound.

HVG.   x   60.
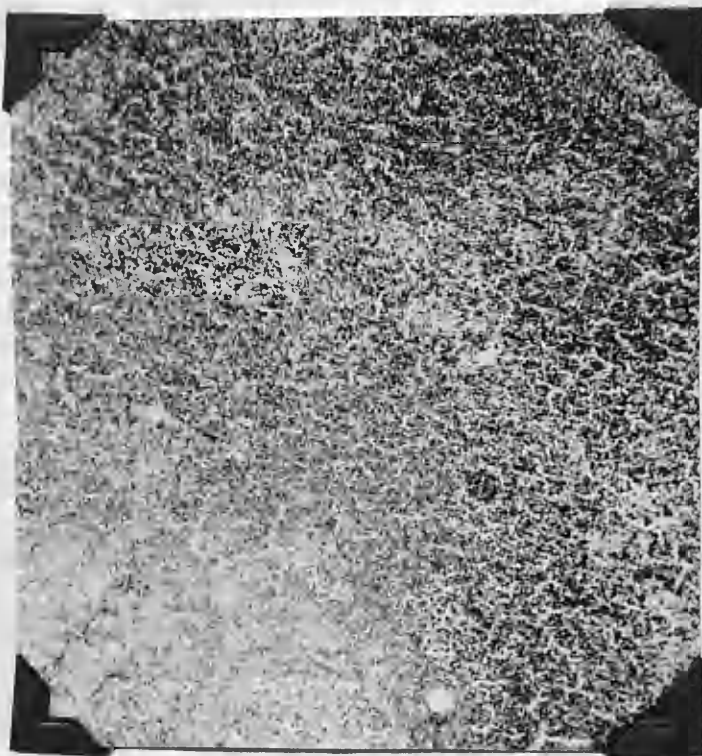
Gross

There was an adhesion present at sacrifice. It extended right the way along the wound. No pus or exudate present.

Microscopic.

The wound edges are widely separated. There is minimal thickening of the meninges. There is a marked inflammatory response around the margins of the wound. Many cell types can be seen. The centre of the wound is occupied by necrotic debris. The gelatin sponge is largely in place and is invaded by inflammatory cells.

Cat 126.51   wt 2.6kg.   Local tablet application.

Survival time   21 days.

Gross

An adhesion was found along the entire extent of the wound.

Microscopic.

Again the wound margins are widely open and separated. There is no inflammatory reaction and no thickening of the meninges. Phagocytosis is evident but this is to a large extent masked by the intense inflammatory reaction. There is an area of necrosis in the centre of the wound. The gelatin sponge is in place, largely unchanged but invaded by inflammatory cells. The adhesion to the dura is well seen

Fig. 25.

Cat 126.51   21 day local cortisone tablet.

Showing well marked strands of
reticulin streaming along wound
edge.

LCT.   x 60.

Fig. 26.

Cat 126.51   21 day local cortisone tablet.

Connective tissue has achieved line
of demarcation from normal brain tissue.
Inflammatory cells much in evidence.

HVG.   x 60.

120

Fig. 45.

Cat 184.G1   21 day   local cantharose tablet.

of composite picture showing the various

inflammatory cells found in this area

where cantharose tablet powder was used

locally.

HVG. x 190.

Fig. 46.

Cat 187.G1   14 day   local cantharose tablet.

This also shows the inflammatory cell

response in the 14 day serial in which

cantharose tablet powder was used locally.

HVG. x 190.

Fig. 27.
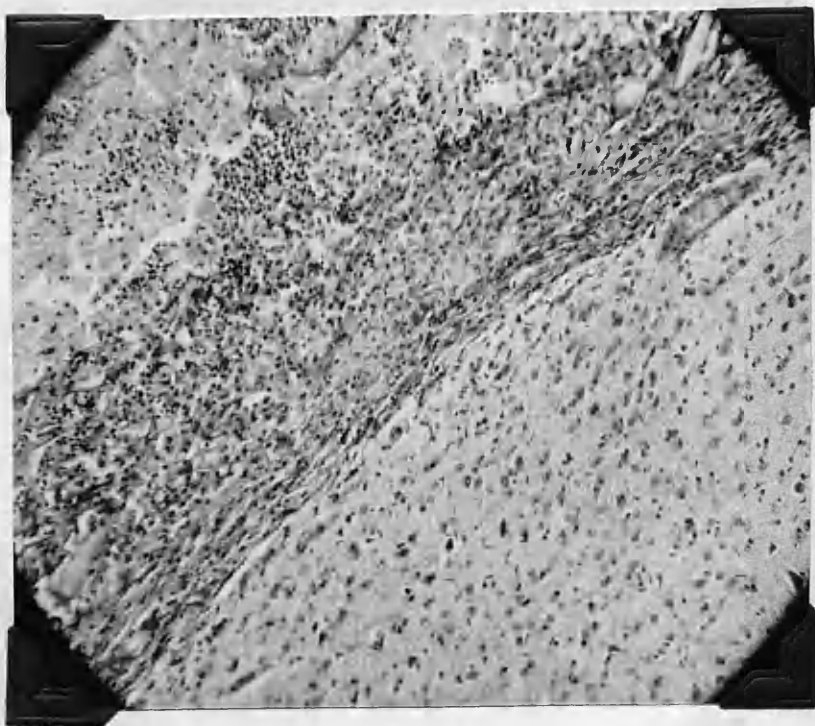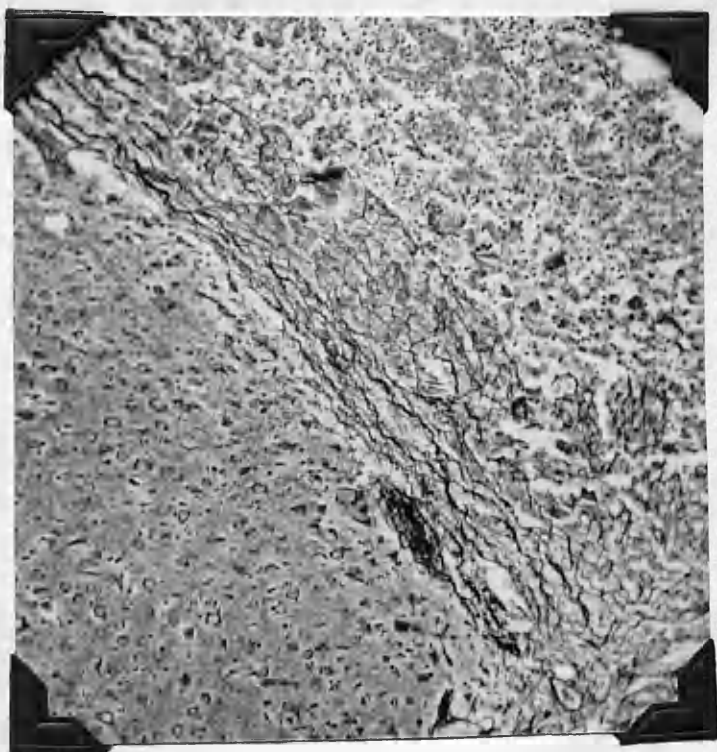
Cat 126.51   21 day local cortisone tablet.

