THE ANESTHETIC EYE: AN INVESTIGATION OF CHANGES IN THE ANTERIOR OCULAR SEGMENT OF THE MONKEY CAUSED BY INTERRUPTING THE TRIGEMINAL NERVE AT VARIOUS LEVELS ALONG ITS COURSE*

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INTRODUCTION

DEGENERATIVE CHANGES IN THE CORNEA AFTER SECTION OF THE TRIGEMINAL nerve were described in 1821 when Magendie[1] and Bell[2] demonstrated the consequences of cutting the sensory root in the rabbit. These changes occur in man as complications after operations on the fifth nerve to relieve the pain of tic douloureux or of head and neck cancer.

Our interest in these complications arose from having observed the eyes of patients who underwent operations on the trigeminal nerve for relief of tic douloureux by two different techniques. We observed that following the Dandy operation[3] on the caudal end of the sensory root performed by suboccipital craniotomy, there was little change in the anterior segment of the ipsilateral eye. On the other hand, after Frazier's operation[4,5] performed on the rostral portion of the posterior root by subtemporal craniotomy, abnormal findings frequently occurred in the ocular anterior segment.

These changes were characterized by periodic episodes of reddened or slightly edematous eyelids, ciliary flush, and faint flare and cells in the anterior chamber. The cornea was frequently anesthetic and often showed staining with fluorescein. Corneal ulceration occurred in some patients but responded to local antibiotics and tarsorrhaphy.

The monkey (Macacus rhesus) was chosen as the experimental animal because the anatomy of the fifth nerve and gasserian ganglion is similar

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to that of man.[6,7,8] The procedure used was to cut the fifth cranial nerve at different sites along its course, to observe the ocular changes postoperatively, and to note the histopathologic changes after sacrificing the animals.

The primary purpose of this investigation was the selection of an operation having the least adverse effect upon the eye. This report describes the results of the study.

METHODS AND MATERIALS

Twenty-four adult rhesus monkeys were used in these experiments. All operations and clinical observations were performed under anesthesia induced by intramuscular sernylan (phencyclidine hydrochloride), 7 mg, per kg of body weight. The operations were performed on the right sides of the animals and the left sides were used as controls.

Lesions were created in the fifth cranial nerve by either mechanical section with a scalpel or by heat transmitted through an electrode measuring 0.4 mm in diameter by 1.0 mm in length. Heat was induced by a radiofrequency generator with 50 milliamperes for 10 seconds yielding a current of 0.5 megacycles.

Following fifth nerve section, temporary tarsorrhaphies were performed on ipsilateral eyes by passing a double armed 4-0 black silk suture through the lid borders and tying over a stint of silicone tubing. By untying the suture the tarsorrhaphy could be taken down for the purpose of observing the eye. After observation the suture was tied again to protect the cornea. Whenever a tarsorrhaphy broke down, keratitis developed immediately, as will be noted below. This was treated by repeating the tarsorrhaphy and giving local and systemic antibiotics.

Anesthesia following resection of the ophthalmic branch or the posterior root of the fifth nerve (N V) was demonstrated by the following techniques:

(1) Skin of forehead, eyelids and face were tested by pinching with a hemostat. Reaction was evidenced by the animal wincing or withdrawing from the stimulus.

(2) Corneal sensation and blink reflex were tested by touching cornea with wisps of cotton, #1 nylon suture and the butt of a muscle hook.[9,10,11]

All photographs of operations and autopsy material were made by using either the Medical-Nikkor or Micro-Nikkor lens. The Zeiss slit lamp was used for evaluation pre- and postoperatively. Anterior segment fluorescein photography was performed with the Nikon slit lamp camera.

The experiment was divided into five groups of operations, as follows (Figure 1):

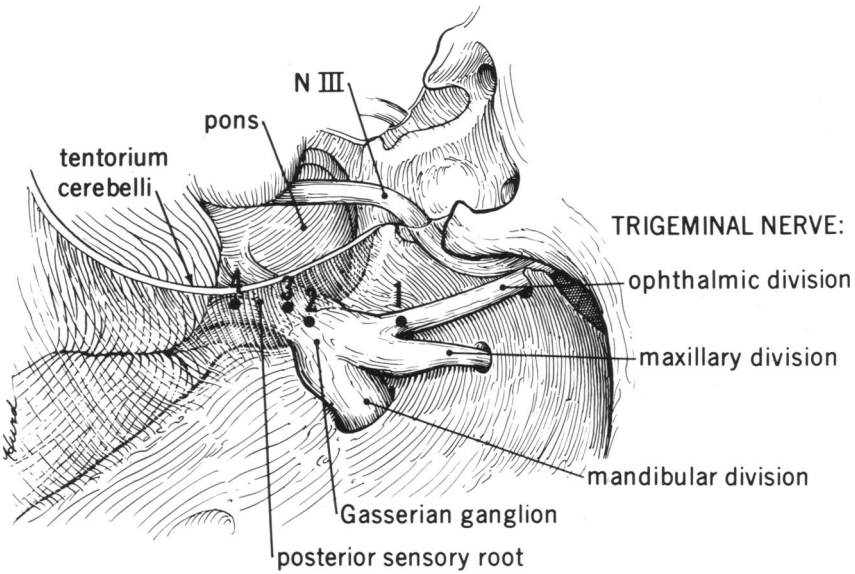


FIGURE 1
Diagram of fifth nerve to illustrate location of lesions created in experiments.

Group I — Division of the ophthalmic branch of the trigeminal nerve immediately anterior to the gasserian ganglion.

Group II — Intradural posterior root rhizotomy of N V in the retrogasserian area between the gasserian ganglion and the tentorium.

Group III — Intradural transtentorial rhizotomy of the rostral portion of the posterior root of N V within the tentorial notch.

Group IV — Suboccipital, subcerebellar, posterior root rhizotomy of N V at its entrance into the pons.

Group V — Control Group.

A. Resection of N III followed by ipsilateral tarsorrhaphy
B. Stimulation of N III followed by ipsilateral tarsorrhaphy
C. Sham operation: exploration of gasserian ganglion and N V with its three divisions by extradural exposure followed by ipsilateral tarsorrhaphy
D. Sham operation: exploration of gasserian ganglion and N V with its three divisions by intradural exposure followed by ipsilateral tarsorrhaphy

E. Sham operation: exploration of the entrance of N V into the pons by the subcerebellar route followed by ipsilateral tarsorrhaphy
F. Tarsorrhaphy alone on a normal monkey
G. Sacrifice of a normal animal

A brief description of operations on each group follows:

The head was prepared for surgery by shaving the operative area and cleansing with soap and water followed by alcohol. Bleeding was controlled by electrocoagulation and was not excessive. No attempt was made to constantly monitor blood pressure during surgery. No animal had an adverse reaction except #16 which died of an aeroembolism as noted below.

Group I: *Division of the ophthalmic branch of the trigeminal nerve immediately anterior to the gasserian ganglion.*

A. Four monkeys underwent a right subtemporal craniotomy with extradural exposure of the gasserian ganglion and the three branches of the trigeminal nerve (Figure 2). An attempt was made to mechanically cut the ophthalmic branch with a scalpel immediately in front of the gasserian ganglion. In the monkey however, this branch lies almost entirely in the cavernous sinus wall until its entrance into the ganglion itself. Because excessive bleeding occurred from entering the cavernous sinus, mechanical section of this branch was abandoned. In-

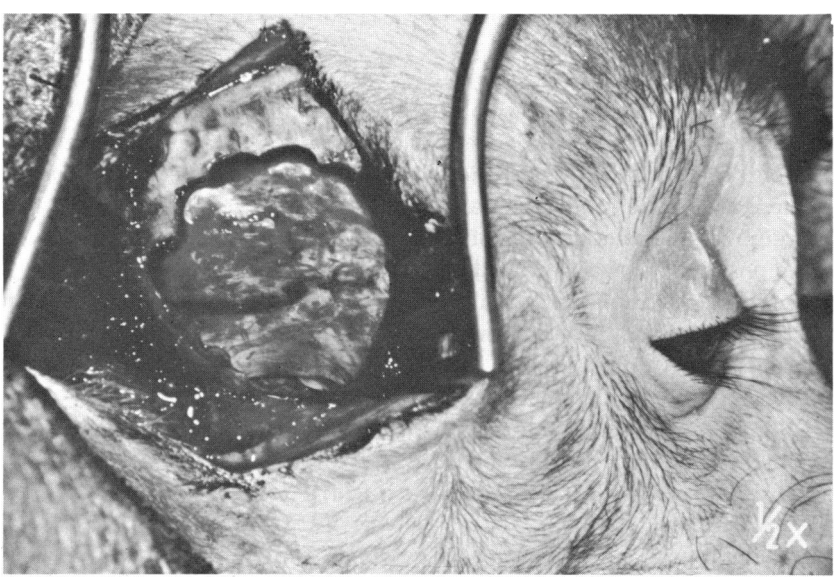


FIGURE 2
Operative field in the subtemporal craniotomy approach.

stead, a specific lesion was created by the radiofrequency lesion generator in the ophthalmic branch of the trigeminal nerve immediately in front of the ganglion. Ipsilateral temporary tarsorrhaphy was then performed as described above.

B. Two monkeys received a right subtemporal craniotomy with intradural exposure of the gasserian ganglion and its three branches. This affords better exposure than the extradural approach but requires intradural elevation of the temporal lobe in order to visualize the structures of interest. Specific lesions were then created in the ophthalmic branch by application of the radiofrequency lesion generator. Ipsilateral temporary tarsorrhaphy was then performed.

Group II — *Intradural posterior root rhizotomy of the trigeminal nerve in the retrogasserian area between the gasserian ganglion and the tentorium.*

Three monkeys were used in this experiment. A right subtemporal craniotomy was performed. The dura was incised and the temporal lobe elevated exposing the gasserian ganglion. The third cranial nerve was located. Care was taken to avoid the third cranial nerve and the gasserian ganglion so that a specific lesion was created only in the posterior root by the radiofrequency lesion generator. Attempts were made to protect

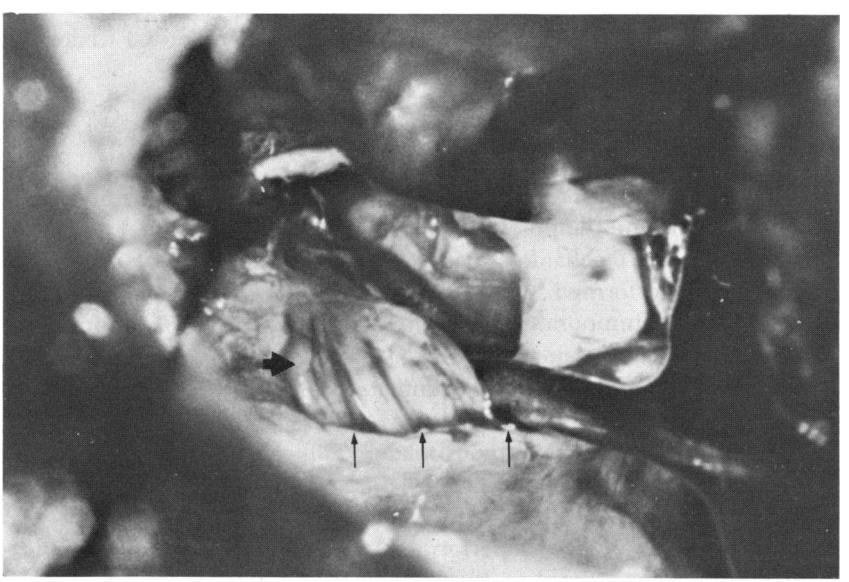


FIGURE 3
Surgeon's view of the posterior sensory root of N V (large black arrow) brought forward on a nerve hook after opening the tentorium (small arrows).

the temporal lobe by cottonoid sponges or Teflon between the retractor and the brain. Ipsilateral temporary tarsorrhaphy was then performed.

Group III — *Intradural transtentorial posterior root rhizotomy of the rostral portion of the trigeminal nerve within the tentorial notch.*

Four monkeys were used in this experiment. A right subtemporal craniotomy was performed. The dura was incised and the temporal lobe elevated exposing the gasserian ganglion and its three branches. The third cranial nerve was located. The tentorium was incised posterior to the third nerve. The posterior root of the trigeminal nerve was identified and brought forward on a nerve hook (Figure 3).

In three of the monkeys, the posterior root was mechanically cut with a scalpel. In one monkey a lesion was created by two applications of the radiofrequency lesion generator. Ipsilateral temporary tarsorrhaphy was then performed.

Group IV — *Suboccipital, subcerebellar posterior root rhizotomy of the trigeminal nerve at its pontine entrance.*

Four monkeys were used in this experiment. A right suboccipital craniotomy was performed and the right cerebellar hemisphere elevated. The trigeminal root was identified between the petrosal vein and acoustic nerve (Figure 4). Mechanical transection of the trigeminal root was then performed at its pontine entrance with a scalpel. Ipsilateral temporary tarsorrhaphy was then performed.

