EXTRAOCULAR FLUID DYNAMICS: HOW BEST TO APPLY TOPICAL OCULAR MEDICATION*

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INTRODUCTION

IT IS INDEED SURPRISING THAT RELATIVELY LITTLE DATA ARE AVAILABLE ON HOW best to apply topical medication to the human eye. In fact, only occasionally will the physician or nurse instruct the patient on how to apply topical ocular solutions. An optimal method is important to obtain maximum therapeutic benefit. Current methods are essentially empirical. It is the purpose of this study to investigate tear flow patterns and, from this, to develop methods which increase the retention of topical ocular medication.

BACKGROUND DATA

The types and locations of the conjunctival and lacrimal secretors are well known.[1] Of major importance in a study of this type is to understand the variables in a system which is known for its wide range of normal values, not only in tear production, but also in the physiochemical properties of tears. For example, normal tears vary in pH from 5.2 to 8.35, glucose from 2 to 65 mg/100 ml, and production from 0.7 to 100μl per minute.[2] A major variable of tear production is the psychic or physical stimulus which causes reflex lacrimal secretion. The hope of any method which measures normal tear flow or ocular contact times is to keep this reflex secretion as uniform as possible and to a minimum. Dilution studies using fluorescein have estimated the normal tear volume in the palpebral aperture to be about 7μl.[3] There are approximately 1.2μl of tears produced per minute (16% volume replacement) in the undisturbed eye,[3] although this rate probably decreases with age.[4,5] If blinking does not

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occur, up to 25+μl may be held on the eye; however, with blinking only about 10μl can be transitionally retained.[3] Commercial ophthalmic dropper bottles deliver from 50μl to 75μl per drop.[6] Obviously, a substantial portion of this volume, when applied to the eye, spills onto the lids with the remainder being rapidly removed by blinking. The applied fluid that remains on the eye is also continuously being removed until the tears return to their normal 7μl volume.

The flow pattern of tears within the palpebral fissure has been previously studied.[7,8,9] However, since only dyes or other nonradioactive tear markers have been used, little data are available for the flow of tears under the eyelids. By using small mirrors inserted in the anterior chamber of rabbits, no pockets of tears were seen in the fornices.[3] Investigators using dye dilution methods have estimated the volume of the conjunctival sacs from 10 to 60μl[10]; however, Mishima never found volumes above 15μl.[3]

The outflow of tears has been extensively studied by a number of investigators. The eyelids aid in the movement of tears nasally[11] with capillarity playing a major role in the passage of tears into the punctum through the canaliculus and into the lacrimal sac.[1] Tear elimination is accomplished by a kind of peristalsis, that is, an alternating movement of the lacrimal sac and canaliculi caused by blinking.[12]

There are basically three ways to prolong the ocular contact time of a drug:

1. To use more viscous vehicles which prolong the contact of medication on the eye[13] and increase its clinical effectiveness.[14,15]
2. To increase or continuously replace the volume of medication in the tear film by utilizing copolymeric plastics, polyvinyl alcohol inserts, conjunctival packs, continuous flow systems, subconjunctival drug injections, or drugs with soft contact lens.[16]
3. To delay the drainage of medication after topical application by patching the lids shut[17] or finger pressure over the lacrimal sac.[18]

Recently, microscintigraphy techniques have been used in ophthalmic research.[19] The dynamics of the lacrimal drainage apparatus[19,20] and the testing of ocular contact times for various drug vehicles were investigated using this method.[17,21] In addition, radiographic documentation that a closed lid will lengthen the contact time of solutions on the eye was reported.[17] Within the past few years, data storage and analysis with a computerized gamma camera for quantitative microscintigraphy have been used in ophthalmology.[21,22] The isotopic compound used in ophthalmic microscintigraphy techniques has been radioactive technetium 99m sulfur colloid (^{99m}Tc). It is a nonabsorbable colloidal solution which

has a half life of 6 hours.[23] In the minute concentrations used, this compound is free of ocular side effects and is now routinely used in diagnostic lacrimal procedures.[19,22]

MATERIALS AND METHODS

Both eyes of 173 volunteers of either sex and varying in ages from 19 to 30 years were studied. In addition, a small series of volunteers older than 50 years of age were tested. The laboratory area was kept quiet, humidity and lighting were constant, air vents were occluded to prevent excessive air currents, and the same physician explained, positioned, and applied the drops to all of the eyes. A physician, a radiation technician, and a nurse were present for each experiment. During each study the patient was continually observed for blink rate, head movement, excessive tearing, and lid movement. In no instance was the same experiment repeated on the alternate eye.

The sterile, room temperature, radioactive solution used is a highly water soluble, isotonic, nonabsorbable ^{99m}Tc with a pH of 6.7 to 7.0 and a viscosity and weight almost identical to human tears (Technetium-99m Liver Scanning Kit, The Radiochemical Centre, Amersham, Buckinghamshire, England). The radiation activity of the tracer for 0.5μl studies was a maximum of 50 μCi/ml and for 13μl experiments, 5 μCi/ml. During the course of each session there was at least a 50+% decay of radioactivity between the first and last patients of each experimental session. The application of 0.5μl of the radioactive solution was delivered by a previously calibrated PE-10 tubing (Intramedic,® Clay-Adams Inc., New York). The 13μl volume was delivered by an automatic pipette (5-50μl Finn pipette, Jencons Scientific Equipment of Hemel Hempstead, Hertfordshire, England) with replaceable tips (Fig. 1).

The following volunteer procedure was followed. The intent and procedure of the experiment, including what the eye drop contained, was explained to each patient. It was also explained that the ^{99m}Tc solution had been used by this Nuclear Medicine Department for lacrimal drainage studies without adverse reactions for over the past two years. An external ocular exam, including evaluation of the inferior marginal tear strip, was done prior to performing the experiment. If any ocular abnormality was found, the subject was excluded from the study. Isotonic saline was used to irrigate the superior and inferior fornix after the completion of the test. The protocol for this experiment was approved by the Human Research Committees of the hospital and the associated Ophthalmology Institute.