A composite picture showing the various
inflammatory cells found in this wound
where cortisone tablet powder was used
locally.

HVG. x 120.

Fig. 28.

Cat 127.51   14 day local cortisone tablet.

This also shows the inflammatory cell
response in the 14 day animal in which
cortisone tablet powder was used locally.

HVG. x 120.
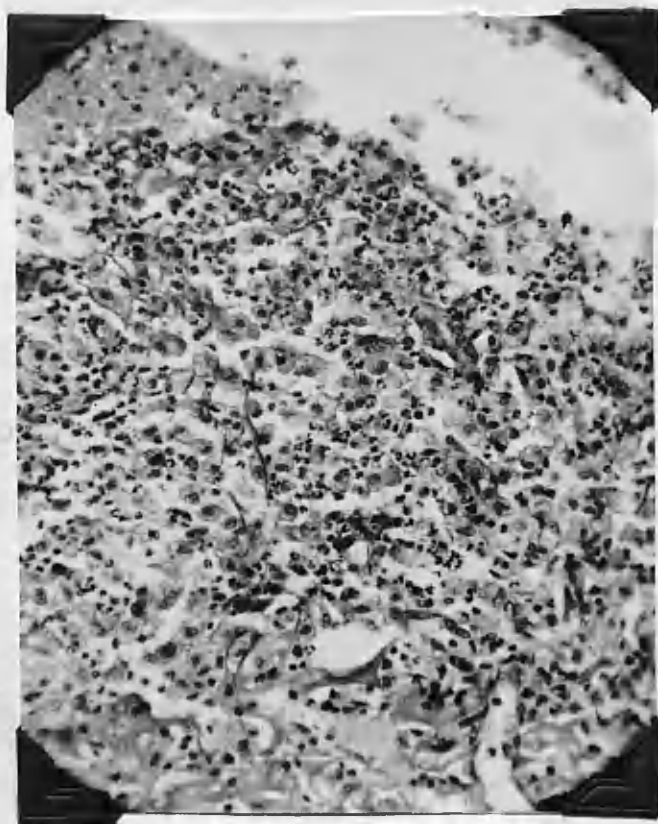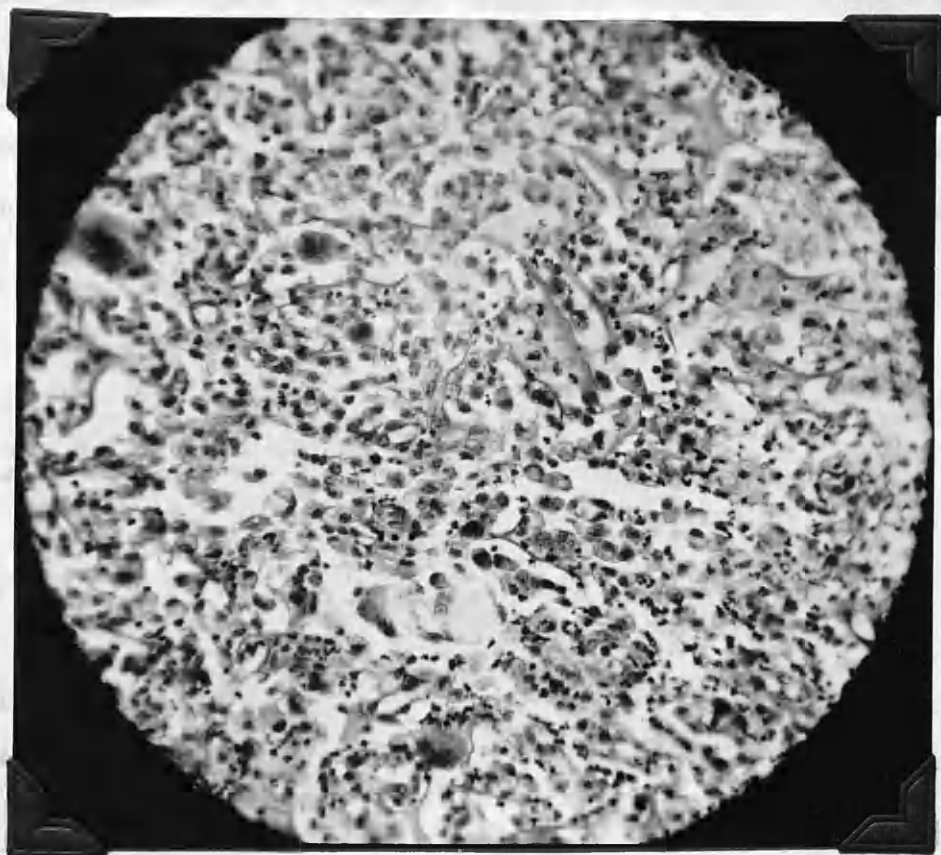
in the microscopic section. There is much well stained
collagen throughout the section. There is a pool of
haemorrhage at the base of the wound. Demarcation of the
wound however is good and this seems to have been acheived
by a rim of collagen and connective tissue.

Cat 132.51   wt2.7kg   Cortisone by mouth.

Survival time   8 days.

Gross

An adhesion was found at sacrifice.

Microscopic.

There is no thickening or inflammatory reaction of the men
inges. The gelatin sponge is for the most part still
completely intact. Phagocytosis is very marked indeed.
Haemorrhage is well controlled. Demarcation not too good.
Collagen is present in the wound and although slight in
amount is quite heavily stained. Many new vessels are
prominent in the base of the wound. Laidlaws connective tissue
stain shows plentiful reticulin at the base of the wound.