Group V — *The control group.*

Seven monkeys were in this group, one being used in each of the experiments listed below.

A. A right subtemporal craniotomy was performed. The dura was incised and the temporal lobe elevated. The third cranial nerve was exposed and mechanically cut. Ipsilateral temporary tarsorrhaphy was then performed.

B. A right subtemporal craniotomy was performed. The dura was incised and the temporal lobe elevated. The third cranial nerve was exposed and electrically stimulated. Bipolar stimulation from 0.5 to 0.8 volts at 50 cycles per second for 30 seconds was performed and observations and photographs made. This was repeated at 75 cycles per second for 30 seconds. Ipsilateral temporary tarsorrhaphy was then performed.

C. A sham operation was performed exposing the gasserian ganglion and its three branches by a right subtemporal craniotomy and extradural approach. An ipsilateral temporary tarsorrhaphy was then performed.

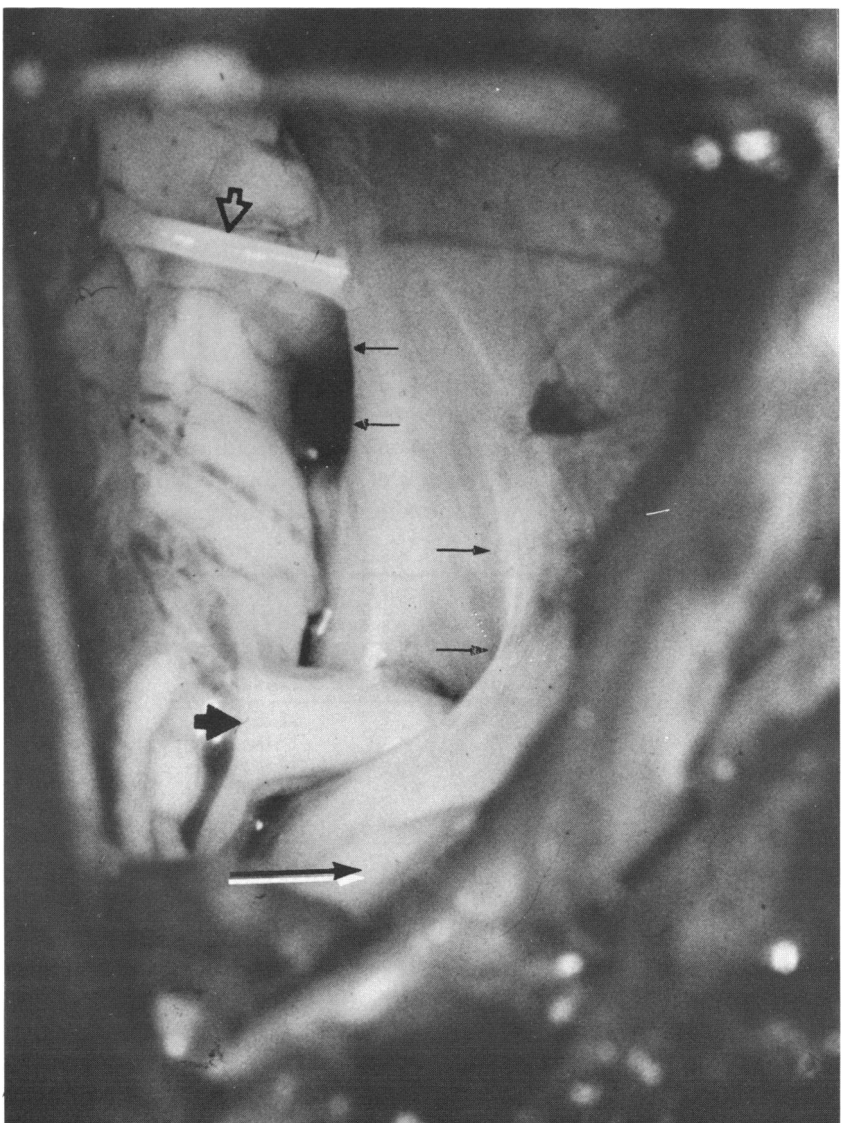


FIGURE 4

Suboccipital view of the pontine entry zone of the posterior sensory root of N V (large black arrow). Note the third nerve (white arrow), eighth nerve (white and black arrow) and tentorium (small black arrows).

D. A sham operation was performed exposing the gasserian ganglion and its three branches by a right subtemporal craniotomy and intradural approach. The temporal lobe was elevated intradurally. An ipsilateral temporary tarsorrhaphy was then performed.
E. A sham operation was performed exposing the entrance of the trigeminal nerve into the pons by a right suboccipital, subcerebellar approach. Ipsilateral temporary tarsorrhaphy was then performed.
F. A right tarsorrhaphy was performed on a normal monkey.
G. A normal monkey was sacrificed as described below.

PREOPERATIVE AND POSTOPERATIVE PROTOCOL

All of the animals used in these experiments were adult monkeys who were kept in quarantine in individual cages for three weeks prior to ophthalmologic evaluation. The veterinarian caring for the animals performed a general physical evaluation and tuberculin test upon arrival in the kennel. After the third week of quarantine, a general physical examination was repeated and ophthalmological examination performed.

TABLE I: GROUP AND INDIVIDUAL IDENTIFICATION OF EXPERIMENTAL ANIMALS, AND NUMBER OF DAYS BEFORE SACRIFICE AFTER SURGERY

Group	Monkey #	Sacrificed No. of Days Post-op.
I	(4)	21 days
	(5)	12 days
	(6)	15 days
	(7)	7 days
	(8)	8 days
	(9)	14 days
II	(10)	21 days
	(11)	12 days
	(12)	7 days
III	(13)	8 days
	(14)	10 days
	(15)	8 days
	(17)	21 days
IV	(1)	6 mos.
	(2)	3 mos.
	(16)	Died aeroembolism
	(3)	21 days
V	(18)	7 days
	(19)	7 days
	(20)	7 days
	(21)	7 days
	(22)	7 days
	(23)	21 days
	(24)	Normal animal

The eye evaluation included the following: (1) External examination; (2) Slit lamp examination; (3) Intraocular pressure measured by the Perkins hand-held applanation tonometer; (4) Sensation of the forehead, eyelids and cornea tested as described above; (5) Schirmer testing for tears under ophthaine anesthesia.

To insure the safety of participants, all preoperative and postoperative procedures were performed under sernylan anesthesia. The operated side was always compared to the unoperated side which was used as a control.

The temporary tarsorrhaphy was taken down and the animals were evaluated as follows:

(1) External examination
(2) Slit lamp examination
(3) Intraocular pressure taken by the Perkins hand-held applanation tonometer
(4) Schirmer test for tears with ophthaine anesthesia
(5) Sensation of forehead, eyelids and cornea tested
(6) Cocaine 4% and adrenalin 1:1000 test for integrity of the sympathetic nerve supply

Temporary tarsorrhaphy was then re-done and the animal returned to the kennel.

SACRIFICE OF ANIMALS AND FIXATION OF TISSUE

Animals were sacrificed from 7 days to 6 months postoperatively according to the schedule listed below (Table I).

The animals were killed by exsanguination under nembutal (sodium pentobarbital) anesthesia followed by perfusion of the entire vascular system with saline and buffered formalin 10% for at least 30 minutes.

The animals were then decapitated at C5 or C6 and the heads placed in buffered formalin 10% for at least 30 days to provide further fixation.

The eyes were then removed and sent to the Armed Forces Institute of Pathology for sectioning and preparation of histopathologic material. For autopsy, the brain stems were removed leaving the trigeminal root and gasserian ganglion attached to the base of the skull. Photographs of these were then taken.

The eyes were embedded in paraffin according to the usual techniques and one-half sectioned for microscopic evaluation. The corneas were removed from the remaining one-half and prepared in flat sections 7 microns thick, for staining by Hematoxylin and Eosin and Bodian's silver staining technique.[12] Study of the corneal nerves was confined to the corneal stroma away from the limbus and well beneath the level of Bowman's membrane as advised by Zander and Weddell.[10,13,14]

The gasserian ganglia from both the operated and unoperated sides together with the posterior roots and three divisions were removed in toto. These specimens were embedded in paraffin and serial transverse sections 7 microns thick were made. They were then stained by the techniques of Nissl, Bodian and Weil,[12] and Fink-Heimer.[15,16]

Serial transverse sections 20 microns thick of the brain stems were made above and below the entrance of the trigeminal root into the pons. These sections were then stained by the techniques of Bodian and Weil.[12]

Monkey #4 was injected with sodium fluorescein solution through the femoral vein with the animal under deep barbiturate (35 mg/kg of pentobarbital) anesthesia according to techniques of Grayson and Laties.[17] The eyes were enucleated and freeze-dried by immersing for 2 minutes in isopentane cooled to −130° C by liquid nitrogen bath. They were then freeze-dried for 5 to 9 days at −35° C. They were sent to Dr. Alan Laties for study.

RESULTS

PREOPERATIVE CLINICAL EVALUATION

The pupils of all animals were equal and reacted normally to light despite the use of sernylan anesthesia. Surprisingly, many of the animals displayed evidence of previous anterior segment inflammatory disease. Table II summarizes these findings. One animal (monkey #17) had an old perforated corneal injury of the left eye that did not involve the lens or iris.

Intraocular pressures ranged from 17 to 25 mm Hg with an average of 21.2 mm Hg as measured by the Perkins hand-held applanation tonometer. Local ophthaine anesthesia was used in addition to the intramuscular sernylan for this examination.

Preoperative Schirmer testing for tears under local ophthaine and sernylan was within normal limits in all of the animals.

All animals had normal sensation of the skin of the forehead, eyelids, and face. The blink reflex was not abolished by sernylan anesthesia in any animal when tested by #1 nylon or by the butt of a muscle hook. Wisps of cotton, on the other hand, failed to elicit this reflex in some.

OBSERVATIONS DURING SURGERY

Mydriasis of the ipsilateral eye was noted in some animals during surgery (Table III). It occurred whenever the temporal lobe was elevated and returned to normal size and shape with release of the pressure necessary for elevation. It was more common during intradural than extradural surgery.

TABLE II: SUMMARY RESULTS OF PRE- AND POSTOPERATIVE OPHTHALMIC EXAMINATION OF EXPERIMENTAL ANIMALS

Monkey #	Group #	Pre-op. IOP	Pre-op. Schirmer	Pre-op. Slit	Post-op. IOP	Post-op. Schirmer	Post-op. Slit
1 O.D.	IV	24	26	± flare & cells	22	28	± flare & cells
O.S.		24	28	± flare & cells post. syn.	21	SAT	± flare & cells post. syn.
2 O.D.	IV	22	17	0	20	26	0
O.S.		22	22	0	22	SAT	0
3 O.D.	IV	23	30	± flare & cells	24	26	± flare & cells
O.S.		24	24	± flare & cells	24	25	± flare & cells
4 O.D.	I	24	25	± flare & cells	22	SAT	2+ flare & cells
O.S.		22	20	± flare & cells	21	SAT	± flare & cells
5 O.D.	I	21	22	0	17	28	± flare & cells
O.S.		20	28	0	22	26	0
6 O.D.	I	18	27	0	20	SAT	+ flare & cells
O.S.		19	32	0	20	SAT	0
7 O.D.	I	25	SAT	0	20	SAT	+ flare & cells
O.S.		24	28	0	24	SAT	0
8 O.D.	I	19	22	0	18	26	2+ flare & cells
O.S.		21	30	± flare & cells post. syn.	22	30	± flare & cells
9 O.D.	I	22	SAT	± flare & cells post. syn.	20	SAT	2+ flare & cells post. syn.
O.S.		24	27	± flare & cells o.u.	24	SAT	+ flare & cells o.u.
10 O.D.	II	23	28	± flare & cells	19	24	2+ flare & cells keratitis ulcer
O.S.		22	25	± flare & cells	23	28	± flare & cells
11 O.S.	II	21	26	0	22	22	2+ flare
O.S.		23	28	Old post. syn.	22	26	Old post. syn.
12 O.D.	II	24	27	0	20	SAT	2+ flare
O.S.		22	25	± flare & cells post. syn.	22	SAT	± flare post. syn.
13 O.D.	III	20	30	± flare & cells	20	28	+ flare & cells
O.S.		19	22	± flare & cells	20	26	+ flare & cells

TABLE II *(Continued)*

Monkey #	Group #	Pre-op. IOP	Pre-op. Schirmer	Pre-op. Slit	Post-op. IOP	Post-op. Schirmer	Post-op. Slit
14 O.D.	III	18	30	± flare & cells post. syn.	20	SAT	Perforated cornea
O.S.		19	30	± flare & cells post. syn.	20	SAT	± flare & cells post. syn.
15 O.D.	III	20	SAT	± flare & cells post. syn.	22	SAT	+ flare & cells
O.S.		19	SAT	± flare & cells post. syn.	22	SAT	± flare & cells
16 O.D.	IV	AEROEMBOLISM					
17 O.D.	III	19	28	0	20	26	2+ flare & cells
O.S.		18	22	Old corneal scar	21	28	Old corneal scar
18 O.D.	V	21	SAT	0	16	26	0
O.S.		20	SAT	0	20	28	0
19 O.D.	V	22	24	0	21	SAT	0
O.S.		24	22	0	22	SAT	0
20 O.D.	V	24	24	± flare & cells post. syn.	22	SAT	± flare & cells
O.S.		24	22	± flare & cells post. syn.	22	SAT	± flare & cells
21 O.D.	V	20	26	± flare & cells post. syn.	19	28	± flare & cells
O.S.		21	28	± flare & cells post. syn.	20	26	± flare & cells
22 O.D.	V	18	28	0	20	SAT	0
O.S.		17	24	0	18	SAT	0
23 O.D.	V	22	SAT	± flare & cells post. syn.	19	SAT	± flare & cells post. syn.
O.S.		21	SAT	± flare & cells post. syn.	20	SAT	± flare & cells post. syn.
24 O.D.	V	19	28	+ flare & cells post. syn.	20	SAT	± flare & cells post. syn.
O.S.		20	26	+ flare & cells post. syn.	20	SAT	± flare & cells post. syn.