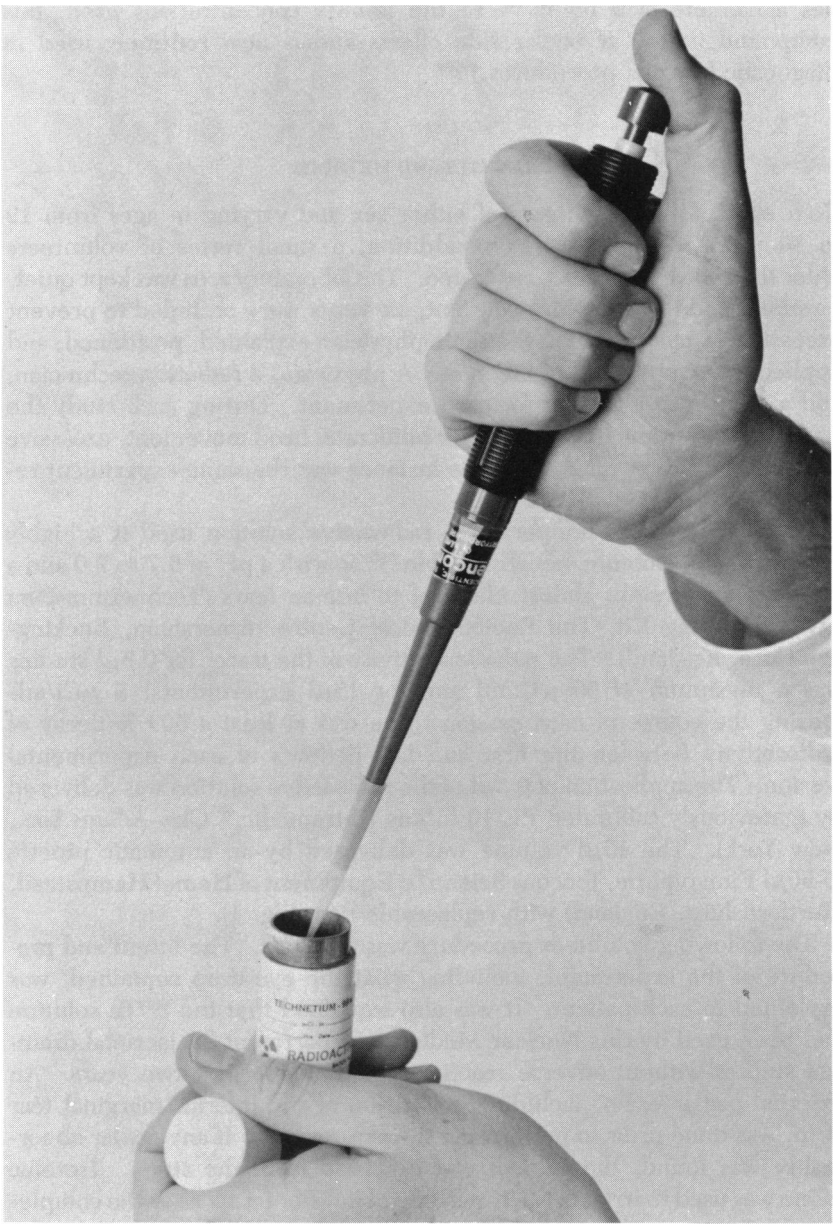

FIGURE 1
Automatic Finn pipette with replaceable tip used to deliver 13μl of ^{99m}Tc to the external eye.

The volunteer's head was placed in a head holder in front of an Anger gamma camera (Ohio Nuclear Series 100), fitted with a standard 3 mm pinhole collimater, and interfaced with an image display and analysis system (D.E.C. Gamma II). The technetium solution was placed on one eye with the eye within a few inches of the gamma camera. The face of the camera was covered with tissue paper to minimize convection currents. Raising the gamma camera from its usual almost floor level storage position to 4 feet for these experiments caused a change in temperature which created air movements that altered the volunteers' blink rates. The ocular area was superimposed on the optimized image display screen on the gamma persistence oscilloscope and at 20-second intervals for the first minute and every 1 to 2 minutes thereafter photographed with a Polaroid camera. Serial photographs were taken at one minute intervals with background subtraction, contrast enhancement, and frame arithmetic from the gamma camera's image display screen. The distribution of the radioactivity was followed as it passed across the palpebral aperture and through the lacrimal drainage system. These results were recorded on computer discs and quantitative analyses of various ocular areas (Fig. 2) were subsequently performed on a digital computer. Other than estimating the corneal size, all other areas can be accurately outlined by frame integration or serial frame viewing. Inadvertent patient movement can be seen on computer playback and corrections made; or if movement is excessive, as occurred on three occasions, they were eliminated from the study. Almost all studies were terminated within five minutes; however, a few with lower radiation dosages than the usual experiments were followed for a maximum of 30 minutes. The computer was programmed to obtain radioactivity printouts every five seconds for the first

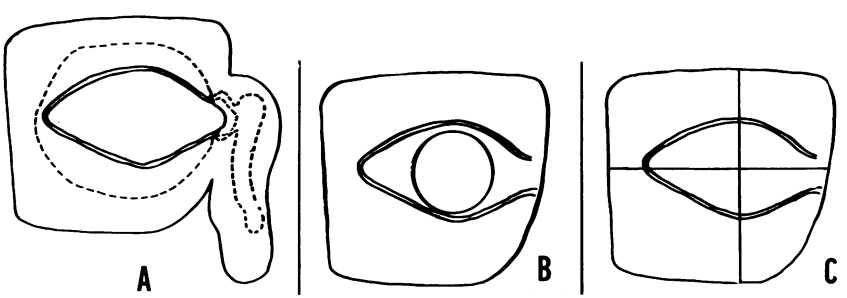

FIGURE 2

The areas quantitatively analyzed on the digital computer. A: The conjunctival sacs, palpebral aperture and the lacrimal outflow system including that side of the nose. This gives the total radioactivity for the solution placed on the eye during the course of the study. B: The ocular and corneal areas (excluding the lacrimal drainage system). C: The area shown in B is divided into the nasal or temporal halves and superior or inferior halves.

TABLE I: AREAS OF SOLUTION PLACEMENT, HEAD POSITION, AND OTHER VARIABLES

Area Placed	Head Position+	Other Variables
Superior — Temporal	Vertical	Normal blink rate (10-20/minute)
Inferior — Temporal	Horizontal	Lids closed
Superior — Nasal	Side	Blink rate less than 5/minute
Inferior — Nasal	Face down	Blink rate 60/minute*
		Pressure over lacrimal sac*

+For each head position the four areas of ocular application were evaluated as per normal blink rate or with lids shut. Variation in blink rates and pressure over the lacrimal sac were only tested in the vertical patient with inferior temporal "depot" applications.
*Not examined in the 0.5 μl series.

minute and every minute thereafter. For both the 0.5μl and the 13μl series, the following methods and areas of application were done (Table I). In all experiments, unless stated otherwise, the technique used to apply a drop on the eye is shown in Figure 3. For the sake of this discussion, this method of drug placement will be called a "depot" application. In two series this method of application was not followed. In one group the

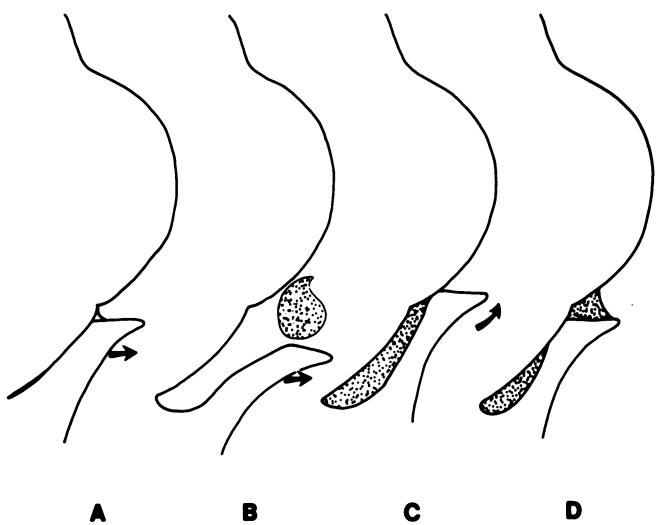

FIGURE 3

The technique used to apply topical solutions to the external eye. A: The lid was gently pulled away at right angles to the plane of the head by the physician's fingers. B: The drop was placed in the conjunctival sac without touching tissue or lashes. C: After waiting a moment to allow gravity to deliver the drop to the most dependent area of the fornix, the lid was then moved parallel to the plane of the head until it came in contact with the globe. D: A portion of the drop is entrapped under the eyelid.

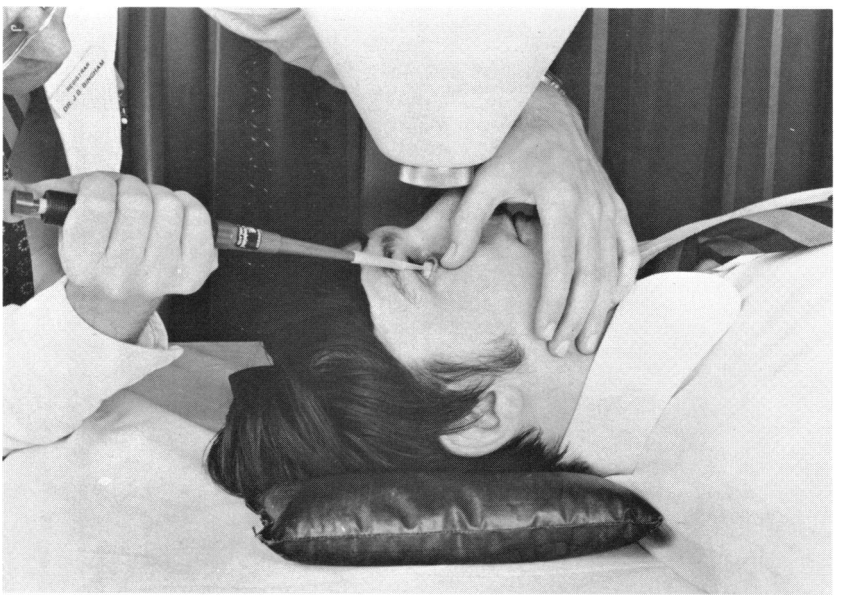

FIGURE 4
Inferior temporal application of 13μl of ^{99m}Tc in the supine patient with the gamma camera placed directly over the eye and the patient's head held in position with sand bags.

drop was placed in the inferior marginal tear strip near the outer canthus, and in the other the drop was just placed on the superior temporal sclera without any attempt to entrap the solution under the upper lid. In studies with the volunteers in vertical, supine, or side positions, ocular drops were applied with the patient already positioned before the gamma camera. Unless stated otherwise, the drop was placed under the inferior temporal lid. In the face down position, the drops were first placed on the eye with the head back, and then the patient was positioned in front of the gamma camera before the recording started. Therefore, in the face down position there was a three to five second delay before the start of the counts.