Fig. 29.

Cat 133.51   22 day Cortisone by mouth.

Showing the well marked though soft
adhesion found at sacrifice.

Photo 51-1491.

Fig.   30.

Cats 133.51 and 136.51   Cortisone by mouth.
        22 days and 14 days

These sections made following fixation
of the brain in 10% formalin show the
adhesions with the overlying dura and
muscle adherent to the scar.

Photo 51-1492.

51. 133.

51. 133.

51. 136.
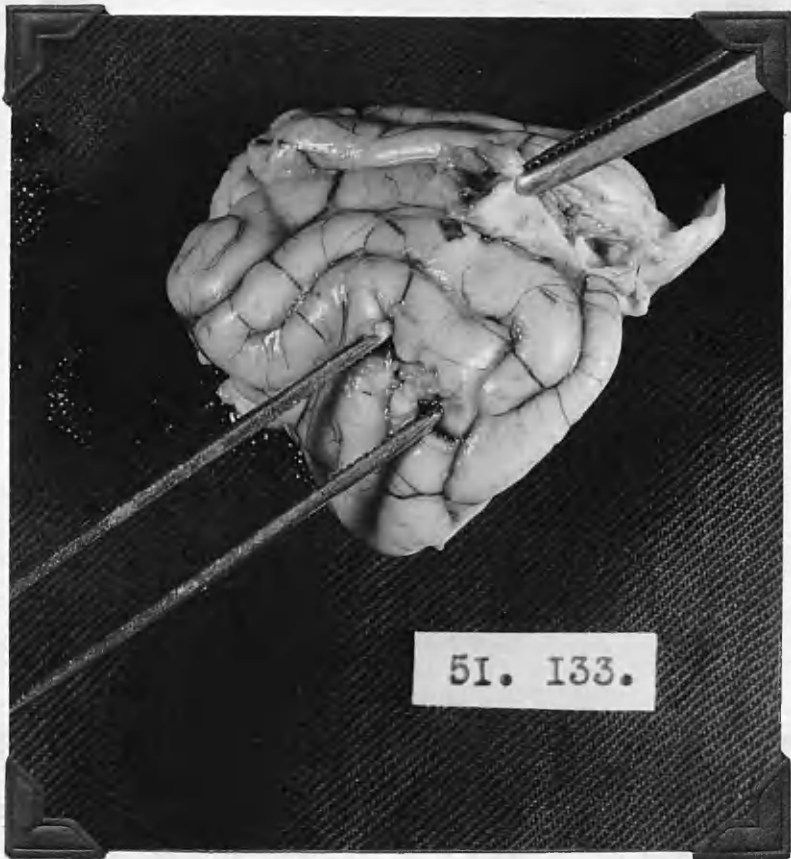
Fig. 31.

Cat 132.51   8 day   Cortisone by mouth.

To show the well marked cicatrix at edge of
wound. The histological processing has
slightly separated the edges of the wound.

HVG.   x 60.

Fig. 32.

Cat 136.51   14 day   Cortisone by mouth.

Showing the cicatrix.

HVG.   x 60.
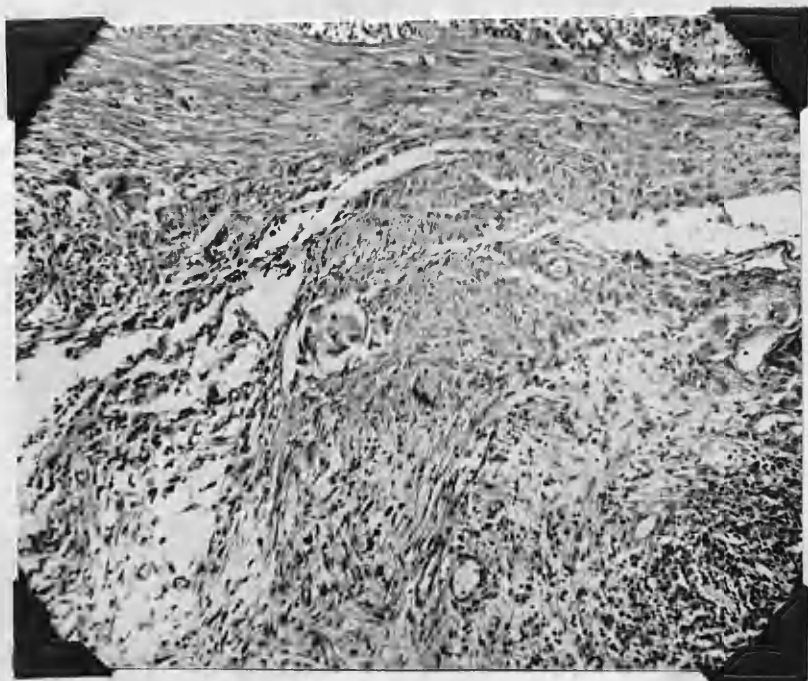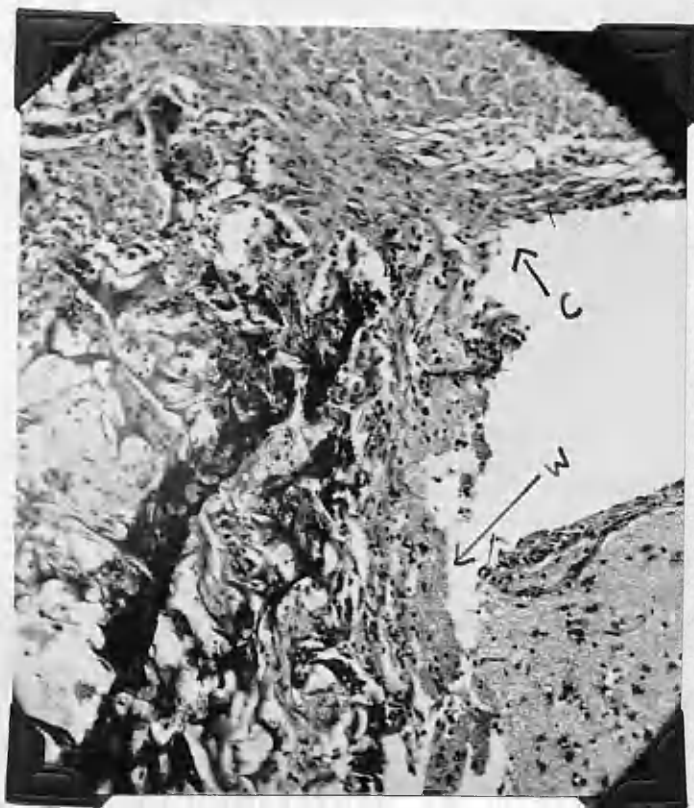
Figs. 22 and 24.