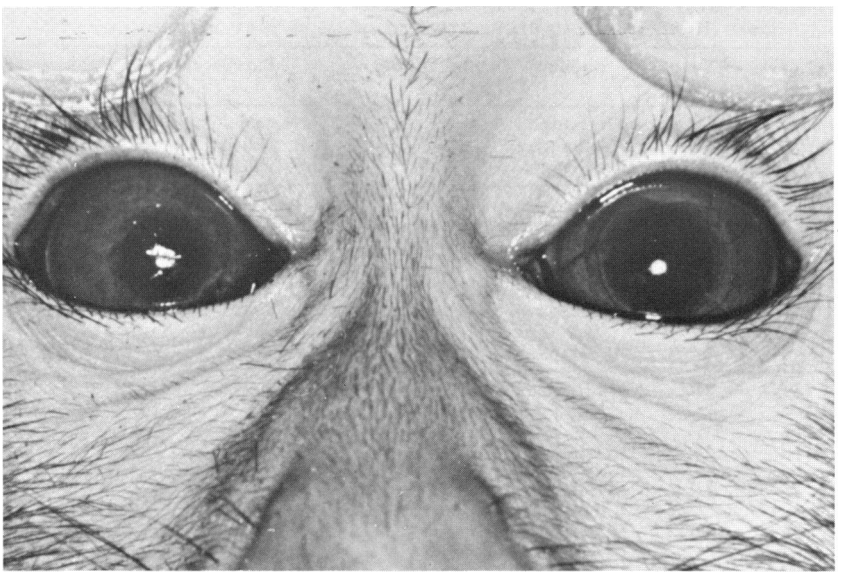


FIGURE 5
Monkey #7 immediately after a lesion was created in the ophthalmic nerve by the radiofrequency lesion generator. Note slight miosis of the right pupil.

Section of either the ophthalmic branch or of the posterior root of the trigeminal nerve by mechanically cutting or by the radiofrequency lesion generator, resulted in miosis of the ipsilateral eye during surgery (Figure 5). The pupil remained miotic in these animals during the postoperative stage (see description under postoperative observations in Table III). In animals in which more permanent third nerve damage occurred, however, this miotic reaction was not elicited.

In the suboccipital approach we encountered very little uncontrollable bleeding despite inadvertently tearing the petrosal vein in two monkeys. In one monkey however, (#16) aeroembolism occurred upon opening the vein and the animal promptly expired. In another monkey (#3), excessive traction in elevating the cerebellum damaged this structure. There were no unusual pupillary reactions observed during surgery with this approach to the trigeminal root.

POSTOPERATIVE CLINICAL EVALUATION

Tables II and III summarize the postoperative clinical evaluation regarding slit lamp examination, pupillary changes, intraocular pressure and Schirmer testing for adequacy of tears.

TABLE III: PUPILLARY CHANGES RELATED TO SURGERY OF THE TRIGEMINAL NERVE

Monkey #	Group #	Pupillary Change During Surgery	Pupillary Change After Surgery
1	IV	No change	Normal
2	IV	No change	R. Miosis
3	IV	No change	R. Miosis
4	I	R. Miosis	R. Miosis
5	I	R. Mydriasis (N III injury)	R. Mydriasis (N III injury)
6	I	R. Miosis	R. Miosis
7	I	Mydriasis on elevating temporal lobe followed by R. Miosis	R. Miosis
8	I	Mydriasis on elevating temporal lobe	R. Mydriasis for 1 week then Miosis
9	I	R. Miosis	R. Miosis
10	II	Mydriasis on elevating temporal lobe followed by R. Miosis	R. Miosis
11	II	R. Miosis	R. Miosis
12	II	R. Miosis	R. Miosis
13	III	Mydriasis on elevating temporal lobe followed by R. Miosis	R. Miosis
14	III	R. Miosis	R. Miosis — then corneal perforation
15	III	R. Miosis	R. Miosis
16	IV	DIED AEROEMBOLISM	
17	III	R. Mydriasis on elevating temporal lobe	R. Mydriasis for 1 week then R. Miosis
18	V	R. Mydriasis after N III cut	R. Mydriasis
19	V	R. Miosis	Normal pupil
20	V	Normal	Normal
21	V	Elevation temporal lobe caused R. Mydriasis	R. Mydriasis for 1 week then normal pupil
22	V	Normal	Normal
23	V	Normal	Normal
24	V	Normal	Normal

A. *Pupillary Effect*

In two animals (monkey #8 from Group I and #17 from Group III) mydriasis persisted postoperatively for 1 week. In one animal, (monkey #5 from Group I), operated upon early in our study, permanent mydriasis occurred.

Following resection of the trigeminal nerve, miosis occurred in every case in the postoperative period with the exception of monkey #5 noted above. In the case of monkeys #8 and 17, miosis occurred one week postoperatively following the mydriasis caused by intradural elevation of the temporal lobe. The cocaine test resulted in mydriasis in all animals with miosis and the adrenalin test had no effect on the pupil.

TABLE IV: INTRAOCULAR PRESSURE CHANGES RELATED TO TRIGEMINAL NERVE SURGERY

Group	Pre-op. Tension		Post-op. Tension	
	O.D.	O.S.	O.D.	O.S.
I	21.5	21.6	19.5	22.1
II	22.6	22.3	20.3	22.3
III	19.2	18.7	20.5	20.7
IV	23.0	23.3	22.0	22.3
V	20.8	21.0	19.5	20.2
Av.	21.4	21.4	20.3	21.5
Av. Group I thru IV	21.6	21.5	20.6	21.8

B. *Cerebellar Damage*

In monkey #3, the cerebellum was damaged in identifying the trigeminal root. This animal was somewhat ataxic and had nystagmus during the first postoperative week. These sequelae of surgery, however, subsided without residual.

C. *Intraocular Pressure*

In Groups I through IV, in which the trigeminal nerve was sectioned (#1 through #17), the average postoperative intraocular pressure measured 20.6 mm Hg in the ipsilateral eye after 1 to 2 weeks, while in the contralateral control eye, the pressure averaged 21.8 mm Hg (Table IV).

In Group V (#18 - 24), the intraocular pressure averaged 19.5 mm Hg in the ipsilateral eye while the fellow eye measured 20.2 mm Hg.

The postoperative pressure measured lowest in the eye of the control animal (#18 of Group V) in whom the oculomotor nerve was divided. Of interest is the observation that in Monkey #5 of Group I, whose oculomotor nerve was permanently damaged during surgery, the intraocular pressure was also lowered considerably.

D. *Schirmer Tear Test*

Schirmer testing for adequacy of tear formation showed no change after operation performed either by the intradural or extradural approach. All animals had normal tearing postoperatively.

E. *Corneal Changes*

Corneal anesthesia developed in all groups, except Control Group V. In Group I, anesthesia was confined only to the area supplied by the ophthalmic branch of N V. In Groups II, III, and IV, anesthesia occurred in the entire area supplied by N V.

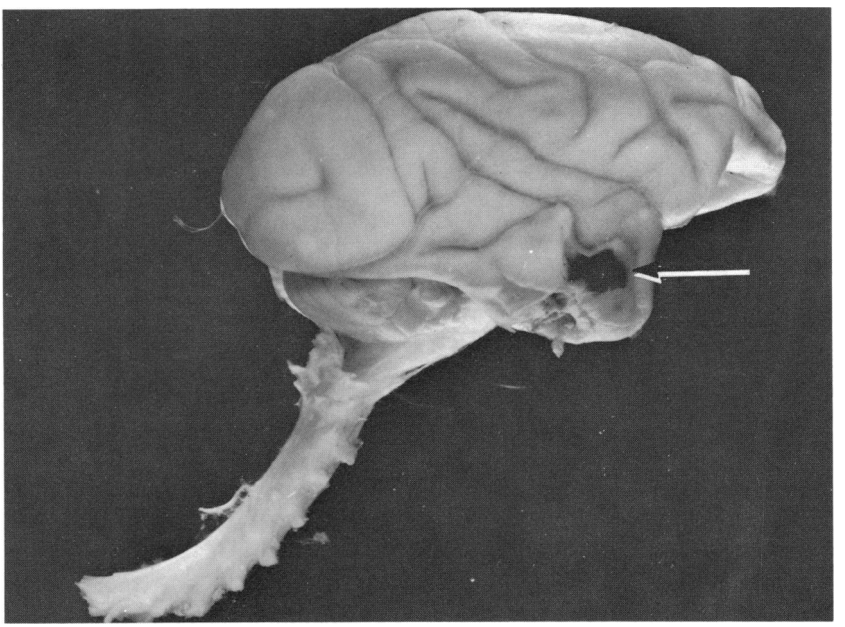


FIGURE 6
Intratemporal lobe hemorrhage in monkey #17 from excessive pressure on elevation for exposure.

When the tarsorrhaphy broke down (monkeys #10 and 14) keratitis and corneal ulceration immediately developed. Despite repeated repair of the tarsorrhaphy and systemic antibiotics, the cornea perforated in monkey #14. We could not determine whether this animal pulled out the sutures and scratched the cornea or whether the sutures sloughed from tissue edema and the cornea developed a "trophic" ulcer.

Most of the animals, however, tolerated the tarsorrhaphies without self-inflicted lesions. In the case of monkey #10, the keratitis subsided under treatment and repeat tarsorrhaphy.

F. *Iritis*

Slit lamp examination preoperatively had revealed the unexpected presence of low-grade iritis in many of the animals. Faint flare and cells were noted as well as posterior synechiae. Postoperatively, the inflammatory reaction usually became worse in the ipsilateral eye while the control eye remained essentially the same.

G. *Fluorescein Angiographic Studies*

In an attempt to determine whether or not vasodilatation and vascular permeability of the iris and ciliary body were present, monkey #4 was