Positioning of the head was done by sitting for the vertical head position, lying on the back for the horizontal (Fig. 4), lying on the side with the head positioned parallel to the floor for the side position, and sitting with face down on the table for the face position (Fig. 5). Holding the head to prevent tilting or movement was done with head holders or sand bags. The volunteer was asked to fixate at the center of the head of the gamma camera. No lateral motion was allowed to either side of the volunteer.

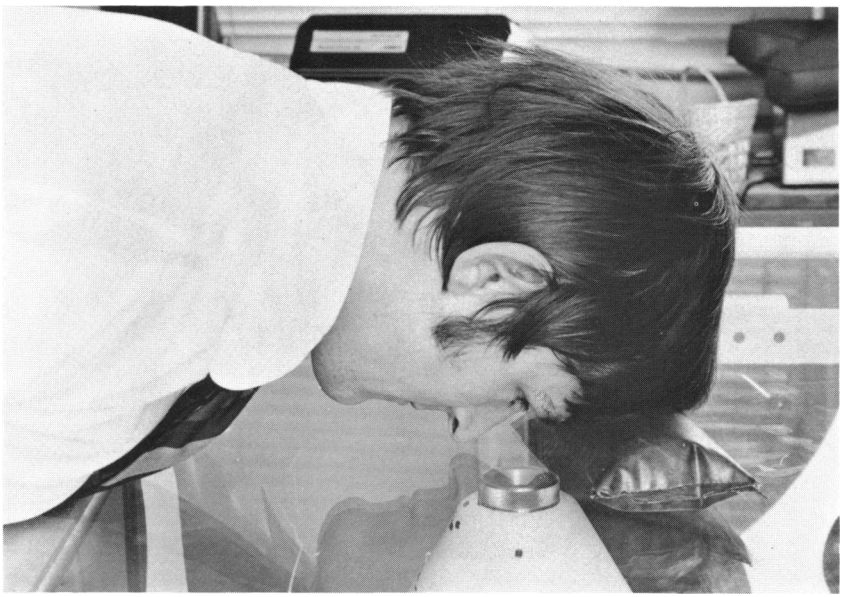

FIGURE 5
Volunteer in the face down position with the gamma camera facing the ceiling with a plastic plate separating it from the eye.

Volunteers with blink rates below 10 or over 20 per minute were excluded except for those series which required specific slow or rapid blink rates. In experiments requiring fewer than five blinks per minute, only contact lens wearers with contact lens removed were used since they could fairly easily decrease their blink rate. In experiments with eyelids closed, patients were watched for quivering of the eyelids. Lacrimal sac occlusion was done by the physician applying pressure with his forefinger directly over the lacrimal sac for the duration of the five minute test period.

RESULTS

The initial study of the 51 patients (102 eyes) was not intended to be a pilot study; however, the large variability of the data obtained was unacceptable. The importance of decreasing variables which may stimulate lacrimal secretion was reemphasized. A quiet laboratory environment, minimal air current, minimal lid manipulation, and standardized light and humidity conditions are most important. We found it necessary to do a complete "dry run" with each volunteer including all manipulations

necessary for drop application and placement in front of the gamma camera along with the noises made by the camera and computer. This was essential so that nothing new was presented to the subject during the test period. Each volunteer also observed the person before him undergoing the experiment so as to decrease his apprehension. In the pilot series, drops were given simultaneously to both eyes to save laboratory and computer time. This, in retrospect, probably was our greatest source of error since simultaneous lid manipulation and drop application stimulated excessive reflex lacrimal secretion. Single eye studies also allowed the eye to be closer to the gamma camera which increased three- to fourfold the magnification of the eye on the oscilloscope screen and computer printout. The positioning of the head was also a major source of error. Head tilt in any axis affected the flow pattern; therefore, in the studies reported here great care was made to insure that the head was in the desired plane and axis. The pilot data were evaluated by measuring the length of time in which half the radioactive tracer was still present in the area of interest (T½). This was found to be inaccurate since ocular contact times in these studies seldom followed a linear decay curve. By analyzing with the computer flow patterns every five seconds, it became obvious that this system had numerous decay curves with variation depending on the various parameters studied in this experiment.

The radioactivity in a 0.5μl drop was sufficient to follow tear flow patterns on the eye without major changes in the volume of the tear film. Pilot studies showed that 13μl was a satisfactory amount to study contact times; since with a normal blink rate, fluid was always present in the lacrimal sac without spillage onto the lid margins.

TEAR FLOW PATTERNS

To study extraocular flow patterns of fluid, 36 volunteers or 72 eyes were tested. A 0.5μl drop of ^{99m}Tc was placed on the eye in the area desired and the patient positioned in front of the gamma camera. The patterns as per head position and area applied were found to be consistent with variations primarily depending upon depth of drop application in the fornix and/or amount of secondary lacrimal secretion. There is no question that application of a drop, if properly placed under a lid, can become entrapped and act like a "depot" deposit (Figs. 6, 7). Even with a normal blink rate and the head vertical, 80+ % of the drop remained in the ocular area for five minutes and with the eyelids closed, 96+ % (Table II). Figure 8 shows the flow pattern of "depot" applications in vertical volunteers with normal blink rates. As can be seen in this diagram and in Table II, in whichever half of the globe the drop was applied, more tracer was found in

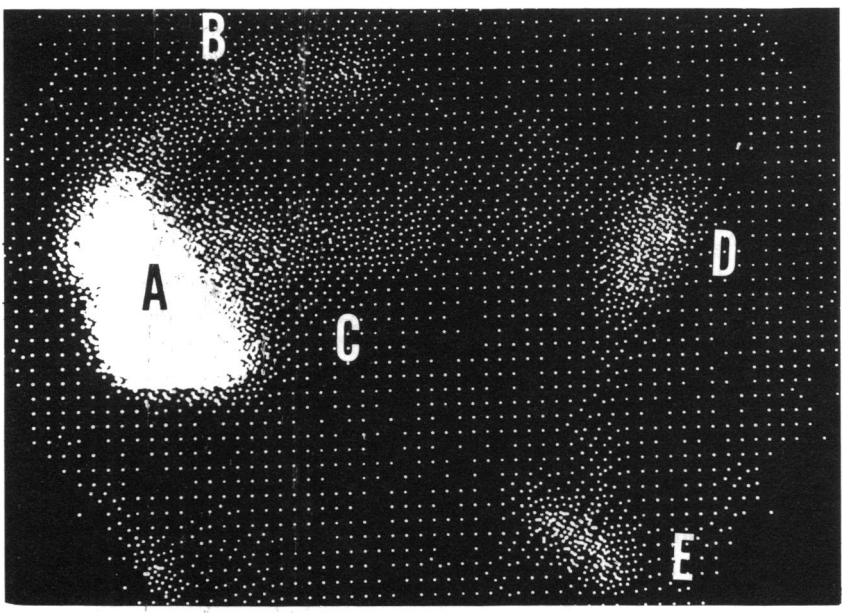

FIGURE 6
Five-minute composite computer printout of an inferior temporal 13μl "depot" application in the right eye of a supine patient with normal blink rate. (A) "Depot" application, (B) Superior and (C) inferior margin tear strip, (D) Lacrimal sac, (E) Solution in the nose.

that area than in the other half. This was true whether the drop was given in the superior, inferior, temporal, or nasal halves. Figure 8-E shows the pattern in a volunteer with a blink rate of less than five per minute. In some instances, tears did not go into the lacrimal sac, especially in volunteers who were trying not to blink and produced only "half blinks" which seldom caused significant lacrimal drainage. In instances where only "half blinks" occurred, the tears ran down onto the cheeks with minimal to no tracer being found in the lacrimal sac.