Oct 182-21   ? days.   Continues by mouth.

These sections show the marked deposition

of reticulin in and around the wound

found in this animal treated for 8 days

with cortions by mouth.

x 60.

Figs.   33 and 34.

Cat 132.51   8 days   Cortisone by mouth.

These sections show the marked deposition
of reticulin in and around the wound
found in this animal treated for 8 days
with cortisone by mouth.

LCT.   x   60.
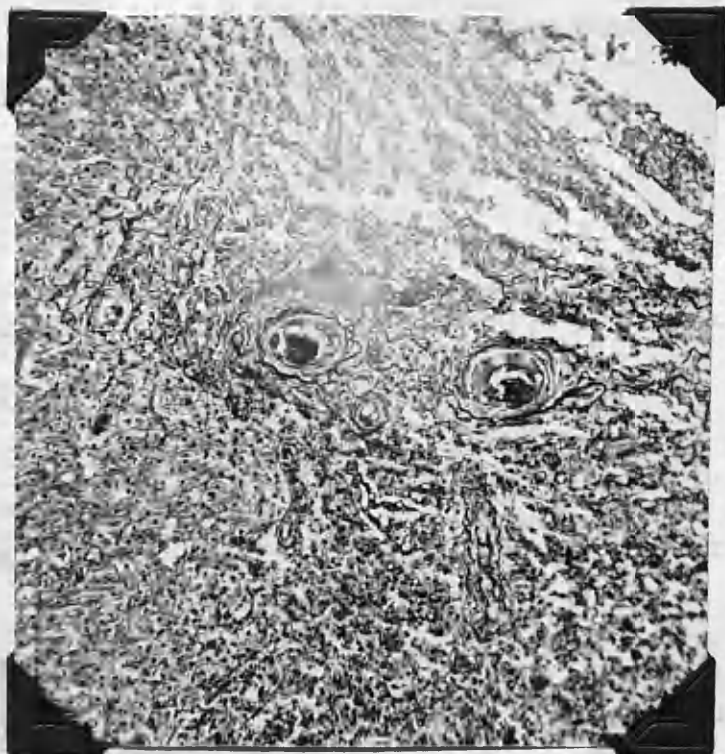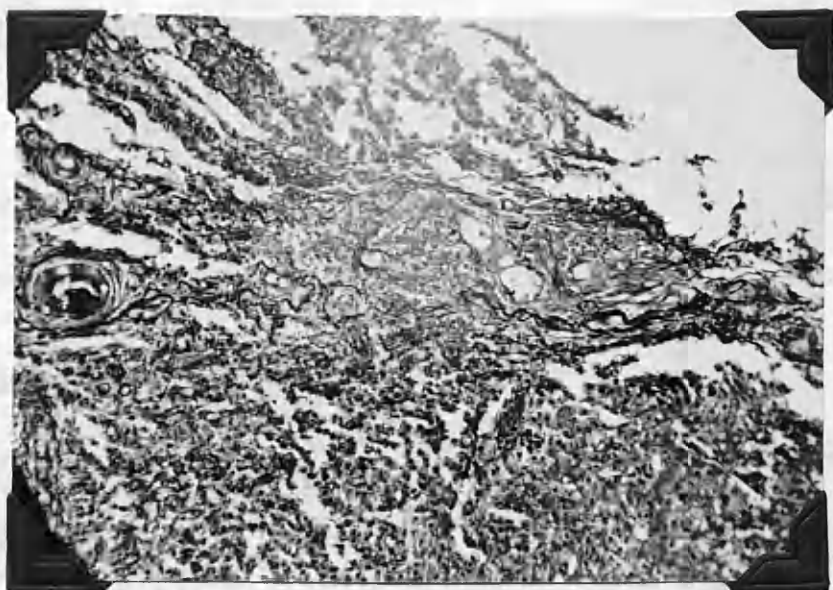
Cat 136.51. wt 4.2kg.   Cortisone by mouth.

Survival time   14 days.

Gross.

There was an adhesion present grossly. The temporalis
muscle was well bound down to the dura. No pus or exudate.

Microscopic.

There is no inflammation or thickening of the meninges.
The gelatin sponge is still completely in place and a
good number of red blood cells can be seen trapped in it.

Collagen is present in the wound though not plentiful and
it is light staining. There is a ring of fibroblasts and

connective tissue around the edges of the wound. The wound
is not too well demarcated. Laidlaws connective tissue stain
shows lots of fine wavy reticulin in the base of the wound.

Cat 133.51   wt 3.3kg.   Cortisone by mouth.

Survival time   22 days.

Gross.

A soft adhesion was found at sacrifice. No pus or exudate.

Microscopic.

The wound margins are widely separated. There is no
inflammation or thickening of the meninges. Phagocytosis

is marked especially in the base of the wound. The wound is well
well demarcated. The gelatin sponge is still intact and is
invaded with phagocytes. There is much collagen present; it
is homogeneous but well stained. Laidlaws connective
tissue stain shows much reticulin. It is fine and wavy around
the edges but in quite definite streams at the base.

Cat 134.51   wt 2.3 kg.   Cortisone by mouth.

Survival time.   28 days.

Gross

No real adhesion was noted although when the removal was
completed the dura was seen to be attached to the wound
in a filmy fashion.

Microscopic.

The wound margins are not separated but it could not
be said that they are in good apposition. There is very
minimal thickening of the meninges. There is still large
numbers of phagocytes present. The gelatin sponge is still
present. There is a lot of collagen present and there is
a stream of fibroblasts and collagen along each side of
the wound.

Cat 137.51   wt2.5 kg.   Cortisone by mouth.

Survival time   36 days.

Gross

A small adhesion was found along the entire extent of the
wound.

Microscopic.

There is no inflammation or thickening of the meninges.
The gelatin sponge although fragmented , is still easily
recognised. The wound is not too well demarcated. Collagen
is plentiful. It is homogeneous but distinctly stained.
Many new vessels can be seen on scrutiny of the sections
but are seen mostly in the base of the wound.