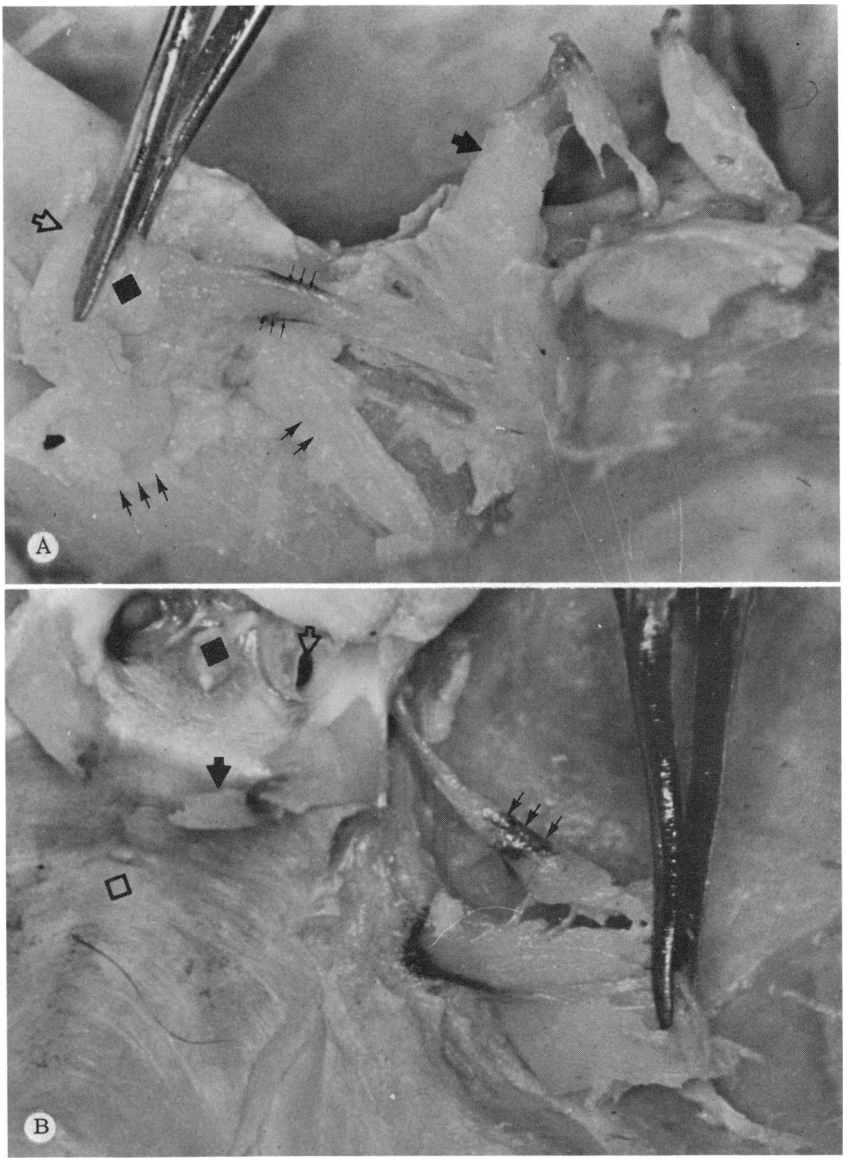
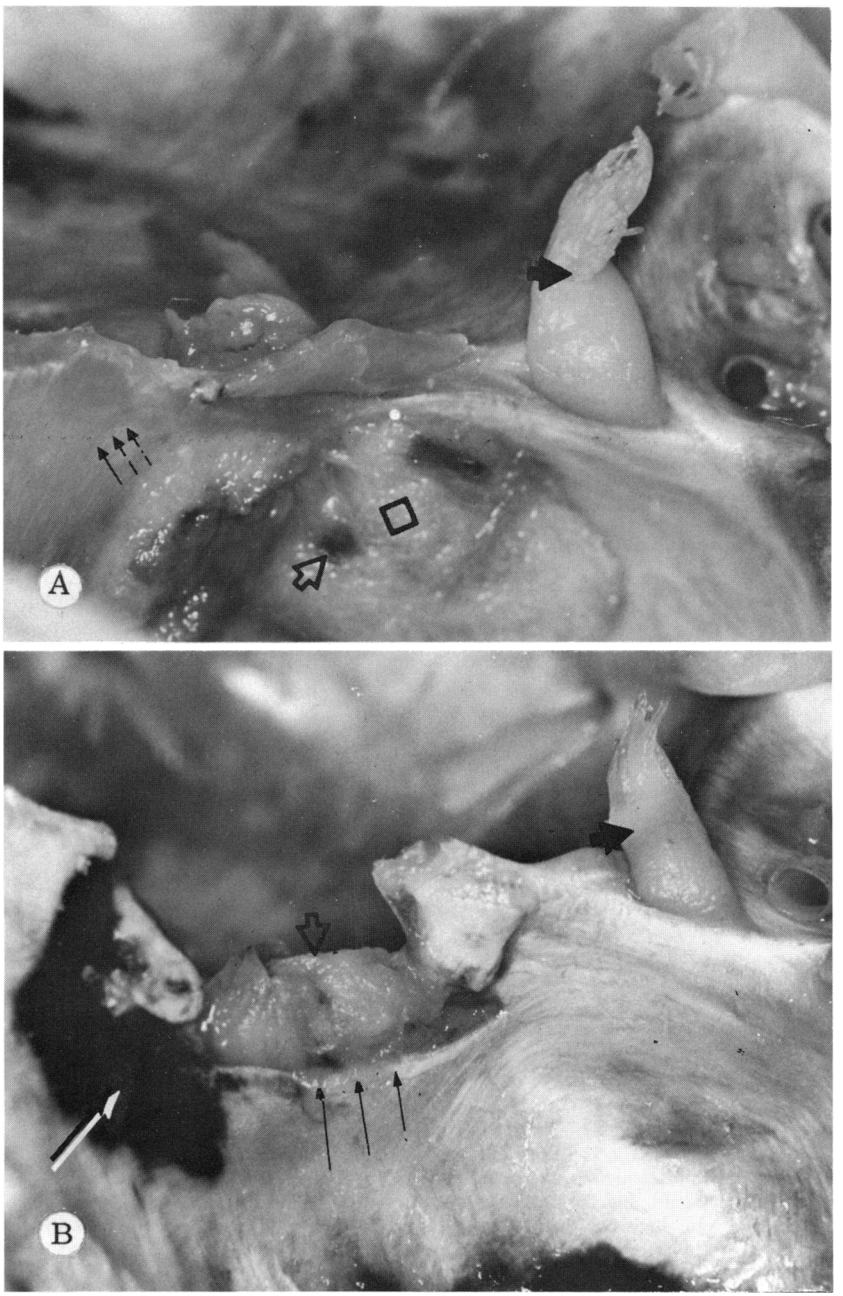


FIGURE 7

A: Autopsy of monkey #7. View from middle cranial fossa. Note burn in ophthalmic division (small arrows). The third nerve is designated by large black arrow, the maxillary division by two black arrows, the mandibular by three black arrows, the gasserian ganglion by a black diamond, and the posterior root by a large white arrow. B: Autopsy of monkey #7. View from clivus (white diamond). Note burn in ophthalmic division (small arrows), internal carotid artery (white arrow), pituitary fossa (black diamond) and third nerve (black arrow).


A
B

injected with fluorescein and immediately sacrificed. The eyes were immersed in liquid nitrogen and sectioned by Dr. Alan Laties.[17] He felt that the vessels of these eyes were not leaking.

Anterior segment fluorescein angiography was unsuccessful in demonstrating fluorescein leakage from the irides *in vivo*.

GROSS FINDINGS AT AUTOPSY

A. *The Brain*

Gross examination of the brains revealed an intratemporal lobe hemorrhage in monkey #17 (Figure 6) in whom subtemporal intradural exposure of the gasserian ganglion and trigeminal nerve had been performed. Cerebellar damage was noted in monkey #1 in whom a suboccipital posterior root rhizotomy was performed. The brains of all animals appeared grossly intact.

B. *The Operative Site*

Figure 7A shows the right side of monkey #7 in whom a specific lesion was created by the radiofrequency lesion generator. In this view, the ophthalmic division of N V has been dissected from the lateral wall of the cavernous sinus which continues almost to the gasserian ganglion. The proximity of the third nerve is well demonstrated. The burn created in making the lesion is apparent. The relationship to the gasserian ganglion and the mandibular and maxillary branches is best seen in Figure 7B. Figure 8A shows the appearance of the lesion created in the posterior root of the right trigeminal nerve of monkey #12. This lesion lies immediately behind the gasserian ganglion, and the tentorium is intact. In monkey #13, a window was created in the tentorium and the radiofrequency lesion generator was applied directly to the posterior root.

In monkeys #15 and 17, a notch was cut into the free edge of the tentorium immediately behind the third nerve. The posterior root was then hooked on a nerve hook and mechanically cut. Figure 8B demonstrates the autopsy appearance of these animals. All third nerves appear grossly intact.

FIGURE 8 *(opposite)*

A: Autopsy of monkey #12. View from middle cranial fossa. Burn in posterior root (white arrow) is behind gasserian ganglion (white diamond) and in front of tentorium (small black arrows). Note third nerve (large black arrow). B: Autopsy of monkey #15. View from middle cranial fossa. A notch was cut in the tentorium (small black arrows) and the posterior root sectioned (clear arrow) at surgery. Hemorrhage is present on the posterior cut edge of tentorium (white and black arrow). Note third nerve (large black arrow).

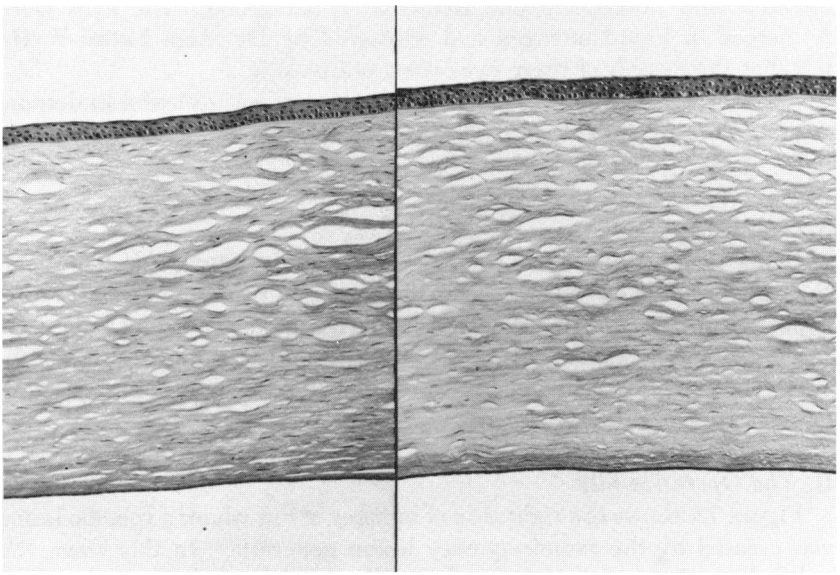


FIGURE 9
Photomicrograph of corneas of monkey #1 printed side by side for comparison of layers. O.D. is to reader's left and O.S. to right. Note that right corneal epithelium is thinner than left but stroma is of same thickness. H. and E. stain. Magnification × 110.

HISTOPATHOLOGIC EVALUATION

A. *Measurement of the Thickness of Corneal Epithelium*

The thickness of the corneal epithelium and stroma was measured by independent observers using the staged micrometer to determine epithelial atrophy.

Corneal epithelial atrophy accompanied anesthesia of the eye, but the stroma remained unchanged in all corneas following trigeminal nerve section. There was no change 21 days after tarsorrhaphy in a normal eye (Figures 9, 10, and 11).

Tables V and VI summarize these findings. The corneal epithelium to stroma ratio × 100 of the operated eye was compared to the control side. The data show that in all of the anesthetic eyes, the corneal epithelium became thinner than in the control eyes while the stroma remained unchanged.

B. *Evidence of Old Inflammation*

It was pointed out in the description of preoperative clinical findings, that many eyes showed considerable evidence of old inflammation.

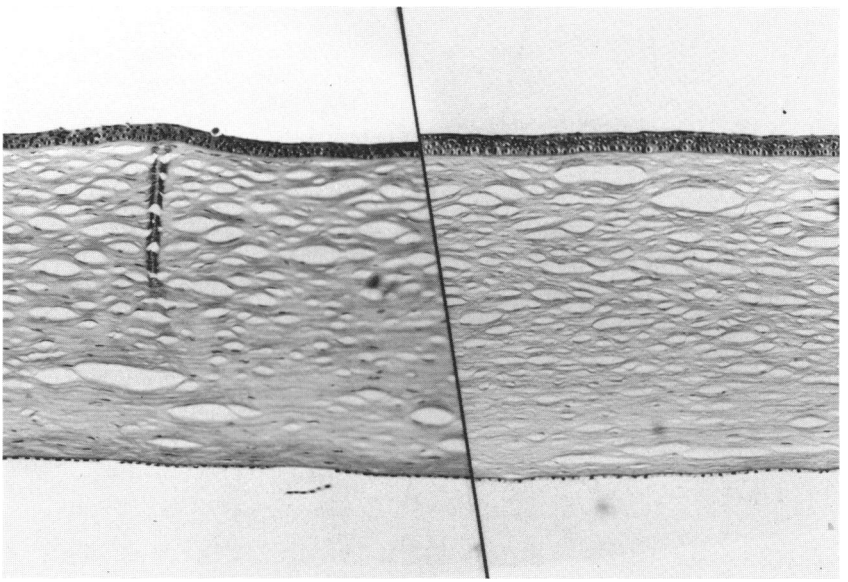


FIGURE 10
Photomicrograph of corneas of monkey #7 printed side by side for comparison of layers. O.D. is to reader's left and O.S. to right. Note that right corneal epithelium is thinner than left but stroma is of same thickness. H. and E. stain. Magnification × 110.

Table II summarizes these observations. Histopathologic examination similarly revealed evidence of previous inflammation.

These changes were characterized by chronic inflammatory cells on the iris surface and in its stroma, inflammatory cells in the trabeculum, fibrovascular membrane on the anterior iris surface, ectropian uveae, and posterior synechiae. These unexpected findings made it difficult to point conclusively to anterior uveal tract changes that were pathognomonic of the anesthetic eye.