With lids closed and the volunteer vertical, whether the solution was given superiorly or inferiorly, the flow patterns were almost identical (Fig. 9). If the drop was applied nasally, the majority of the solution under the closed lid stayed nasal to the midline and if given temporally, the majority stayed temporal (Table II). There is, however, a much greater tendency even under the closed lid for nasal flow than temporal flow (Table II). Closed eye series in the vertical, supine, or face down position have a greater percentage of the solution inferiorly than the open eye series. This may occur since most of the fluid accumulates between and

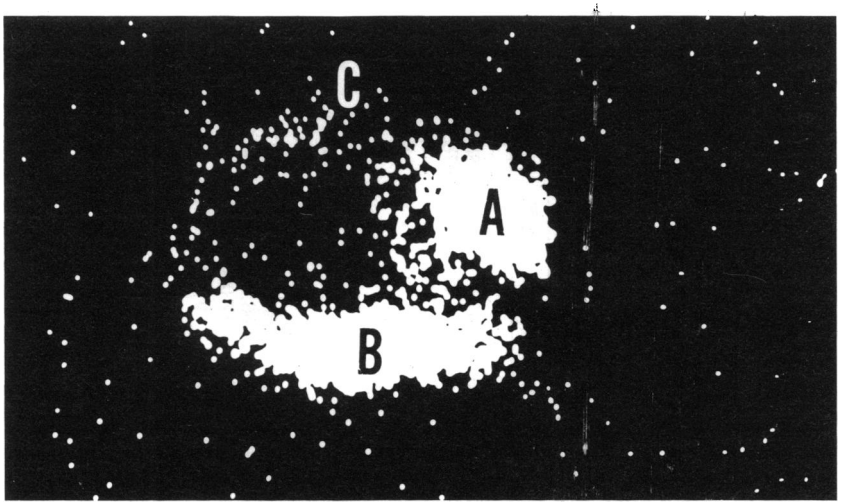

FIGURE 7
Polaroid photo of the gamma persistence oscilloscope (15-sec exposure) 5 minutes after a superior temporal 13μl "depot" application in the left eye of a supine volunteer with closed eyes. (A) "Depot" application, (B) Solution under and between eyelids, (C) Superior fornix flow. Note flow pattern from "depot" to lid margin and in superior fornix.

just under the lid margins and this area lies below the horizontal midline with the closed lid. Flow into the lacrimal sac with lids closed was negligible and empirically directly proportional to the force of squeezing or blinking on instillation of the drop and the amount of quivering of the closed lid. Quivering was found in nervous individuals and increased in some volunteers towards the end of the five minute closed-eye time period. Quivering lid movements enhanced temporal flow and significantly increased lacrimal outflow.

Figure 10 shows the flow patterns in the supine patient with normal blink rate or with eyelids closed. In the supine position the drop was easier to apply high in the superior fornix especially if the volunteer had loose eyelids. Significant nasal flow under the upper lids was seen only with high fornix applications (Figs. 7, 10-A). If the solution is applied in the area of the tarsal plate which occurs in the majority of cases, the flow pattern is almost always directed toward the nearest lid margin and into the marginal tear strip (Figs. 10-B,C,D, 11). In Figure 12, a diagrammatic sketch of flow patterns of solutions placed in the base of the cul-de-sacs with eyelids open is shown. With volumes of 0.5μl, seldom more than 20% of the solution took a route other than directly to the lid margin. With

TABLE II: PERCENT RETENTION OF A 0.5μL DROP OVER A 5-MINUTE PERIOD*

Area of Application and Head Position	Ocular Area**				Corneal Area**				Temporal Half***			
	Normal Blink Rate		Lids Closed		Normal Blink Rate		Lids Closed		Normal Blink Rate		Lids Closed	
	A.M.	S.E.	A.M.	S.E.	A.M.	S.E.	A.M.	S.E.	A.M.	S.E.	A.M.	S.E.
Vertical												
Inferior Temporal	87.0%	2.8	98.0%	0.6	28.0%	3.2	35.0%	6.4	83.0%	6.7	85.0%	2.5
Superior Temporal	82.0%	1.4	96.0%	0.9	14.0%	4.1	42.0%	6.9	78.0%	5.7	78.0%	9.9
Inferior Nasal	77.0%	1.7	96.0%	1.2	25.0%	3.2	40.0%	2.6	33.0%	4.6	6.0%	2.9
Superior Nasal	83.0%	10.2	94.0%	0.6	21.0%	6.4	32.0%	6.5	18.0%	4.9	9.0%	1.2
Side												
Upper Eye — Inferior Temporal	—	—	91.0%	1.7	—	—	30.0%	4.0	—	—	16.0%	2.5
Lower Eye — Inferior Temporal	—	—	98.0%	1.0	—	—	44.0%	3.0	—	—	46.0%	3.1
Supine												
Inferior Temporal	68.0%	7.0	96.0%	1.3	15.0%	1.8	40.0%	2.6	63.0%	4.0	88.0%	1.4
Superior Temporal	73.0%	7.3	97.0%	1.2	19.0%	8.1	35.0%	6.4	66.0%	2.0	66.0%	3.2
Inferior Nasal	57.0%	8.1	80.0%	5.8	16.0%	5.2	23.0%	0.6	17.0%	5.5	12.0%	2.6
Superior Nasal	55.0%	2.9	88.0%	1.7	14.0%	2.7	36.0%	2.1	6.0%	1.8	18.0%	4.4
Face												
Inferior Temporal	97.0%	3.7	96.0%	0.8	77.0%	2.0	68.0%	2.0	31.0%	1.2	40.0%	5.2

TABLE II:—*Continued*

Area of Application and Head Position	Nasal Half***				Superior Half***				Inferior Half***			
	Normal Blink Rate		Lids Closed		Normal Blink Rate		Lids Closed		Normal Blink Rate		Lids Closed	
	A.M.	S.E.	A.M.	S.E.	A.M.	S.E.	A.M.	S.E.	A.M.	S.E.	A.M.	S.E.
Vertical												
Inferior Temporal	13.0%	9.8	15.0%	2.3	12.0%	5.5	18.0%	3.9	88.0%	5.5	82.0%	4.3
Superior Temporal	22.0%	5.7	22.0%	9.9	53.0%	1.4	31.0%	1.4	47.0%	1.4	69.0%	1.4
Inferior Nasal	67.0%	4.1	94.0%	2.9	11.0%	5.4	14.0%	7.4	89.0%	5.5	86.0%	7.4
Superior Nasal	72.0%	11.0	91.0%	1.2	42.0%	6.2	27.0%	4.0	58.0%	6.2	73.0%	4.0
Slide												
Upper Eye — Inferior Temporal	—	—	80.0%	7.5	—	—	26.0%	10.6	—	—	75.0%	3.5
Lower Eye — Inferior Temporal	—	—	54.0%	3.0	—	—	18.0%	9.5	—	—	83.0%	9.5
Supine												
Inferior Temporal	37.0%	4.0	12.0%	1.4	30.0%	5.5	8.0%	3.1	70.0%	5.5	92.0%	2.5
Superior Temporal	30.0%	2.0	34.0%	3.2	69.0%	2.0	52.0%	1.2	31.0%	2.0	48.0%	1.2
Inferior Nasal	83.0%	5.5	88.0%	2.6	32.0%	4.7	6.0%	2.3	68.0%	4.7	94.0%	2.3
Superior Nasal	94.0%	1.8	82.0%	4.4	79.0%	2.1	26.0%	2.7	21.0%	2.0	75.0%	2.6
Face												
Inferior Temporal	70.0%	1.2	60.0%	5.2	33.0%	2.1	24.0%	0.8	68.0%	2.0	76.0%	0.8

*All series have 3 eyes per trial except those in the side position which has only 2 eyes each.