Cat 7.51   wt 3 kg.   Large lacerated wound and
                               intra muscular cortisone.

Survival time   8 days.

Gross.

In this case a lacerated wound had been made. Some of the
damaged brain had been removed by the sucker and the
remainder allowed to remain. Overlying the skull defect
there was a dense adhesion of muscle and fascia. On further
dissection it was seen that muscle and dura were

adherent to the brain wound.

Cat 8.51. wt 3.3 kg   Lacerated wound and
                                        intra muscular cortisone.

Survival time 15 days.

Gross

As above a dense adhesion of muscle and dura to the wound

site was found.

Cat 21.51.   wt 3.35 kg   Lacerated wound and
                                        intra muscular cortisone.

Survival time 28 days.

Gross.

The animal had pursued an uneventful course and had

received a full series of intra muscular cortisone

injections, 10mgm/kg body weight. At sacrifice a dense

tough adhesion was found between the brain and the overlying

structures.

Cat 442.50   wt 2.5 kg.   Lacerated wound with cortisone
                                        inj. locally through scalp.

Survival time   9 days.

Gross

On incising the scalp at sacrifice a large amount of
yellowish fluid escaped which was taken to be unabsorbed
cortisone acetate. There was no adhesion encountered.

Cat 459.50   wt4.5 kg.   Lacerated wound with
                              cortisone inj. locally
                              Through scalp.

Survival time   14 days.

Gross.

In this case also, a large amount of yellowish serous
fluid escaped when the skin of the scalp was incised
at sacrifice. No adhesion was found but the cortex in
the region of the wound was soft and lacked the normal
texture and lustre.

Cat 443.50   wt 2.65 kg.   Lacerated wound with
                              cortisone inj. locally
                              through scalp.

Survival time   20 days.

Gross

Fig. 35.

Cats 247.51 and 249.51   polythene film and
    14 days   33 days.   intra musc. cortisone

No evidence of adhesion found at sacrifice

by naked eye inspection.

Fig. 36.

Cats 247.51 and 249.51   polythene film and
    14 days   33   intra musc. cortisone.

Sections of the brains following fixation

in 10% formalin. There are no adhesions to

be seen grossly.
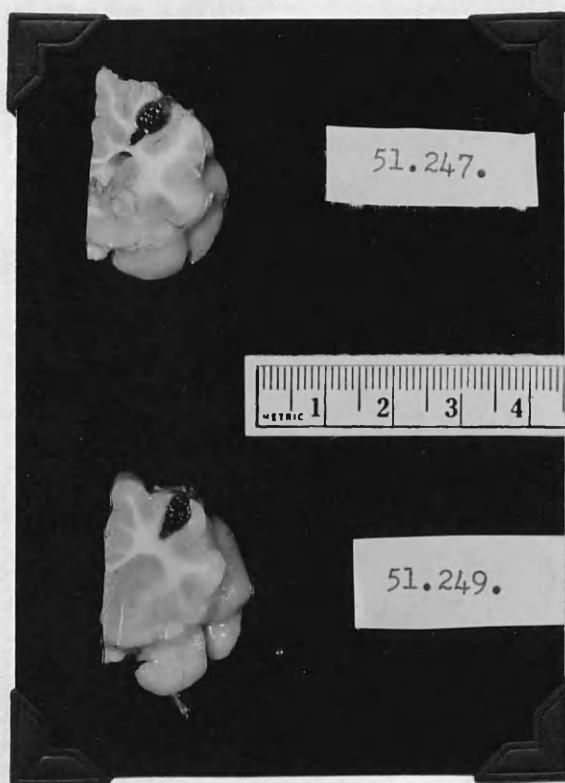
51.24

51.249.

51.247.

51.249.

Fig. 37.

Cat 250.51   45 day   Polythene film and
                             intra musc. cortisone

This shows the brain at sacrifice and

there is no evidence of an adhesion.

Fig. 38.

Cats 150.51 and 250.51   polythene film and
     5 days and   45 days   intra musc. cortisone.

Sections of brains fixed in 10% formalin

following sacrifice with no evidence of

adhesions.

Gross

The animal resisted the usual directions strenuously. The

day prior to ... ... fluid which was

expressed fr... ... ... next type of

fluid was p... ... ... pressure from

the scalp wo... ... ... was a

firm mass of ... ... myrist and

fibrinous ma... ... ... by ...

and was in ... ... vessel.

51.25

Rat level. ... ...

Physical siz...

Group at th... ... ... had had

death. Four... ... ... missing

pleural. Th... ... ...

nodule. ...

Microscopic... ... ... with

marked thi...

Rat ... XIX. ... ...

Survival ti...

51.150

51.250.
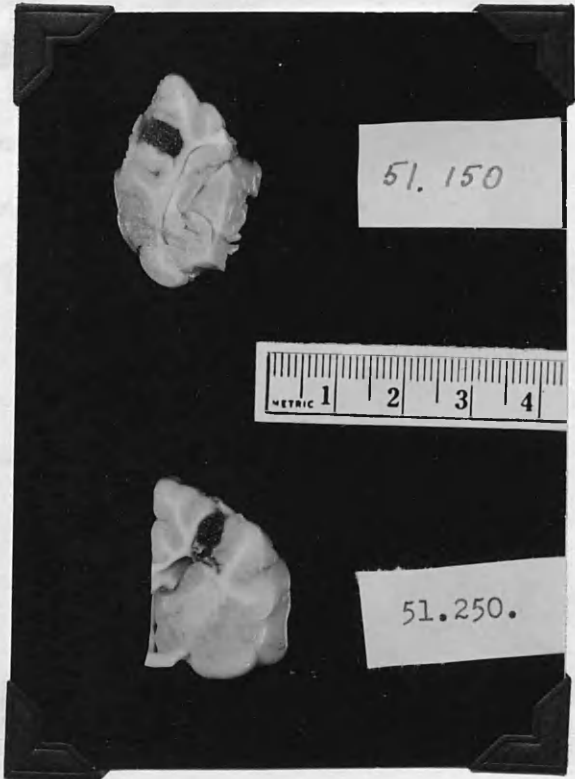
Gross

The animal resisted the local injections vigorously. The day prior to sacrifice a small amount of yellow fluid was expressed from the wound. At sacrifice this same type of fluid was present and escaped under slight pressure when the scalp was incised. Occupying the burr hole was a firm mass of what appeared to be cortisone crystals and fibrinous material. This was firmly tucked around by adhesions and was in its turn connected firmly to the wound.