C. *Round Cell Invasion*

On the other hand, the episcleral limbal area displayed accumulations of chronic inflammatory round cells in Groups I and II but not in the other groups (Figures 12 and 13). These cells were mostly lymphocytes, monocytes, and plasma cells with an occasional eosinophile and mast cell. This was the only characteristic histopathologic change in the eye that distinguished the different groups. No protein was noted in the anterior chambers. The posterior portions of the eye were normal in all groups. There were no changes noted in the sclera, choroid,

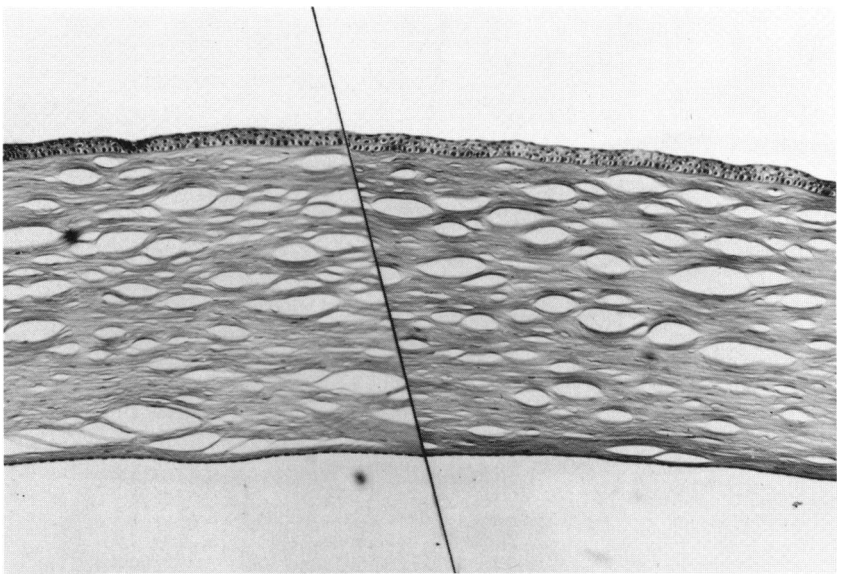


FIGURE 11
Photomicrograph of corneas of monkey #23 printed side by side for comparison of layers. O.D. is to reader's left and O.S. to right. Corneal epithelium is of same thickness despite tarsorrhaphy in right eye for 21 days before sacrifice. H. E. stain. Magnification × 110.

or retina. The vitreous was clear. The corneas were clear in all animals except those in which the tarsorrhaphy had broken down. Monkey #10 displayed evidence of acute keratitis. Monkey #14 showed corneal perforation.

NEURAL DEGENERATIVE STUDIES

A. *The Corneal Nerves*

Neural fibers in the cornea were studied by flat preparations cut at 7 microns and stained as described in Methods and Materials. We could not detect changes in the corneal corpuscles or Schwann cells that were pathognomonic of the anesthetic eye.

Wallerian degeneration of corneal stromal nerves was noted only in the monkeys of Group I. Monkey #7 is a prime example of this type of degeneration (Figures 14A and 15A). All other groups had a preponderance of normal nerve fibers as did the control eyes of Group I animals (Figures 14B and 15B).

The Wallerian degeneration in the corneal nerves of Monkey #7 was characterized by swelling of the nerve fiber, increased tortuosity,

TABLE V: CORNEAL EPITHELIAL AND STROMAL CHANGES (MEASURED IN MICRONS) RELATED TO TRIGEMINAL NERVE SURGERY

O.D.	#1	#2	#3	#4	#5	#6	#7	#8	#9	#10	#11	#12	#13	#14	#15	#16	#17	#18	#19	#20	#21	#22	#23	#24
Epith.	21	19	16		18	21	19	18	21		22	18	20		20		23	23	25	23	25	23	22	25
	20	20	18		20	19	20	19	19		20	21	22		18		23	24	25	25	23	23	22	22
Stroma	460	347	300		310	406	422	400	423		430	442	424		340		423	502	330	345	345	370	390	380
	470	345	335		285	365	400	420	411		410	428	432		390		410	473	361	360	325	340	370	390
Av. Epith.	20.5	19.5	17		19	20	19.5	18.5	20		21	19.5	21		19		23	23.5	25	24	24	23	22	23.5
Av. Stroma	465	346	317		298	386	411	410	417		420	435	428		365		417	488	345	353	335	355	380	385
Epith./Stroma × 100	4.4	5.63	5.36		6.37	5.18	4.74	4.51	4.79		5.0	4.48	4.91		5.19		5.51	4.81	7.25	6.79	7.16	6.48	5.78	6.10
O.S.	#1	#2	#3		#5	#6	#7	#8	#9		#11	#12	#13		#15		#17	#18	#19	#20	#21	#22	#23	#24
Epith.	30	22	24		22	27	25	24	27		24	26	27		25		26	24	25	26	24	23	22	23
	30	22	23		23	28	25	26	25		23	28	29		24		27	22	25	27	25	23	22	23
Stroma	480	340	305		308	330	420	420	430		458	442	425		379		387	459	320	410	360	350	420	400
	430	330	308		310	320	380	410	410		432	450	410		369		385	483	336	400	360	344	400	410
Av. Epith.	30	22	23.5		22.5	27.5	25	25	26		23.5	24	28		24.5		26.5	23	25	26.5	24.5	23	22	23
Av. Stroma	455	335	306.5		309	325	400	415	420		445	446	418		374		386	471	328	405	360	347	410	405
Epith./Stroma × 100	6.59	6.57	7.67		7.28	8.4	6.25	6.02	6.19		5.27	6.05	6.69		6.55		6.86	4.87	7.62	6.54	6.80	6.62	5.36	5.68

SPECIMEN NOT AVAILABLE

DISCARDED — KERATITIS

DISCARDED — CORNEAL PERFORATION

AEROEMBOLISM

TABLE VI: RATIO OF CORNEAL EPITHELIUM TO STROMA × 100

Monkey #	Group #	O.D.	O.S.	Diff.
1	IV	4.40	6.59	2.19
2	IV	5.63	6.57	0.94
3	IV	5.36	7.67	2.31
4	I	Sent to Dr. Laties		
5	I	6.37	7.28	0.91
6	I	5.18	8.41	3.23
7	I	4.74	6.25	1.51
8	I	4.51	6.02	1.51
9	I	4.79	6.19	1.40
10	II (Keratitis)			
11	II	5.00	5.27	0.27
12	II	4.48	6.05	1.57
13	III	4.91	6.69	1.78
14	Perf. cornea			
15	III	5.19	6.55	1.36
16	Aeroembolism			
17	III	5.51	6.86	1.35
18	V	4.81	4.87	0.06
19	V	7.25	7.62	0.37
20	V	6.79	6.54	(0.25)
21	V	7.16	6.80	(0.36)
22	V	6.48	6.62	0.14
23	V	5.78	5.36	(0.42)
24	V	6.10	5.68	(0.52)

ALL RATIOS = Corneal Epith./Corneal Stroma × 100
Diff. ( ) = O.D. > O.S.
Diff. of all other eyes = O.S. > O.D.

beading, fragmentation, and eventual loss of the nerve fiber (Figures 14A and 15A).

B. *The Gasserian Ganglion*

The normal gasserian ganglion is formed at the junction of the three branches of the fifth nerve and serves as a repository for the unipolar ganglion cells subserving these divisions. The ophthalmic and maxillary branches lie on the medial aspect and their ganglion cells are adjacent to each other. The mandibular branch lies on the lateral portion and its ganglion cells appear more confined to the lateral aspect of the ganglion itself. In addition, the ganglion cells subserving the mandibular branch occupy a greater portion of the ganglion than either of the other two branches.

The ganglion cell bodies tend to be grouped in clusters or nests. Myelinated and unmyelinated fibers, capillaries and collagen fill the

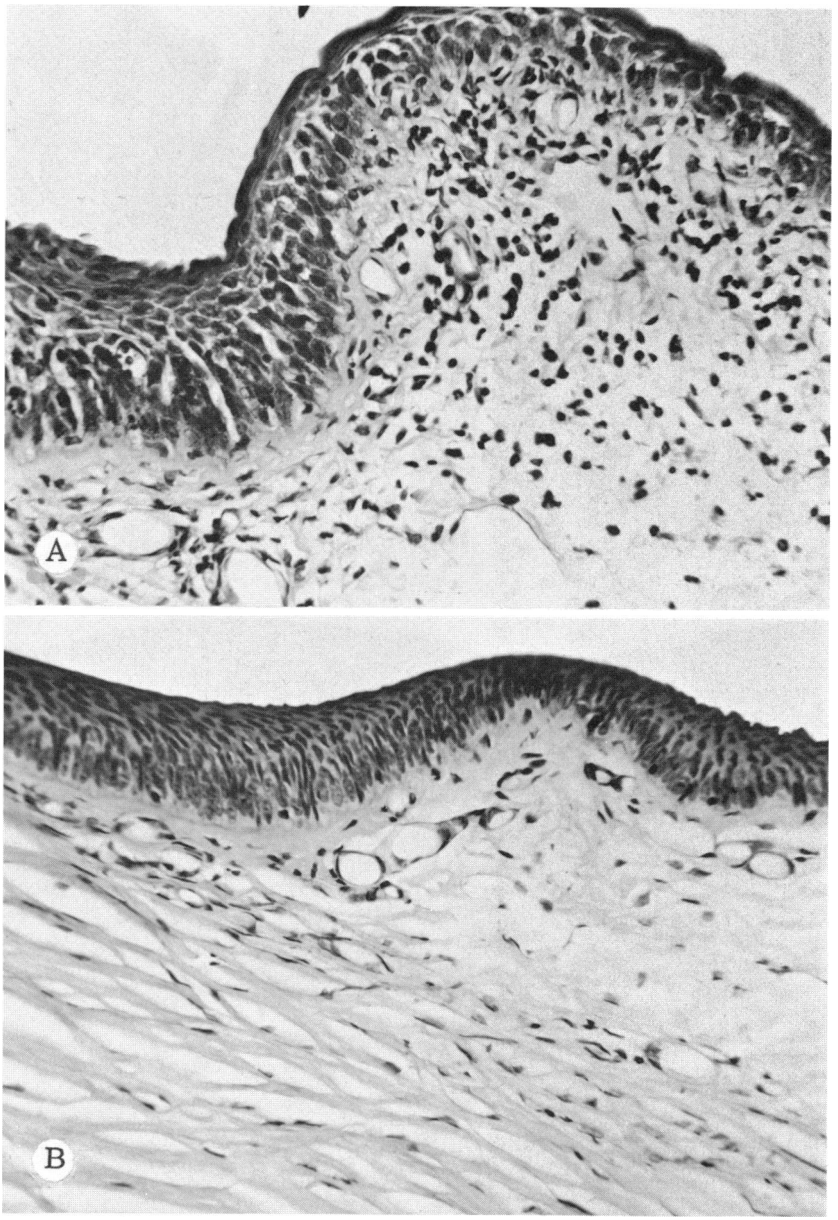


FIGURE 12

A: Higher power photomicrograph of perilimbal area of O.D. in monkey #7 demonstrates that cellular types are mostly round cells. H. and E. stain. Magnification × 340. B: Photomicrograph of perilimbal area of O.S. in monkey #7 shows normal cellular structure and no inflammatory cells. H. and E. stain. Magnification × 340.