**The percent of drop present is calculated as to the area shown in Figure 2-B.

***The percent of drop present is calculated only as to the area shown in Figure 2-C disregarding the amount lost due to lacrimal drainage.

A.M. = arithmetic mean, S.E. = standard error of mean.

—Data invalidated due to overflow of fluid from palpebral aperture.

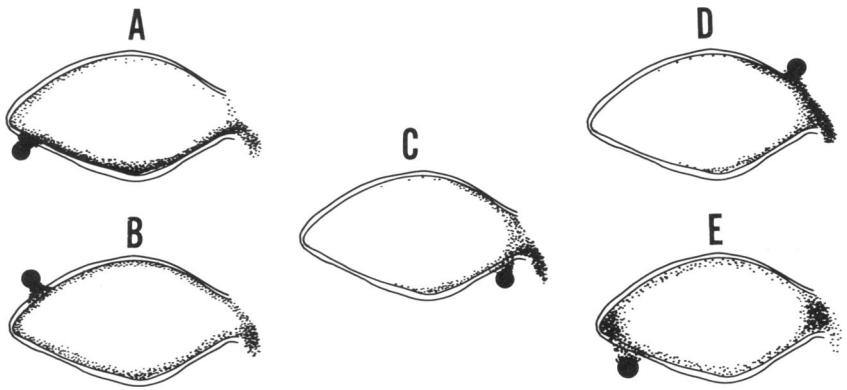

FIGURE 8
Flow patterns of 0.5μl "depot" applications in right eyes of vertical volunteers with normal blink rates. A: Inferior temporal B: Superior temporal C: Inferior nasal D: Superior nasal E: Inferior temporal. Blink rate less than 5/minnute.

the lids shut and the patient supine, the solution may primarily stay in the temporal half of the lid area for five minutes (Fig. 10-C) or go along the lid margin (Fig. 10-D). The latter occurred primarily when the solution was not placed very high in the fornix of the upper or lower lid. However, if the drop was placed high in the fornix and observed for 10 minutes, the solution may follow the superior or inferior contour of the globe (Fig. 10-E).

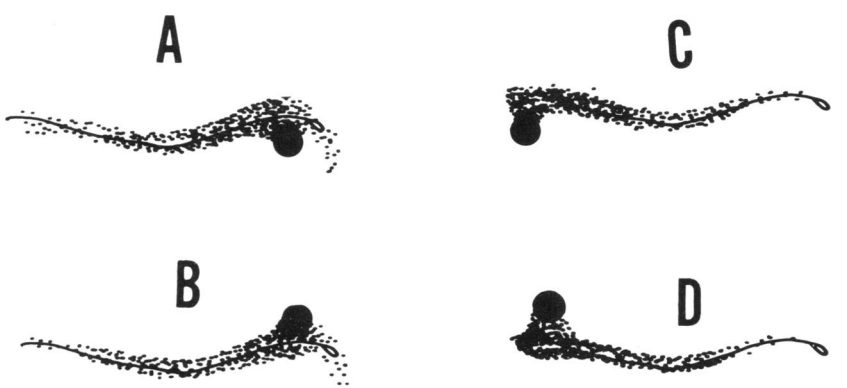

FIGURE 9
Flow patterns of 0.5μl "depot" applications in right eyes of vertical volunteers with lids closed. A: Inferior Nasal B: Superior nasal C: Inferior temporal D: Superior temporal.

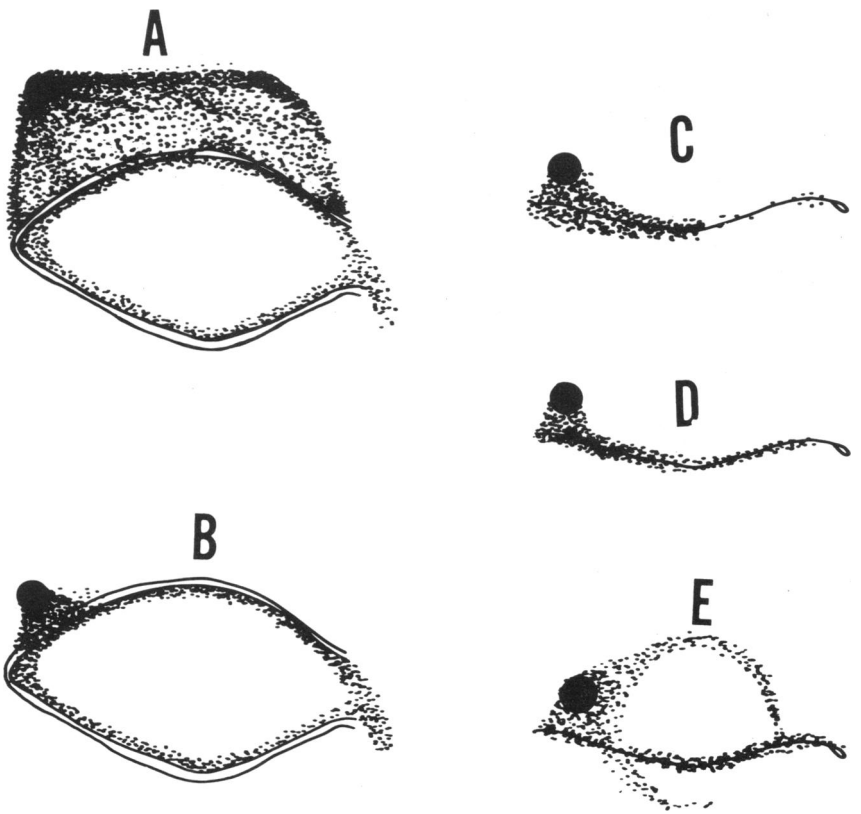

FIGURE 10
Flow patterns of 0.5μl "depot" applications in right eyes of supine volunteers. A: Normal blink rate—high superior temporal fornix application. B: Normal blink rate—low superior temporal application. C: Lids closed—high tarsal plate superior temporal application. D: Lids closed—low tarsal plate superior temporal application. E: Lids closed—10-minute high tarsal plate superior temporal application.

With the volunteer lying on his side and a drop placed inferior temporally on the upper eye, 95% of the solution was in the nose within one minute with the lids open. If placed inferior temporally in the lower eye with eyes open, less than 5% reached the lacrimal sac in five minutes; however, a significant amount had also run onto the skin in the outer canthal area (Fig. 13-B). Immediately after "depot" application with lids shut, the solution remained primarily in the dependent half of the eye with 80% nasally in the upper eye series compared with 46% present temporally in the lower eye (Table II).

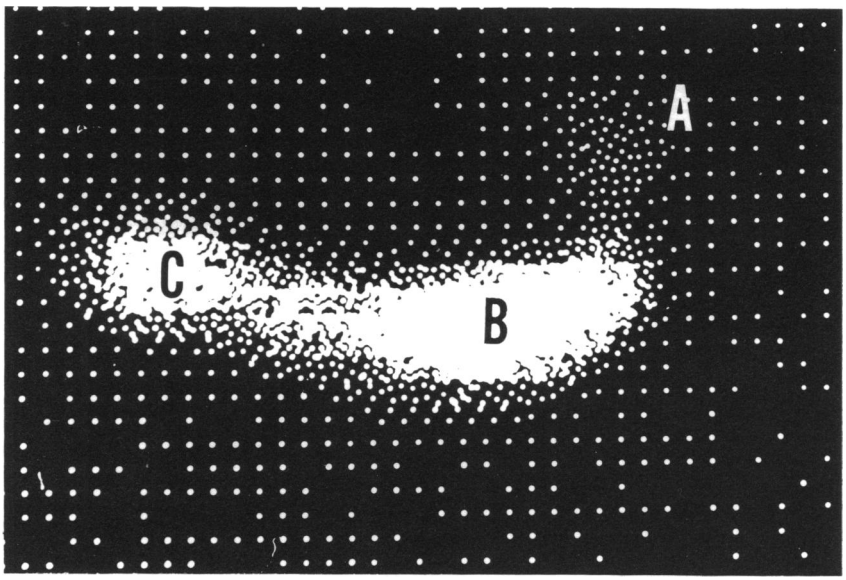

FIGURE 11
Computer printout taken of the 5th minute of a superior temporal "depot" application in the left eye of a supine volunteer with lids closed. A: Resolving "depot" application. B: Solution between and under closed lid. C: Inner canthal area.