Cat 149.51   wt 3.6kg.   Polythene film and
                                intra musc. cortisone.

Survival time   3 days

Gross At sacrifice the polythene film looked new and fresh. There was no adhesion and the film was easily removed. There was no evidence of haemorrhage or sepsis.

Microscopic. A definite inflammatory reaction with marked thickening of the meninges.

Cat   150.51   wt 3.3 kg.   Polythene film and
                                 intra musc cortisone.

Survival time   5 days.

Fig. 41.

Cat 247.51   14 day   polythene film and
                                       intra musc. cortisone.

This shows some mature looking collagen but no

instreaming of connective tissue such as was

seen in the controls and in 248.51 in which

the polythene had slipped from its original

position.

HVG.   x 120.

Fig. 42.   Fig. 43.

Cat 247.51   14 day   polythene film   Cat 247.51   14 day polythene
                        intra musc. cortis.   intra musc
                                                                 cortisone.

Showing inflammatory cell reaction
                                            Showing the gelatin sponge
and thickening of the meninges.
                                            in place - many blood corpusc

HVG.   x 120.   laked but no evidence of

                                            phagocytosis.

                                            HVG.   x 120.
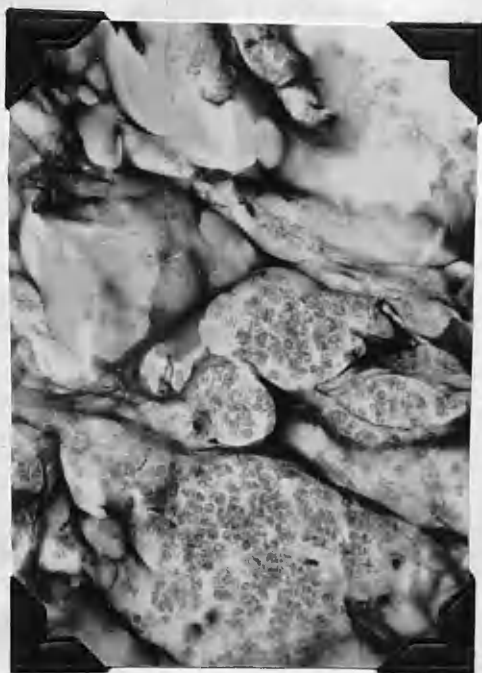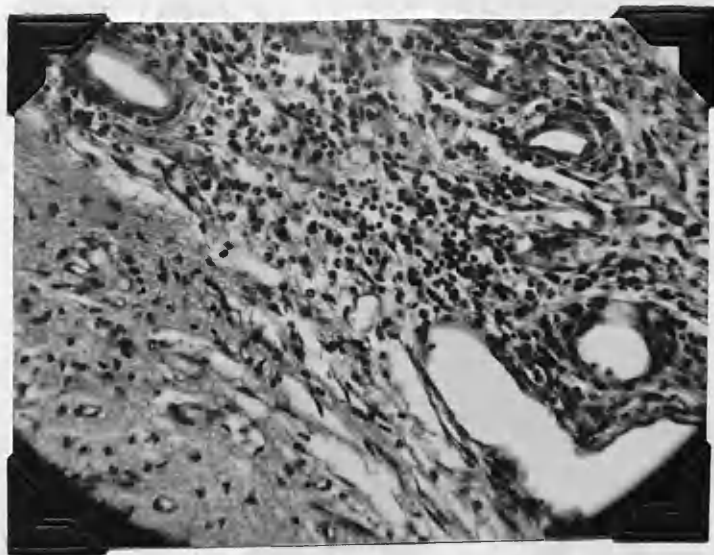
<u>Gross</u>. No adhesion was found. The polythene film looked fresh and was cleanly and freely removed. No evidence of haemorrhage.

<u>Microscopic</u>. The microscopic picture was almost identical to that of 149.51 (above) showing inflammatory reaction and thickening of the meninges.

<u>Cat 247.51</u>   wt 4 kg.   Polythene film and
                                      intra musc. cortisone.

<u>Survival</u>   14 days.

<u>Gross</u> No adhesion was found at sacrifice. The polythene film had a mucoid surface but was easily removed.

<u>Microscopic</u>. There was a marked inflammatory reaction and thickening of the meninges (fig 42). There is a lack of phagocytosis and in some areas lakes of what may be taken to be red blood corpuscles can be seen in the gelatin sponge without evidence of phagocytes. (fig 43)

<u>Cat 248.51</u>   wt 3.4kg.   Polythene film and
                                      intra musc. cortisone.

<u>Survival</u>   21 days.

<u>Gross</u> On sacrifice it was found that the film had slipped a little from its original position over the wound and at that point a small gelatinous adhesion was present.

<u>Microscopic</u>. There is again inflammation and thickening of the meninges. (fig 39) Also, where the polythene film

Fig. 39.

Cat 248.51   21 day   polythene film and
                                       intra musc. cortisone.

Showing the persisting thickening and

inflammatory reaction of the meninges

adjacent to the wound.

HVG.   x   120.

Fig. 40.

Cat 248.51   21 day   polythene film and
                                       intra musc. cortisone.

Showing the well marked connective tissue cicatrix

extending into the wound and thickening and

inflammatory reaction of the meninges.

In this case the polythene film had slipped

from its original position over the wound.