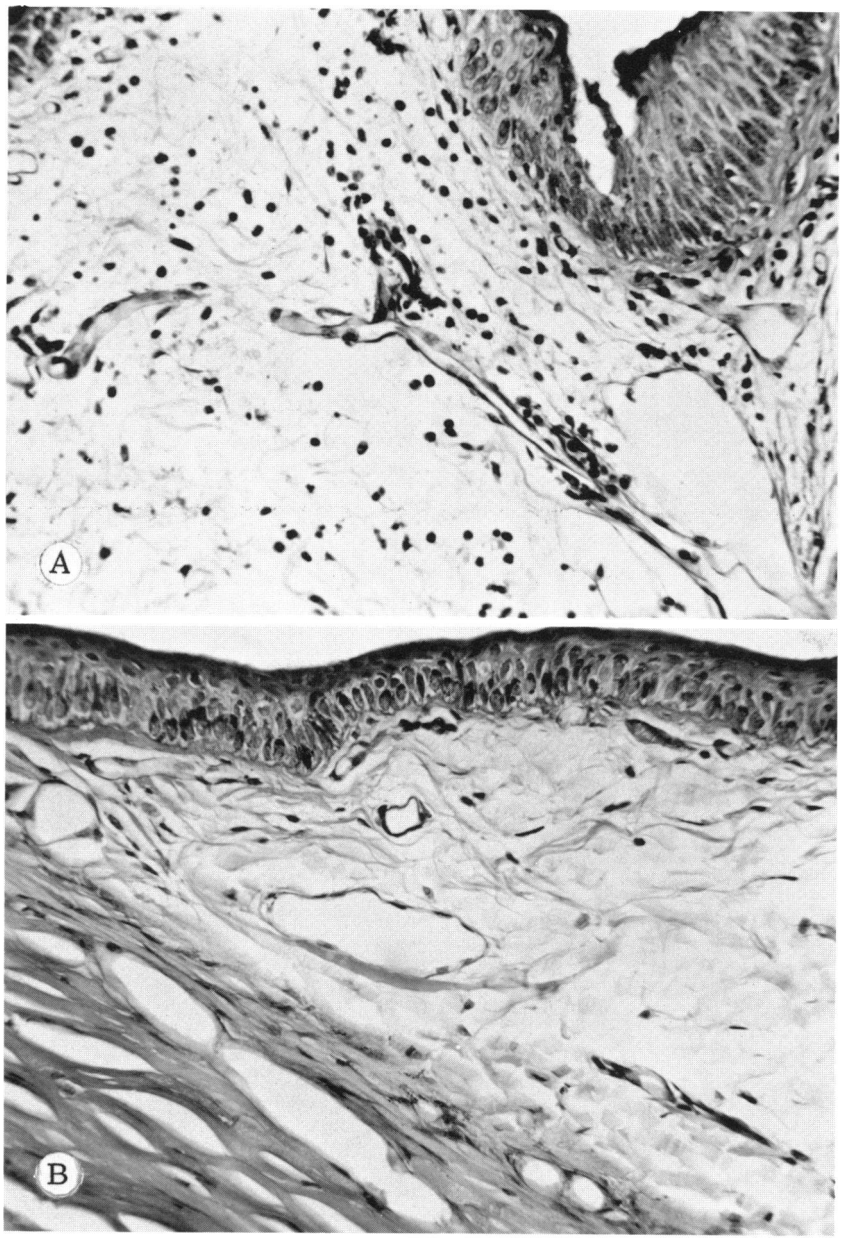


FIGURE 13

A: High power photomicrograph of area in O.D. of monkey #12 demonstrates round cell types. H. and E. stain. × 340. B: Photomicrograph of perilimbal area of O.S. in monkey #12 demonstrates normal cellular architecture and absence of inflammatory cells. H. and E. stain. Magnification × 340.

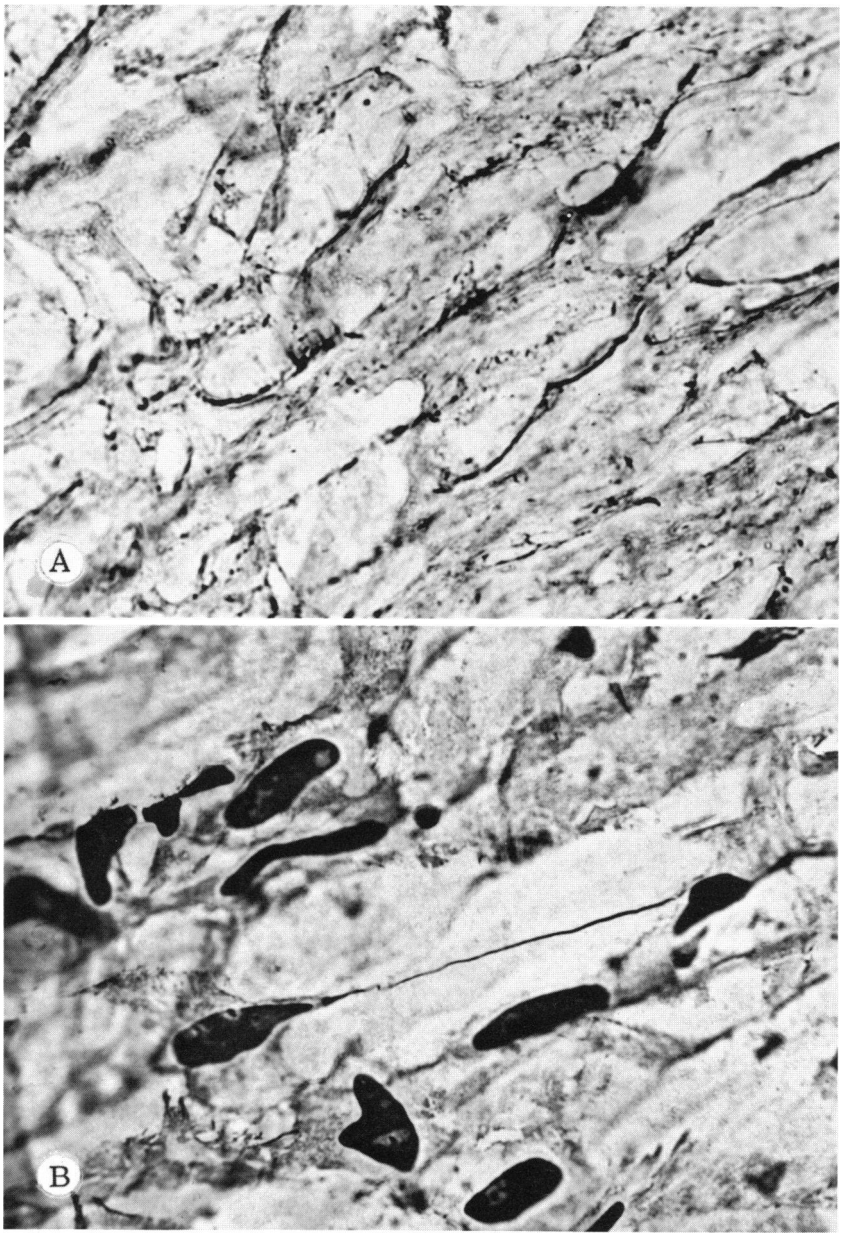


FIGURE 14

A: Wallerian degeneration of nerves in stroma of right cornea in monkey #7. Ophthalmic division of N V sectioned seven days before sacrifice. Note beading, fragmentation and increased tortuosity of fibers. Compare to Figure 14B. Bodian stain. Magnification × 800. B: Normal nerve fiber in stroma of right cornea in monkey #23. Contrast the continuity of the course of the fiber with that in figure 14A. Bodain stain. Magnification × 800.

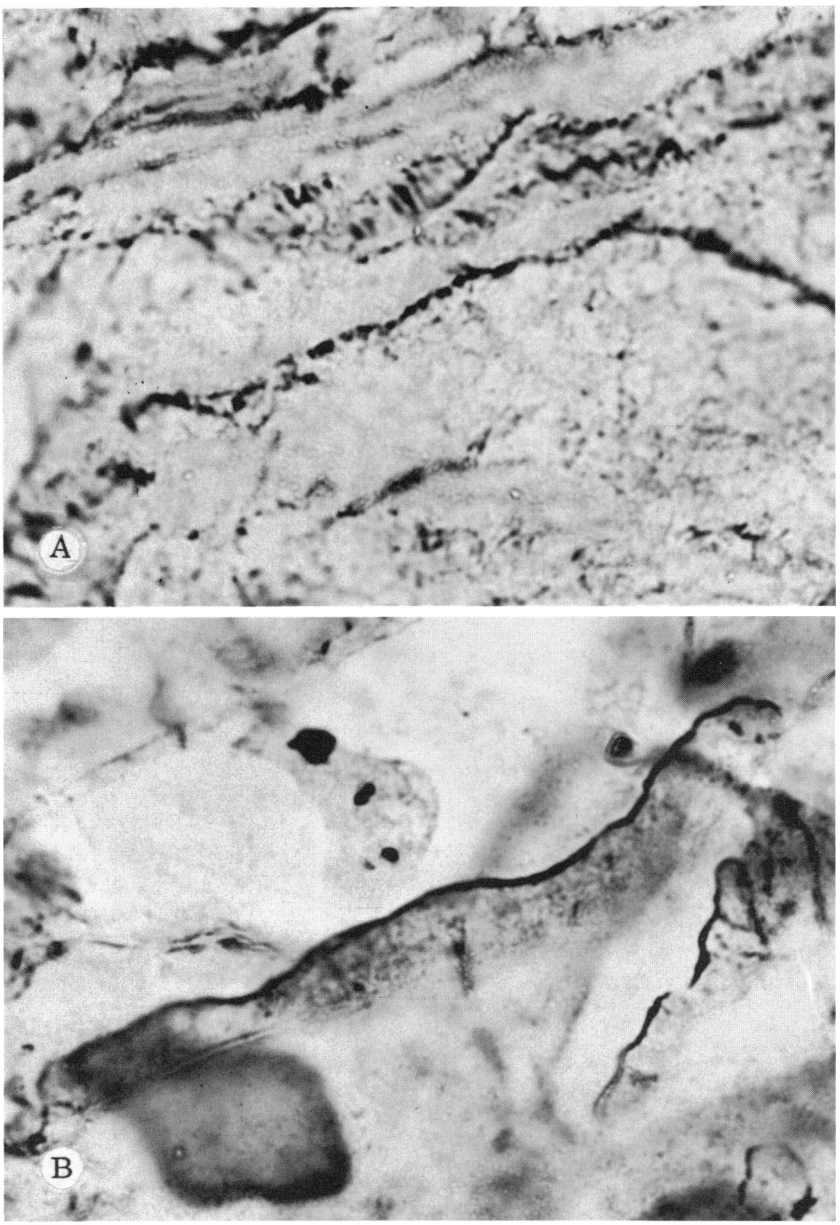


FIGURE 15

A: Oil emersion view of Wallerian degeneration of corneal nerve fibers in right eye of monkey #7, noted in Figure 14A. Beading and fragmentation are the prominent features. Bodian stain. Magnification × 1700. B: Oil emersion view of a normal nerve fiber in the corneal stroma of the left eye in monkey #7. Compare the continuous course with that of the degenerating fiber in figure 15A. Bodian stain. Magnification × 1700.

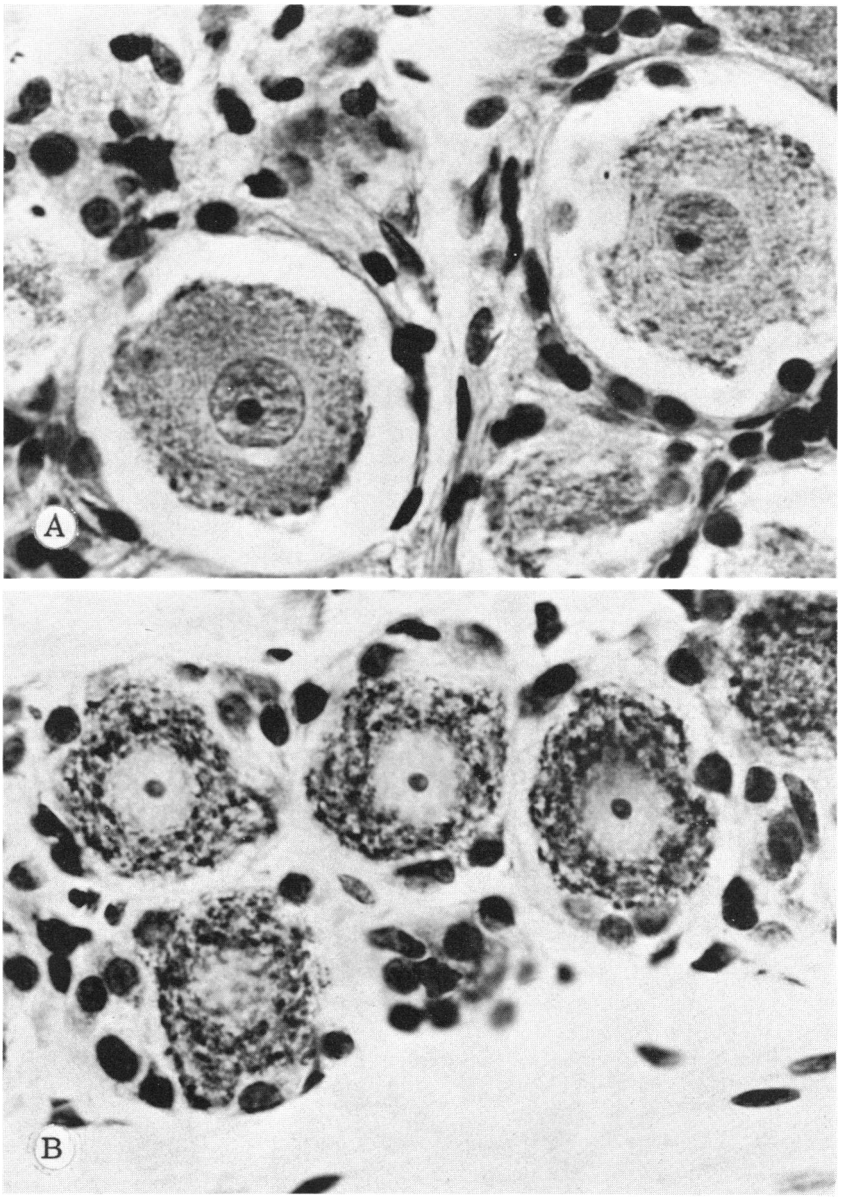
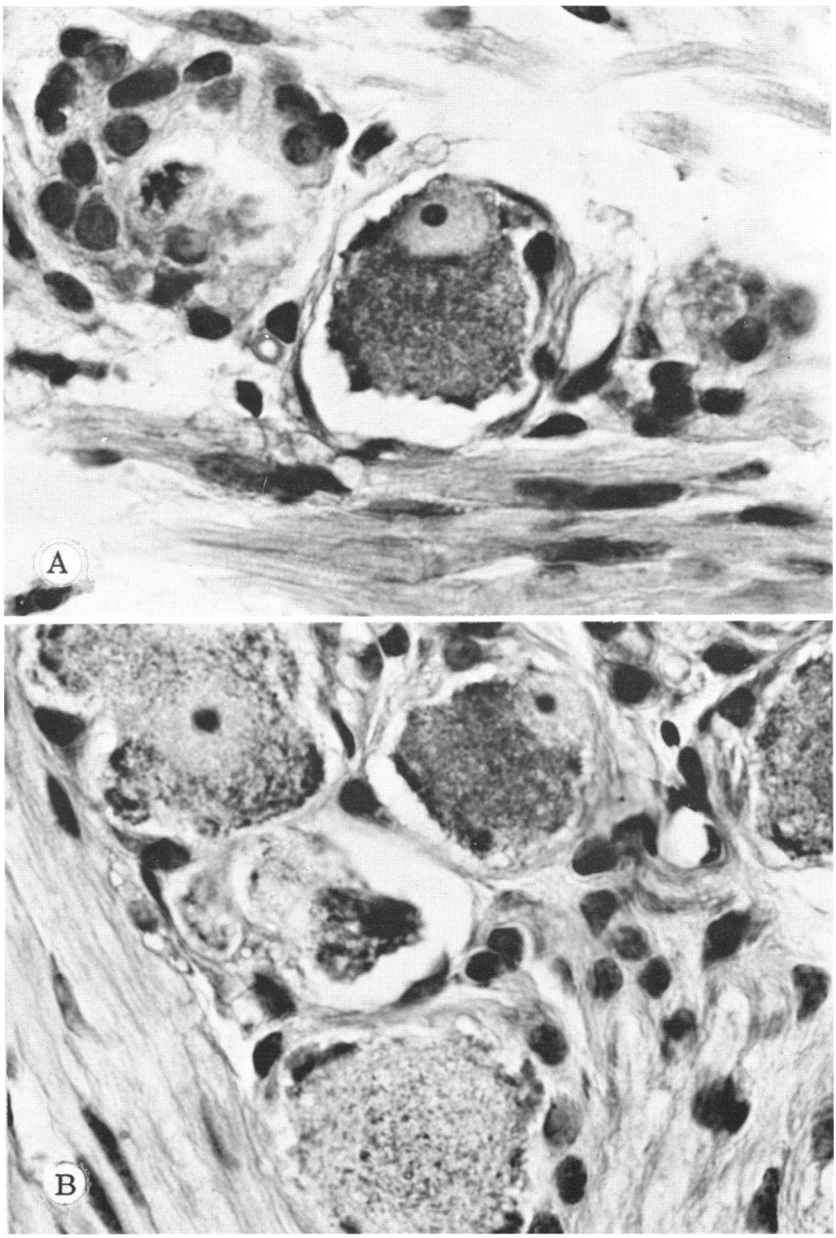