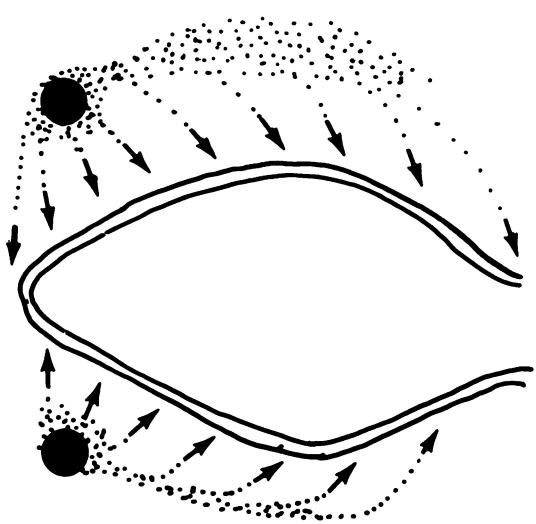

FIGURE 12
Diagrammatic flow patterns of ^{99m}Tc in the temporal fornices of a right eye. Not infrequently rivus-like flow is seen crossing the tarsal plate to the lid margin.

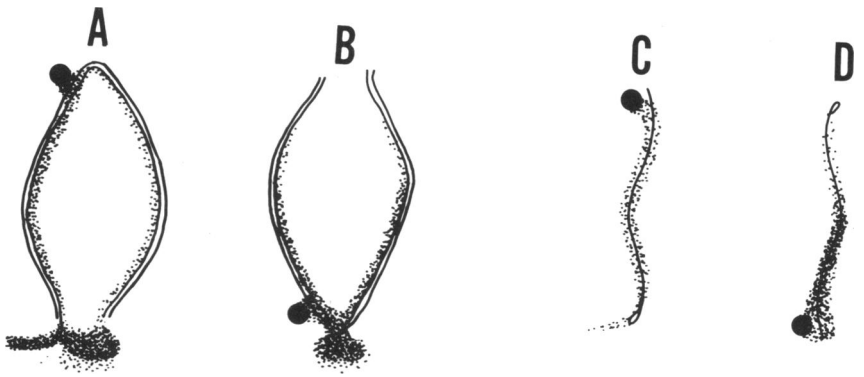

FIGURE 13
Flow patterns of 0.5μl inferior temporal "depot" applications with volunteers on their sides. A: Upper eye—Normal blink rate. B: Lower eye—Normal blink rate. C: Upper eye—Closed lid. D: Lower eye—Closed lid.

If the patient was on his face and the solution given inferior temporally, there was a greater tendency for the tracer to accumulate centrally in either the superior or inferior marginal tear strip than with any other method (Fig. 14-A). Central accumulation was also seen with the lids closed (Fig. 14-B). The highest percent of tracer found over the corneal area was also found in the face down series (Table II).

OCULAR CONTACT TIMES

In this series there were 86 volunteers (172 eyes). Table III compares the ocular amount retained in the vertical position, normal blink rate, of a 13μl drop over a five minute period depending on how the solution was applied. The areas where the drop was placed were inferior temporal

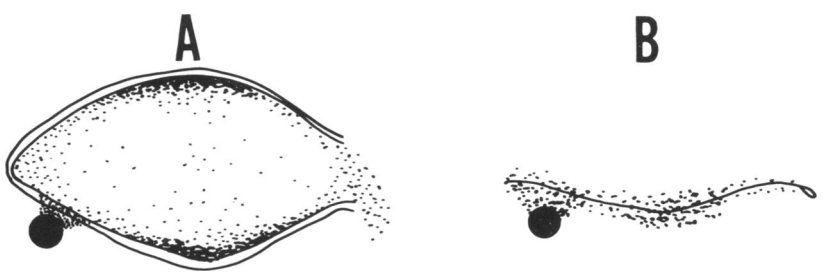

FIGURE 14
Flow patterns of 0.5μl inferior temporal "depot" applications in right eyes of volunteers in a face down position. A: Normal blink rate. B: Zero blink rate (lids closed).

TABLE III: PERCENT RETENTION OF A 13μL DROP OVER A 5-MINUTE PERIOD WITH NORMAL BLINK RATES—VERTICAL POSITION

Location	N	Cornea		Ocular	
		A.M.	S.E.	A.M.	S.E.
Inferior temporal marginal tear strip	5	4.8%	1.0	16.2%	4.6
Superior temporal sclera—no attempt to trap beneath the upper lid	8	6.3%	0.7	27.2%	5.1
Inferior temporal—"depot"	7	12.6%	1.6	52.7%	3.2
Inferior temporal—"depot" Over age 50	4	20.0%	5.1	63.8%	9.0

The comparison of the inferior temporal ("depot") application to each of the other three groups of application in this table was statistically significant for both the corneal and ocular series.

N = number of samples, A.M. = arithmetic mean, S.E. = standard error of mean.

marginal tear strip, superior temporal sclera, and under the lower lid inferior temporal ("depot"). The "depot" applications were tested for age groups 20 to 30 and above 50 years of age. In this series the superior temporal sclera application was an attempt to simulate the clinical method of drug application whereby a drop is given by simply elevating the upper lid, having the patient look down, and applying the medication on the sclera. No attempt was made to trap the solution under the upper lid. In comparison to this is the method described for inferior cul-de-sac "depot" application which simulates with modifications the other most

TABLE IV: COMPARISON OF BLINK RATE WITH PERCENT OCULAR RETENTION OF 13μL DROP OVER A 5-MINUTE PERIOD
INFERIOR TEMPORAL APPLICATION — VERTICAL POSITION

Blink Rate	N	A.M.	S.E.
	Cornea		
Rapid (50-60/min)	4	8.0%	3.0
Normal (10-20/min)	7	12.6%	1.6
Slow (less than 5/min)	2*	44.5%	15.4
Zero (closed lids)	4	50.3%	10.6
	Ocular		
Rapid (50-60/min)	4	24.0%	8.0
Normal (10-20/min)	7	52.7%	3.2
Slow (less than 5/min)	2*	93.5%	0.5
Zero (closed lids)	4	80.5%	6.1

*Excluded 3 additional eyes from series due to tears overflow onto the eyelids.

The comparison of the normal blink rate with each of the other three in either the corneal or ocular series was statistically significant.

N = number of samples, A.M. = arithmetic mean, S.E. = standard error of mean.

TABLE V: COMPARISON OF PERCENT RETENTION OF A 13μL DROP OVER A 5-MINUTE PERIOD DEPENDING UPON AREA APPLIED — VERTICAL POSITION

Location	Normal Blink Rate			Lids Closed		
	N	A.M.	S.E.	N	A.M.	S.E.
		Cornea				
Inferior — Nasal	5	18.2%*	2.1	4	45.5%	2.4
Superior — Nasal	4	14.8%	6.6	5	19.8%*	4.6
Superior — Temporal	7	16.7%*	1.9	4	30.0%*	7.9
Inferior — Temporal	7	12.6%	1.6	4	50.3%	10.6
		Ocular				
Inferior — Nasal	5	47.4%	5.1	4	84.0%	4.2
Superior — Nasal	4	48.8%	4.7	5	84.6%	7.5
Superior — Temporal	7	52.5%	5.0	4	79.3%	8.4
Inferior — Temporal	7	52.7%	3.2	4	80.5%	6.1

If the comparison of inferior temporal application of solution was statistically significant in comparison to any of the other three in each of the series, it is marked with a *. The effects of lid closure compared to normal blink rate was statistically significant for each location except for superior nasal in the corneal series.

N = number of samples, A.M. = arithmetic mean, S.E. = standard error of mean.

common method of topical ocular medication. The "depot" application is twice as effective in increasing both corneal and ocular contact times compared to applying the solution to the superior scleral area. An increase in contact times was also seen in the over 50 years age group compared to those 20 to 30 years of age.