HVG.   x 60.
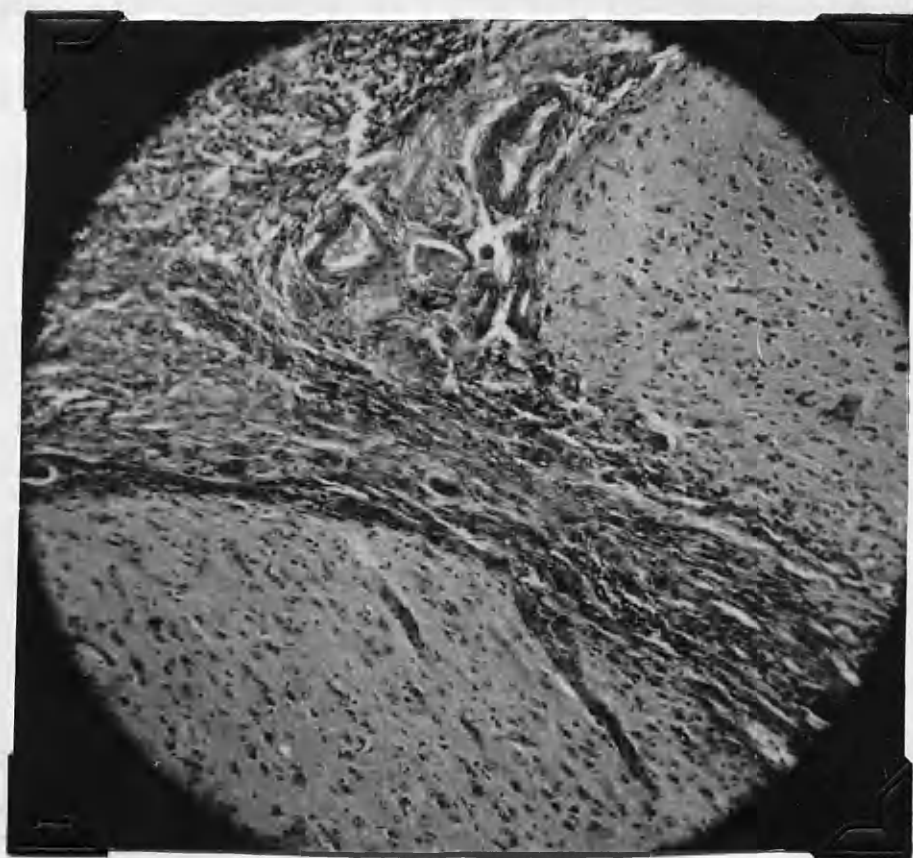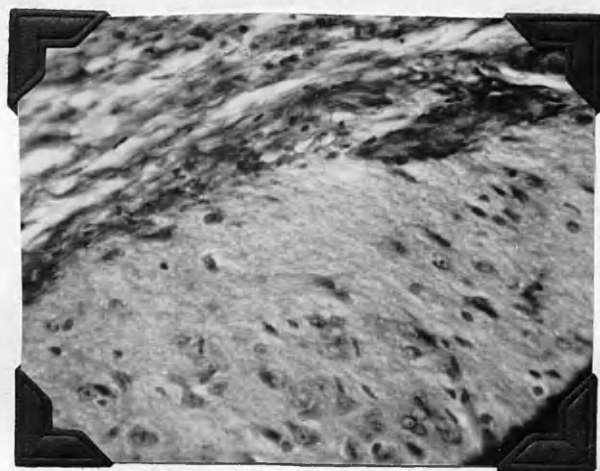
Fig. 44.

Cat 250.51   45 day polythene film and
                         intra musc. cortisone.

This shows again the marked inflammatory
response and thickening of the meninges
found in the animals treated as shown
above.

HVG. x 120.
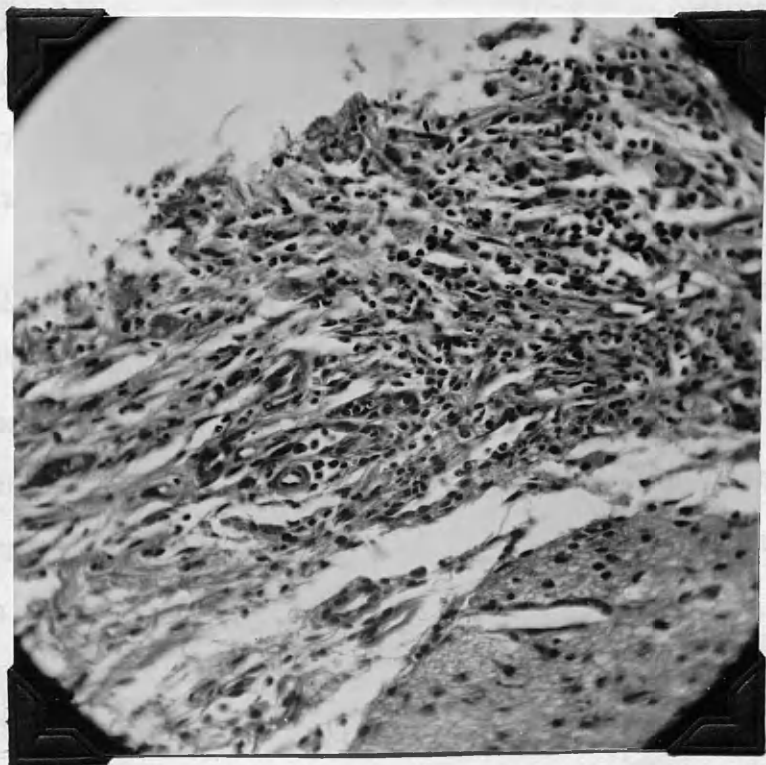
had slipped the cicatrix of connective tissue can be
seen (fig 40). The film itself was enclosed in a mucoid
looking capsule which was composed of fibroblasts and
inflammatory cells.

Cat 250.51   3.3kg.   <u>Polythene film and
                                     intra musc. cortisone.</u>

<u>Survival</u> 45 days.

<u>Gross</u> At sacrifice no adhesion was found (fig 38) but
the polythene film was enclosed in a mucoid capsule which
was separated from the brain and dura without much diffi-
culty.

<u>Microscopic.</u> The picture is that associated with the
previous animals described in this group. An inflammatory
cell reaction associated with thickening of the
meninges (fig 44). Even for 45 days the wound is not
well organised and large areas of the homogeneous
gelatin sponge are still present.

SUMMARY OF EXPERIMENTAL EVIDENCE.

Examination of the cellular elements throughout all the cortisone treated sections confirmed the view obtained from previous work, that there is no recognisable general effect of cortisone on the glial and neuronal elements.

It appears that the wounds in the animal treated with intra muscular cortisone and local acetate application are well demarcated from the surrounding brain and the architecture of the adjacent cerebral tissue showed less disturbance than in the control series. The wounds treated with local application of cortisone acetate in gelatin sponge in particular showed little derangement of adjacent tissue.

Moderate thickening and inflammatory reaction of the meninges was seen in some of the control series. It was particularly well marked in the animals where polythene film had been inserted and intra muscular injection of cortisone given as well. The membranes were greatly thickened and oedematous, and contained a great variety of inflammatory cells. In the case of the local application of powdered cortisone tablet marked thickening of the meninges and inflammatory reaction was noted. The animals treated with cortisone by mouth showed a complete series without reaction or thickening of the membranes.