FIGURE 16

A: Normal unipolar gasserian ganglion cells from monkey #23. Note large central nucleus, darkly stained nucleolus, and uniform cytoplasm. Satellite cells surround the ganglion cell in an orderly fashion. H. and E. stain. Magnification × 800. B: Normal unipolar gasserian ganglion cells from left side of monkey #7. Clumps of Nissl substance are evenly distributed throughout the cytoplasm. Satellite cells stain darkly with Nissl stain. Nissl stain. Magnification × 800.


A
B

spaces between the clusters of ganglion cells. The ganglion cells display a uniform cytoplasm with a central nucleus that occupies about one-third to one-half of the total volume of the perikaryon (Figure 16). A large nucleus is centrally placed and stains darkly with Nissl stain. Clumps of Nissl substance are evenly distributed throughout the cytoplasm.

Satellite cells surround the normal ganglion cell in an orderly fashion and stain darkly with the Nissl stain. Schwann cells have the same dark stain as the satellite cells but are oriented to the nerve fibers instead of the ganglion cells (Figure 16).

Variations from this normal pattern tend to occur as described by Moses.[6] In monkey #17, calcification of the ganglion cell was noted and confirmed by the von Kosca Stain. In the left normal control ganglion of monkey #1, degenerated fibers were present adjacent to normal fibers when stained by the Fink-Heimer method.[15,16] These same findings have been described by Moses.[6] In general however, these abnormal findings were minimal both in the control ganglia of the operated animals and in the ganglia of the control Group V.

Marked derangement from the normal gasserian ganglion architecture described above occurred only in Groups I and II. In both groups the ganglion cells underwent chromatolysis. In Group I, changes were confined to the medial aspect of the ganglion while in Group II, all areas were involved.

Chromatolysis was characterized by disintegration of the Nissl substance into a powdery appearance. A clear cytoplasm appeared in many instances and the perikaryon became swollen. In some instances the perikaryon appeared empty and shrunken. The nucleus became eccentrically displaced to the periphery of the cell. Satellite cells became substantially fewer in number and dropped out in many instances (Figure 17).

C. *Brain Stem and Descending Tract*

The posterior trigeminal root at its entrance into the pons was normal in Groups I and II. In Groups III and IV, however, there was evidence of neural degeneration.

This was characterized by loss of myelin and fragmentation of the neural axons. Axonal degeneration was noted below the level of the fifth nerve nucleus in the spinal tract to the level of C_2.

FIGURE 17 *(opposite)*

A: Abnormal gasserian ganglion cells of right side in monkey #7. Note eccentric nucleus with loss of satellite cells. The adjacent cells display shrunken perikaryon. Nissl stain. Magnification × 800. B: Abnormal gasserian ganglion cells from right side of monkey #12. Note eccentric nucleus, powdery appearance of Nissl substance, shrunken perikaryon and absence of satellite cells. Nissl stain. Magnification × 800.

DISCUSSION

For 150 years it has been known that experimental extirpation of the gasserian ganglion or interruption of the ophthalmic branch of the fifth cranial nerve leads to ocular changes in various species of animals. A large body of literature on this subject has been documented by Duke-Elder.[18] There has been little interest in studying experimentally the effect on the eye of interrupting the retrogasserian sensory rootlets at different selected levels along its course into the pons.

Until recently, most observations of this nature were clinical. Dandy[3] claimed, from clinical studies, that pain fibers of tic douloureux were situated in a specific portion of the trigeminal root at the pons, and tactile sensation was mediated by accessory fibers lying between the motor and sensory roots at the root entry zone. He demonstrated in patients that operations on the fifth nerve at this level could preserve the important corneal reflex while relieving pain. Frazier,[5,6] on the other hand, thought that the functional representation of the three branches of N V maintained an anatomic relationship throughout its course without reorganization at the pons.

Recent experimental studies have utilized anatomical methods for investigating the effects of sectioning the posterior root. These studies have been mainly concerned with attempts to substantiate or invalidate Dandy's anatomic observations.[19,20,21,22] Only the work of Lende and associates[7,8] has involved a study of functional localization in the trigeminal root. Although Moses[23,24] has studied the eyes in rats after creating a massive lesion with a diathermy electrode in the general region of the gasserian ganglion, to our knowledge, there have been no studies on the eye after selectively sectioning the trigeminal nerve at various locations.

The studies on the eye reported here compare the reaction in the anterior segment following selective section of the fifth nerve at different sites along its course.

CORNEAL CHANGES

Early investigators noted that following resection of the trigeminal nerve in the rabbit, the ipsilateral eye became red and purulent and the cornea, opaque.[1,2] In the experiments reported here, care was taken to protect the cornea by tarsorrhaphy in order to study other changes in the anterior segment which may be masked by such results.

Tables V and VI summarize the measurements of the corneal epithelium and stroma noted in these studies. These data demonstrate that the corneal epithelium becomes thinned even though the cornea has been

protected by tarsorrhaphy after fifth nerve section. The stroma, on the other hand, remains essentially unchanged.

We found no effect on the normal corneal epithelium or stroma from tarsorrhaphy alone. In addition, there was no evidence that inflammatory cells were stimulated in the perilimbal subconjunctival tissue by this procedure.

Moses and Feldman[23] investigated the effect of tarsorrhaphy on normal rat corneas. They observed no change in corneal tissue prepared in paraffin but noted edema of the basal epithelial cells in epon-embedded material.

Despite the protection from tarsorrhaphy, the epithelial cells are subject to more mechanical stress than the stroma which is protected on all sides by contiguous tissue. It may be that minor mechanical stresses combined with "trophic" changes account for the atrophy of the epithelium and absence of change in the stroma. Our studies did not determine the mechanism for epithelial atrophy. It should be noted however, that the control eyes displayed corneal epithelium of normal thickness whereas the anesthetic eye, regardless of the location of section along the course of the trigeminal nerve, displayed thinning of the epithelium in all instances (Figures 9-11).

This is in contrast to the perilimbal, episcleral invasion of round cells which occurred only in the eyes of Groups I and II (Figures 12 and 13). These cell types have been noted to invade denervated muscles and to surround "trophic" skin ulcers in the absence of infection. They are also well known to occur in response to humoral or cellular immunologic reactions.[25] It is interesting to speculate on their appearance in only Groups I and II animals.

In these groups the gasserian ganglion cells showed a marked reaction, in contrast to Groups III, IV and V in which the ganglion cells appeared quite normal. Although only Group I displayed a great number of degenerating corneal nerve fibers (Figures 14 and 15) morphologically, the fibers in the corneas of Group II must have been affected at functional levels because their ganglion cells were so disturbed.

Beresford[26] cites Young's observations in 1945 that the cell body not only produces the axoplasm necessary for neural function, but maintains it under pressure great enough to hold the nerve fiber in a tubular form against surface tension. When axoplasmic pressure is released the distal segment is isolated from the source of pressure and is fragmented. This concept could well explain the fact that the Group II corneas developed a similar "neural milieu" which stimulated the same perilimbal cellular response as Group I. Thus, if Groups I and II had developed a similar

corneal milieu on a neurologic functional level rather than morphologic, a similar cellular response would be expected. The stimulus for this inflammatory response, however, remains unanswered. Further speculation along these lines suggests that actual morphologic changes in corneal nerves might have been observed in Group II if more time had elapsed before sacrificing the animals.

In contrast to our finding predominantly round cells in the perilimbal area and superficial cornea in Groups I and II, Moses and Feldman[23] reported the appearance of polymorphonuclear leukocytes in rats following diathermy destruction of the fifth nerve and adjacent structures. They attributed the appearance of these cells to an unidentified mechanism involving vasodilatation. Zaiko[27] reported similar findings in rabbits.

The difference in cellular characteristics between Moses' animals and ours may be due to the fact that he sacrificed his animals within 48 hours, thereby capturing the acute reaction. Our animals were sacrificed after one or more weeks so that we captured the more chronic reaction. Vasodilatation and vascular permeability remain a moot question. We were unable to demonstrate vasodilatation and increased vascular permeability in our animals either *in vivo* by anterior segment fluorescein photography or post mortem by the fluorescein perfusion and freezing techniques of Grayson and Laties.[17]

Perilimbal and superficial corneal cellular invasion occurred in our animals only when section of the fifth nerve was located near the gasserian ganglion (Groups I and II) and was always associated with chromatolysis of the ganglion cell, (Figure 17). This appears to be a significant observation.

Both Moses and Zaiko produced fifth nerve lesions by a technique which involved pushing instruments in a blind fashion intracranially toward the gasserian ganglion. Moses[23] plunged a diathermy electrode, made from an insulated screw driver, through the roof of the mouth in rats. Zaiko[27] used a method originated by Magendie[1] and later practiced by Bernard[28] in which a double-edged neurotome was blindly passed through the skull towards the sella turcica.

None of these investigators reported histopathology of the gasserian ganglion. The chances are that they either sectioned the fifth nerve near the ganglion or destroyed the ganglion itself with their techniques.

Whether ganglion cell chromatolysis can initiate a reaction stimulating vasodilatation and vascular permeability is speculative and not answered by our experiments. Nevertheless, ganglion cell death must be related in some way to the cellular invasion in the eye since in our studies this reaction was absent in those animals with normal gasserian ganglia.

In monkeys #10 (Group II) and #14 (Group III), the tarsorrhaphy inadvertently broke down and both animals developed severe keratitis. In the latter, the cornea perforated despite efforts to prevent progression of the condition. These very same corneal changes were observed by Rose in 1891[29] in three of five patients on whom he performed the first intracranial ganglionectomy for relief of trigeminal neuralgia.