TABLE VI: COMPARISON OF PERCENT RETENTION OF A 13μL DROP OVER A 5-MINUTE PERIOD DEPENDING UPON THE AREA APPLIED — SUPINE POSITION

Location	Normal Blink Rate			Lids Closed		
	N	A.M.	S.E.	N	A.M.	S.E.
		Cornea				
Inferior — Nasal	4	6.3%*	1.3	5	34.2%	12.1
Superior — Nasal	4	12.0%*	3.0	4	41.3%	9.6
Superior — Temporal	4	13.3%	4.0	4	42.5%	9.0
Inferior — Temporal	4	19.3%	5.5	4	28.0%	6.9
		Ocular				
Inferior — Nasal	4	35.5%*	2.4	5	83.4%	4.3
Superior — Nasal	4	53.3%*	10.6	4	94.0%	1.2
Superior — Temporal	4	45.5%*	15.4	4	93.5%	1.7
Inferior — Temporal	4	77.5%	7.6	4	86.8%	7.7

If the comparison of inferior temporal application of solution was statistically significant in comparison to any of the other three in each of the series, it is marked with a *. The effects of lid closure compared to normal blink rate was statistically significant for each location except for inferior temporal in the corneal series.

N = number of samples, A.M. = arithmetic mean, S.E. = standard error of mean.

The more frequently one blinks, the more rapidly solution leaves the eye (Table IV). There was about a sixfold corneal and threefold ocular increase in solution retention with a zero blink rate (lids closed) compared to 60 blinks per minute. The retention percentage with lids closed was increased fourfold for the cornea and almost twice as much in the ocular area compared to the normal blink rate group. In Table V various areas of drop placement are compared for corneal and ocular solution retention percentages in vertical patients with normal blink rate versus zero blink rate (closed eyelids). In both the corneal and ocular areas with either normal or zero blink rates, contact times were surprisingly similar regardless of the area of application except for corneal contact values under closed lids. Table VI compares the percentage of a 13μl drop retained over a five minute period in both corneal and ocular areas depending upon the location applied and lid position in the supine patient. The location in which the drop was placed in open eyes had little influence on comparative retention values except in the normal blink series where inferior temporal application had the highest percent retention. In all locations whether ocular or corneal series, the percent reten-

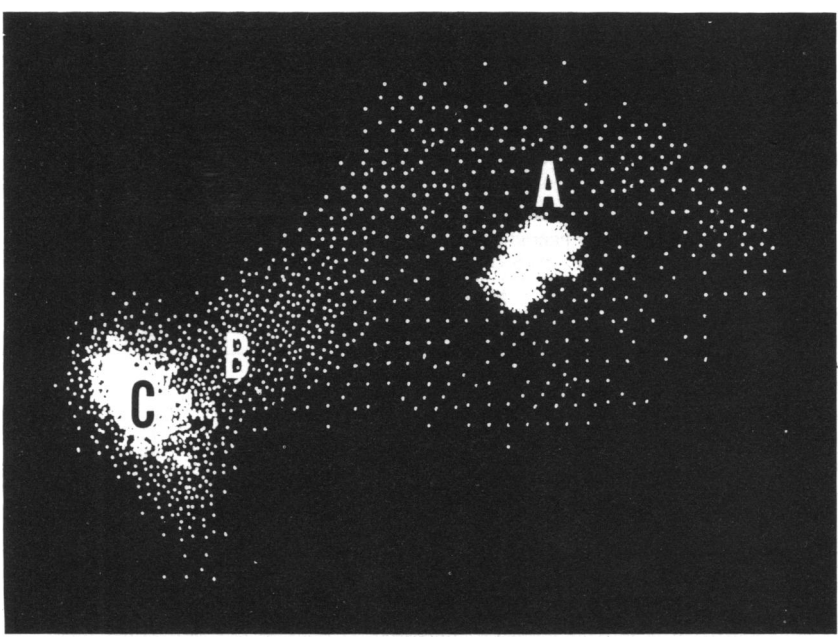

FIGURE 15
Computer printout 3 minutes after a 13μl drop of ^{99m}Tc was placed on a deep neurotrophic corneal ulcer in the left eye of a supine patient with normal blink rate. A: Neurotrophic ulcer. B: Inner canthus. C: Lacrimal sac.

TABLE VII: COMPARISON OF PERCENT RETENTION OF A 13μL DROP OVER A 5-MINUTE PERIOD DEPENDING UPON THE AREA APPLIED — FACE DOWN, SIDE, OR VERTICAL POSITION WITH PRESSURE OVER THE LACRIMAL SAC

Position and Location	Normal Blink Rate			Lids Closed		
	N	A.M.	S.E.	N	A.M.	S.E.
		Cornea				
Side-Upper eye	6*	—	—	5	36.4%	5.3
Side-Lower eye	5*	—	—	7	35.1%	4.9
Face Down	4	30.8%	14.7	9	52.3%	8.3
Vertical-Pressure over lacrimal sac	5	40.2%	5.4	7	37.3%	4.2
		Ocular				
Side-Upper eye	6*	—	—	5	85.2%	5.3
Side-Lower eye	5*	—	—	7	88.4%	3.7
Face Down	4	68.5%	14.7	9	96.2%	1.0
Vertical-Pressure over lacrimal sac	4**	94.0%	1.6	7	92.9%	3.1

*Fluid ran onto the cheek invalidating the experiment.

**Two additional eyes were removed from the series due to overflow of tears in the inner canthal area.

N = number of samples, A.M. = arithmetic mean, S.E. = standard error of mean.

tion was markedly increased with lid closure. In a large neurotrophic corneal ulcer, the ulcer was dried and a 13μl drop was placed on the ulcer while a normal blink rate was allowed. Significant amounts of solution were clearly observed in the defect even three minutes later (Fig. 15).

A comparison of percent retention of a 13μl drop over a five minute period with volunteers on their sides, on their face, or in a vertical position with pressure over the lacrimal sac is shown in Table VII. Experiments with patients on their sides with eyelids open were difficult since the tears in the upper eye flowed onto the inner canthal skin area; whereas, in the lower eye the tears ran onto the outer canthal skin area. Excellent retention times for both the corneal and ocular areas, however, were obtained with closed lids. In the vertical volunteer, pressure over the lacrimal sac was very effective in retaining solutions with lids open or closed since over 90% of the drop in the ocular area was retained over the five minute test period. After a few minutes with the lids open and pressure over the lacrimal sac, tears often accumulated with overflow in the inner canthal area.

Table VIII shows the ocular areas where the solution applied has primarily accumulated over the five minute test period in the vertical or supine volunteer. Almost twice as much solution was available temporally in the vertical patient with lids open when the drop was given in the temporal half of the eye than was available nasally under the same conditions.

TABLE VIII: PERCENT RETENTION OVER A 5-MINUTE PERIOD OF TRACER IN THAT HALF OF EYE IF PLACED IN THAT AREA

	Vertical					Supine				
		Normal Blink Rate		Closed		Normal Blink Rate		Closed		
Ocular Areas	N	A.M.***	S.E.	A.M.***	S.E.	N	A.M.***	S.E.	A.M.***	S.E.
Temporal Half* (solution applied temporally)	8	39.7%	3.7	31.5%	5.3	8	41.0%	4.0	66.6%	2.7
Temporal Half* (solution applied nasally)	8	22.1%	2.3	39.0%	5.1	9	29.9%	5.5	28.5%	7.2
Inferior Half** (solution applied superiorly)	8	70.0%	4.8	81.7%	4.7	8	52.2%	5.0	80.0%	2.3
Inferior Half** (solution applied inferiorly)	8	78.2%	3.6	72.2%	7.0	9	54.4%	6.4	78.3%	2.9

*Groups were bunched regardless if drop was given superiorly or inferiorly.

**Groups were bunched regardless if drop was given nasally or temporally.

***This is a percentage only of the tracer present in the ocular area and is not a percentage of the total drop applied.

N = number of samples, A.M. = arithmetic mean, S.E. = standard error of mean.