Early in the study it was found that the gelatin sponge was invaded by phagocytes in the 7 day intra muscular cortisone, whereas this was not the case in the 8 day control. The sponge was clearly visible undergoing various degrees of disintegration up to 35 days in the control and intra muscular cortisone preparations ; by 40 days no definate outline of the sponge could be seen but various homogeneous crystals, presumably representing its end

stages, could be recognised. As far as the controls were concerned, this was in agreement with previous writing on the subject and it was thought that the sponge did not disappear earlier under cortisone therapy. Later in the study it became apparent that wounds treated by the local application of cortisone acetate (saline suspension) in gelatin sponge presented a totally different picture. Here it was found that the gelatin sponge had mostly disappeared by 8 days and by 21 days only odd fragments of it still persisted around the edge of the wound. Haemorrhage was excellently controlled. Grossly the wounds looked well and microscopically the appearance remaining was that of a small cyst.

Phagocytosis was evident in all the sections irrespective of the mode of treatment. As was to be expected it was most marked in the early stages. It was difficult to appreciate differences in the relative degree of phagocytosis in the different groups but it was clear that in the animals treated by the local application of cortisone acetate in gelatin sponge phagocytosis was very marked (fig 22)

Well marked meningo cerebral adhesions were found in all the control animals and in all but two treated with intra muscular cortisone. All those treated with cortisone by mouth presented adhesions. Local powdered cortisone tablet presented well marked adhesions. Where irregular lacerations had been made the cicatrices were marked and firmly attached. Where polythene film had been placed over the defect and intra muscular cortisone used in addition it was found, as might be expected, that there were no adhesions. However, the polythene film was in most cases encased in a thin mucoid membrane. In addition the presence of the film was associated with an intense inflammatory

reaction and thickening of the meninges. In one instance (248.51) the polythene film had slipped from its original position and a meningo cerebral cicatrix was present. Where cortisone acetate had been used locally in gelatin sponge no adhesions were found in two cases and in the third a small, soft gelatinous looking adhesion presented.

The question of the relative amount of connective tissue found in the wounds, and its maturity is a difficult problem. Fibroblasts appear in number in the cortisone as well as the control animals. No difference in size structure or staining could be determined with certainty. The amount of collagen is interesting and important. In the control, intra muscular cortisone and cortisone by mouth group the amount of collagen in the early stages appeared equal. At any rate there was no diminution of it in the cortisone treated animals. However there would appear to be an appreciable difference in the texture or consistancy of the collagen in the later animals. The collagen of the control animals was loose, fibery, wavy in outline and stained lightly. That of the animal treated by intra muscular cortisone was thicker more condensed and appeared more mature. (figs 8 & 9). In the animals treated by the local application of cortisone acetate in gelatin sponge there was definately much less connective tissue to be seen than in the control animals (fig 21)

Attention was paid to the relative number of blood vessels and capillaries in and about the wound. The best sections in this connection were those done in celloidin and stained with cresyl violet. By this means the endothelial cells lining the capillaries were clearly outlined. Observations in this

regard were not constant and over all it appeared that there was little

difference in the number of new capillaries in control and treated groups.

The animals were weighed daily. They were found almost without exception,

even those under prolonged cortisone therapy, to gain weight. This increase

was no doubt due to the regular and better feeding which most of the animals

received in the laboratory.

CONCLUSIONS.

The injection of intra muscular cortisone in the dose of 10mgm/kg. body wt. did not prevent meningo-cerebral adhesions nor materially influence the healing of incised or lacerated wounds of the brain in cats. This is a fairly large dose representing something of the order of 700mgm. per day in the human. There was no increase in the rate of absorption of the gelatin sponge.

The oral administration of cortisone in the dose of 10mgm/kg. body wt. did not prevent meningo-cerebral adhesions nor materially influence the healing of the wounds of the brain. There was no increase in the rate of disappearance of the gelatin sponge. Demarcation of the wound from the surrounding brain tissue was no better than in the controls.

The local application of powdered cortisone tablet in gelatin sponge caused marked inflammatory response and thickening of the meninges. There was definite meningo-cerebral cicatrix formation. The centre of the wound was occupied by a mass of inflammatory and necrotic debris. Wound healing was delayed. Demarcation from surrounding brain tissue was poor.

The local application of the saline suspension of cortisone acetate in gelatin sponge proved most successful. Two of the three animals in which this was used had no meningo-cerebral

adhesions, the remaining one had a small soft looking adhesion. The gelatin sponge achieved haemostasis in the normal fashion but disappeared from the wound much earlier. The 14 day animal and the 7 day animal showed little evidence at all of the sponge microscopically. The wound margins had fallen together well. There was no thickening of the meninges. No inflammatory reaction. Phagocytosis was well marked. Demarcation of the wound from the surrounding brain tissue was very good. There was definitely less connective tissue to be seen in relation to that seen in the other groups and in the controls. Only one dose of cortisone was required to treat these animals (about $1\frac{1}{2}$ cc. = 40 mgm) in contrast to the average dose of 30 mgm per day over varying periods in the other animals.

Polythene film has been reported by several investigators as a suitable material for duroplasty and the prevention of meningo-cerebral adhesions (p27). In this study intra muscular cortisone was used in conjunction with the film in an attempt to prevent the encapsulation of the film in the thin membrane of connective tissue. The injection of 10mgm./kg body wt. failed to prevent this. As was to be expected from previous writing (p27) the presence of the film prevented the formation of a distinct meningo cerebral adhesion. However, there was invariably associated an inflammatory reaction and thickening of the meninges. The healing process in the wound, notably phagocytosis, was delayed and connective tissue was plentiful throughout.

This work bears relationship to that of Baker and Whitaker (1949 and 1950: pp 69) who demonstrated that adrenocortical steroids inhibited growth of hair and epidermis by local action and that the application of hog adrenal extract dissolved in 25% alcohol to cutaneous wounds in the rat interfered with the formation of granulation tissue. It does not confirm the work of Howes et al (1950) who found that intra muscular cortisone prevented the formation of granulation tissue in the rabbit and rat. In this present work it must be remembered that the part played by the"blood brain barrier" is not known.

It remains to be seen whether or not the local administration of cortisone acetate in wounds of the brain in the human subject will substantiate the promise suggested.

ACKNOWLEDGEMENTS.

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