These corneal changes have concerned the neurosurgeon and ophthalmologist ever since and even today constitute the most serious complication of the surgical treatment of tic douloureux. Pannabecker[30] reported corneal lesions in 18% of 878 patients treated at the University of Michigan by various surgical techniques. Grant[31] and Peet and Schneider[32] noted that 15% of their patients had trophic changes and/or ulceration of the corneas. Only recently, Sweet and Wespic[3] reported that in a series of 214 patients treated by percutaneous controlled thermocoagulation of the trigeminal ganglion and rootlets, 28 (13%) sustained anesthetic corneas with loss of sight in one eye due to corneal scarring.

Our experiments have not determined the reason for these corneal changes, but have pointed out that the gasserian ganglion cells may have a vital role to play.

LACRIMAL FUNCTION

Normal lacrimal secretion in all ipsilateral eyes after fifth nerve section (Table II) indicates that innervation of the lacrimal gland was not interrupted in any of our procedures. Duke-Elder[33] describes the lacrimal gland as being innervated by the ophthalmic division of N V, the greater superficial petrosal nerve, and the sympathetic nerves. Which part of this innervation is concerned with tear formation remains unknown. Section of the ophthalmic branch in Group I animals, however, had no apparent effect on lacrimation.

This refutes the observations of Kraus[34] and Cushing[35] who felt that the lacrimal branch of the ophthalmic division supplied the lacrimal gland with tear function. They believed that drying was an important factor in producing corneal lesions in an anesthetic eye.

Dandy[3] believed that neither drying nor exposure caused corneal ulceration. He felt that extradural approaches to the gasserian ganglion resulted in damage to the greater superficial petrosal nerve and that this prevented lacrimation. He also pointed out that neither Magendie nor Bernard had observed absence of lacrimation in their rabbits because all of their operations were intradural. Dandy's view is further supported by the experiments of Moses and Holekamp[24] who produced N VII paralysis in rats without causing an adverse effect on the eye from exposure.

Our experiments which were performed primarily by an intradural route, tend to confirm Dandy's observations. Even in our extradural approaches, however, we apparently did not damage the greater superficial petrosal nerve.

IRITIS

We had noted in humans after the Frazier operation to relieve tic douloureux, that flare and cells sometimes appeared in the anterior chamber without corneal involvement. Paton[36] reported similar observations in his patients after alcohol injection of the gasserian ganglion and Hartmann[37] noted an identical reaction following retrogasserian neurotomy. Duke-Elder[18] attributes this type of iritis to a mechanism involving reflex vasodilatation.

We experienced difficulty in interpreting postoperative inflammatory changes in the anterior chamber of the animals in these experiments because of the totally unexpected finding that many of the monkeys had pre-existing iritis. Monkeys are known to have many endemic virus diseases which could well have been the cause for this reaction noted in all five groups.

Following section of N V, however, all ipsilateral eyes, (except in monkey #2, Group IV) exhibited an anterior chamber reaction (see Table III). In many instances, this reaction was worse than the preoperative condition or appeared in an eye that was uninvolved before surgery. It was thus our definite feeling that section of the fifth nerve, regardless of group, either created iritis de novo, or enhanced a previously existing inflammatory change.

Histologically, we did not capture protein in the anterior chamber as demonstrated by Moses in the rat[23] or by Zaiko[27] and Perkins[38] in the rabbit. We did see many inflammatory cells in the iris as well as in the filtration angle. These changes were not felt to be pathognomonic of the anesthetic eye, however, because the same cells were found in many of the control eyes due to pre-existing iritis. From these histologic observations, we could not tell which reaction was due to fifth nerve surgery and which preceded the experiment.

INTRAOCULAR PRESSURE

Table IV compares, by Group, the pre- and postoperative measurements of the intraocular pressure. The data show that the average postoperative tension of the ipsilateral eye was slightly lower than the preoperative pressure when measured one or two weeks after fifth nerve section. In addition, the pressure of the eye on the side of section tended to be

slightly lower than on the fellow normal control side. Neither of these differences, however, is considered statistically significant.

These findings confirm the work of Perkins[38] who investigated the influence of the fifth cranial nerve on the intraocular pressure of the rabbit eye. He reported that mechanical stimulation of the intact fifth nerve caused an ipsilateral rise in intraocular pressure while resection of the nerve caused a slight hypotensive effect when measured 2 to 4 weeks later. After allowing Wallerian degeneration to occur, stimulation of the cranial portion of the fifth nerve caused no change in ocular tension, indicating that these effects are mediated through the peripheral portion rather than being under central control.

It is interesting to note that the lowest postoperative tension was noted in the animal (monkey #5) in whom the third nerve was permanently damaged and in monkey #18 in whom N III was cut as a control. This fall in pressure was attributed to loss of extraocular muscle tonus.

PUPILLARY PHENOMENA

Mydriasis of the ipsilateral eye noted during surgery, was probably due to pressure upon the third nerve at the tentorial edge caused by elevating the temporal lobe. It was more common during intradural than extradural operations because more pressure was directly exerted on the tentorium during the former than the latter procedure.

In the case of monkey #5 (Group I), however, mydriasis persisted permanently. This monkey underwent surgery early in our experiments, before we were fully acquainted with the anatomy of the area. We felt that we had damaged the third nerve with the radiofrequency current in this animal. Two other animals (monkeys #8 and #17) had temporary mydriasis for one week after surgery, but these nerves appeared normal at autopsy and on histologic examination. The ipsilateral eyes of all of these animals, as well as that of control monkey #18 (Group V), in whom N III was cut intentionally, and monkey #19, in whom N III was stimulated, revealed no histologic change that could be attributed to third nerve damage.

Moses and Feldman[23] were never able to obtain solitary fifth nerve section in their experiments on rats. They always found coincidental third nerve damage with a mydriatic pupil. They also found no ocular pathology that could be attributed to N III paralysis.

The curious pupillary phenomenon of ipsilateral miosis noted in our animals after fifth nerve section (Table III) was first reported in 1821 by Magendie[1] after cutting N V in the rabbit. Bernard[28] confirmed these findings in 1858. It was further investigated in 1864 by Donders[39] who

noted that despite section of the fifth nerve, the sympathetic supply remained intact. In recent years, Maurice and Perkins[38] demonstrated that antidromic stimulation of the fifth nerve caused miosis in rabbits even after previous sympathectomy. Perkins concluded that since this phenomenon only disappeared after complete degeneration of the fifth nerve, it may be due to liberation of an active substance at the nerve endings which causes miosis. He quotes the work of Ambache[41] to substantiate his thesis.

Hartmann in 1924[37] reported on his clinical observations following retrogasserian section of the fifth nerve. He noted slight enophthalmos, narrowing of the palpebral fissure and miosis 3 to 4 days after surgery. These changes usually lasted more than one year. Dilatation of the pupil occurred with cocaine and adrenalin on the operated side in his patients. These findings indicated that some of the sympathetic fibers were resected along with those of the fifth nerve, but Hartmann considered them due to increased irritability of the peripheral axon following loss of central control.

In our animals, cocaine dilated the ipsilateral pupils in a normal fashion and adrenalin 1:1000 had no effect. This indicated that the sympathetic nerve supply remained intact after section of N V. Furthermore, it was noted that miosis was greater in those animals displaying more severe iritis. These findings led us to conclude that miosis was related to the iritis and was produced by the same undetermined mechanism creating the inflammation.

NEURAL DEGENERATIVE STUDIES

The role of the gasserian ganglion in ocular complications after fifth nerve section appears important from these studies. Chromatolysis of the unipolar gasserian ganglion cells was always associated with perilimbal round cell invasion of the subconjunctival tissue and superficial cornea (Figures 12 and 13).

Chromatolysis of the ganglion cells was seen only after division of the ophthalmic branch or after section of the posterior sensory root at a point in the middle cranial fossa before the tentorium is penetrated. Chromatolysis was absent when transtentorial section of the posterior root or suboccipital rhizotomy was performed.

This is of importance clinically because the most popular operation to relieve trigeminal neuralgia is the Frazier operation performed in the middle cranial fossa upon the posterior root at a point before it enters the tentorium. Our clinical observations of patients who had undergone this operation revealed a greater incidence of ocular complications than in those after suboccipital rhizotomy.

The mechanism of an ocular effect from chromatolysis of the gasserian ganglion cells remains unanswered by our experiments. Many questions, however, are posed by these results. Perhaps axoplasmic flow studies will answer some of these in the future. Perhaps more viral studies will implicate the herpes simplex virus as has been suggested by Behrman[42] and recently has received further implication by recovery of the virus in human trigeminal ganglia.[43]

BRAIN DAMAGE FROM SURGERY

An intratemporal lobe hematoma occurred following intradural, transtentorial section of the posterior sensory root. This was due to excessive pressure upon elevating the temporal lobe and is certainly a dangerous complication. Jannetta[44] has recently discontinued the transtentorial approach to the trigeminal nerve at the brain stem because of this same complication. We would agree with him that a new, safer approach should be used to the posterior root at the pontine root entry zone.

In operating on the posterior root at the pons, we experienced technical problems damaging the cerebellum and tearing the petrosal vein. With more experience, however, these complications can be avoided.

CONCLUSIONS

Operations were performed at four different levels on the fifth nerve of the monkey to determine which procedure offers the best chance of avoiding ocular complications after surgical treatment of trigeminal neuralgia (Figure 18).

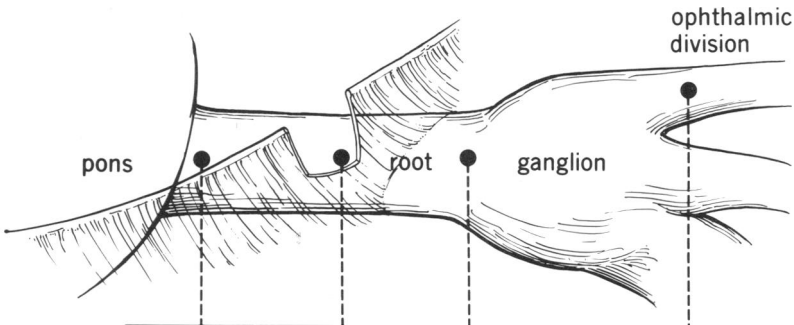
(1) Section of the ophthalmic branch of N V results in immediate corneal anesthesia. After one week, chromatolysis of the unipolar gasserian ganglion cells subserving the first division occurs and Wallerian degeneration of the corneal nerves of the ipsilateral eye is seen.

This is associated with perilimbal round cell invasion of the superficial cornea and subconjunctival area. In addition, iritis develops de novo or becomes worse if it pre-exists.

Miosis occurs, but the chemodiagnostic tests of cocaine and adrenalin indicate an intact sympathetic system. The cause for this inflammatory reaction and pupillary change is unexplained by this study.

The intraocular pressure is slightly lower on the side of the section than in the normal fellow control eye after surgery, but the difference is not statistically significant.

(2) Section of the posterior sensory root of N V in the middle cranial fossa at a point between the gasserian ganglion and the tentorium results



	Lesion	4	3	2	1
	Ganglion cells	normal	normal	chromatolysis	chromatolysis
effects on the eye	Limbus	normal	normal	chronic inflammation	chronic inflammation
	Corneal nerves	normal	normal	normal	Wallerian degeneration
	Corneal epithelium	atrophy	atrophy	atrophy	atrophy

FIGURE 18
Diagramatic summary of effects on the gasserian ganglion and eye resulting from operations at four different levels of the fifth nerve in the monkey.

in similar ocular changes as is seen after interrupting the ophthalmic division alone. Wallerian degeneration of the corneal nerves, however, is not seen after seven, twelve or twenty-one days.

(3) Transtentorial section of the trigeminal posterior sensory root, performed in the middle cranial fossa, results in immediate corneal anesthesia. The gasserian ganglion cells, however, remain healthy and there is no perilimbal round cell invasion of the superficial cornea or subconjunctival tissue. Miosis occurs but the chemodiagnostic tests of cocaine and adrenalin indicate an intact sympathetic system. The intraocular pressure is only slightly lower on the side of section than in the control eye, but the difference is not statistically significant.

(4) Suboccipital rhizotomy of the posterior sensory root of N V at the pons results in immediate corneal anesthesia. The gasserian ganglion cells remain healthy and there is no perilimbal round cell invasion of the superficial cornea or subconjunctival tissue. Miosis occurs in most animals

(2 of 3) and is associated with an intact sympathetic system as indicated by the chemodiagnostic tests of cocaine and adrenalin. Intraocular pressure is very slightly lower on the side of section than in the control eye, but the difference is not statistically significant.

(5) Thinning of the corneal epithelium occurs in an anesthetic eye regardless of the location of the section of N V and is not adversely affected by tarsorrhaphy. The corneal stroma, however, remains unchanged.

(6) The experimental data demonstrate that to decrease ocular complications, operations on the trigeminal nerve should be performed on the caudal end of the sensory root as far from the gasserian ganglion as is technically feasible.

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