There was much less solution available under identical conditions in the supine position. If the drop was given in the nasal half of the eye with normal blink rates as compared to the temporal half, almost twice as much was also available nasally in the vertical position, (100-22.1) 77.9% versus 39.7%, and in the supine position, (100-29.9) 70.1% versus 41%. These same principles are not as clear-cut for superior versus inferior applications of solutions in the vertical volunteers since the majority of the solution regardless of area applied was found in the inferior half of the eye due to gravity. In the supine patient with normal blink rates, there was almost an equal amount in the superior and inferior marginal tear strip which agrees with the laws of gravity. In the lids closed series, more solution was trapped temporally with temporal placement in the supine volunteer than in the vertical volunteer. This may be due to the necessity of solution traveling against gravity, that is, with temporal applications the solution had to travel up over the cornea to reach the inner canthus. The percent retention as per half of the eye for closed lids in the superior or inferior ocular area may be misleading since as with 0.5μl applications the closed lids meet below a line drawn between the inner and outer canthus. Even so, the differences between vertical and supine patients with lids closed was slight since gravity probably plays a smaller role and takes longer to occur under closed lids especially since the solution is channeled by the lid margin.

DISCUSSION

The use of technetium 99m has been most useful in examining tear flow and ocular contact times. Even though lid manipulation or the application of solutions to the eye immediately triggers secondary lacrimal secretion,[24] these are clinical requirements for applying topical medication. The variability between humans in the amount of secondary lacrimal secretion due to emotional or physical stimuli is probably the primary reason for variability in some of the data. The conclusions from this study, however, should have direct clinical application since humans were used, ^{99m}Tc physical properties (pH, viscosity, weight, and molarity) are very similar to human tears, and the same techniques of drug application are used clinically.

The extraocular fluid movement may be influenced by six mechanisms:

1. *Tarsal Plate and Fornix.*—Solutions applied so as to come in contact with the tarsal plate will move to the nearest lid margin. That portion of a drop which remains in the fornix may follow a nasal course near the distal border of the tarsal place and at various intervals move to the lid

margin (Fig. 12). This movement is in part overflow from the drop but probably also from reflex lacrimal secretion. In long term studies, pockets of radioactive material remained in the fornix long after all other ^{99m}Tc had left the eye. This suggests that after initial reflex lacrimal flow or medication overflow, fornix flow is indeed minimal.

2. *Gravity.*—The effect of gravity on tear flow has been known[1,25] but has not been fully appreciated in the application of ocular medication. Gravity affected every series and required continuous head position monitoring so as not to modify flow patterns. In the vertical patient with normal blink rates, higher concentrations were found in the inferior half of the globe compared to the supine patient where concentrations were more equally distributed superiorly and inferiorly (Table VIII). With volunteers on their sides with lids open, there was rapid flow toward the nose if the drop was given on the upper eye with the opposite effect on the lower eye (Fig. 13). In the face down position, tears collected in their most dependent position, that is, over the cornea or in the mid-third of the marginal tear film. While gravity is of major importance with the lids open, it is also a factor in the series with lids closed. Gravity's force is probably counteracted in part by physical and physiochemical factors under the closed lid.

3. *Lid Margins.*—In this young "tight lid" population with eyelids open, once the tracer came in contact with the marginal tear strip it remained in the palpebral aperture and did not reenter under an eyelid. Only in rare instances, except in closed lid experiments, was the ^{99m}Tc solution seen under an eyelid unless initially placed there. This was also true in the older age group with loose lids, however, too few volunteers were tested. Therefore, the lid margins essentially act as a channel for the tears keeping them in the palpebral fissure and directing them nasally.[11]

4. *Lid Closure.*—The closed lid allows for greater retention of tears. This is a known fact of every ocular surgeon who after a dressing change has opened the lids and a large pool of tears appeared. Since in most eyes with lids closed or during sleep, usually little to no lacrimal secretion occurs; this phenomenon is primarily seen in irritated eyes with reflex lacrimal secretion.[26] In fact, some authors feel that the lacrimal gland secretion occurs intermittently and may be secondary only to stimuli.[25,26] This may well be true since the T½ from fornix deposits measured long after the initial reflex lacrimal secretion from lid manipulation and drop placement was infinity. In some 30-minute studies with lids closed, there was no radioactivity in the lacrimal sac and no tear overflow on the lids; however, excess tears were still found after opening the closed lid. These

tears may be from the initial reflex secretion due to drop placement, psychic reflex stimulation, or possibly the lacrimal gland does continue to secrete some fluid even with lids closed and no apparent physical stimulus. These experiments reconfirm, however, that the lids can hold fluid and thereby increase the volume the eye can hold. The primary areas where the fluid is held under the closed lid as found with ^{99m}Tc are under the lid adjacent to the lid margin, between the lids, and in areas distal to the non-lid border of the tarsal plate. This, in retrospect, is not surprising since these are also the areas where most foreign bodies are found; they may well have been placed there by tear flow patterns. Unless initially placed under the closed lid, applied solutions would probably not reach the opposite cul-de-sac without aid from fluid buildup under the lids. The increased fluid volume buildup probably elevates the lid from the globe allowing gravity to carry the solution to new areas. In this series, this was apparent in the superior and inferior cul-de-sac in supine volunteers and in the inferior cul-de-sac in vertical studies.

5. *Blinking.*—It is clear that the lid margins channel the tear flow, and with fluid buildup or blinking it is pushed nasally.[11] Some temporal movement also occurs, but it is no doubt mainly due to overflow of medication, mixing caused by blinking, or gravity such as head tilt to that side.

6. *Entrapment of Solution Underneath the Lids.*—Using these radiographic techniques, it is obvious that fluid can be entrapped even for hours depending upon its location in the conjunctival sac (Figs. 6, 7). The "depot" type application increases the volume of fluid that the eye can hold. The amount of radioactivity is directly proportional to the volume of solution present so that increased concentrations in an area indicate pooling of fluid. There may be also some impedences to free flow of solutions across the lid margin and at the distal border of the tarsal plate. This resistance is easily overcome, however, with reflex lacrimal secretion.

The primary intent of this overall study was to find the optimal method of applying topical ocular solutions to increase corneal and ocular contact times. Currently two methods of topical ocular solution applications are commonly used: to have the patient look down and apply one to two drops on the superiorly exposed sclera or to have the patient look up, pull the lower lid down, and apply the drops in the inferior cul-de-sac. We have modified this latter method to include gentle pulling of the lower lid away from the globe and applying the solution to this potential pouch. After waiting a moment, lift the lid upward to touch the globe

and thereby trap some of the solution in the inferior conjunctival sac. This method ("depot" application) has increased the retention rate of a 13μl drop on the eye twice as much over simply applying drops to the superior sclera and was even more striking with "looser" lids in the older age groups (Table III).

Some generalization can be made on how best to apply topical ocular solutions (Table IX) and the methods that give the highest contact times in specific ocular areas (Table X). To remember the best method to apply topical ocular medication, one only needs to remember (a) closure of the lid markedly increases the ocular and corneal contact times, (b) the importance gravity has on the tear flow, (c) it is difficult for solutions to flow under an eyelid unless specifically placed there, and (d) place the medication in the area of pathology.

Overall corneal or ocular contact times are generally not significantly different by placement of the solution in a specific ocular area (Tables V and VI). However, whether the drop is placed superiorly, inferiorly, nasally, or temporally, the percentages retained are greater on that half of the eye (Table VIII). These results would have been much more dramatic if they would have been calculated for just that quadrant where the solution was initially applied. With lid closure and putting the patient in a position which allows gravity to play a role, there is the potential to increase tissue concentrations in that area both to treat disease and as a tissue "depot" deposit.[27] The area of application, if under an eyelid, has some residual tracer long after other areas are free of radioactivity. In some studies, especially under a closed lid, up to 70% of the applied solution remained in the quadrant applied for over a five minute period. Therefore, the drug should be placed under a lid in the area of the primary pathology.

Gravity is of major importance in the understanding of how to increase ocular contact times of medication. The comments on gravity for tear flow are also true for retaining ocular medication in the area of greatest therapeutic value. In the case of a corneal ulcer, gravity allowed a high concentration of solution to fill the crater much like a hole on a hill will retain water where normally the fluid would have run off (Fig. 15).

Chrai suggested that smaller volumes of more concentrated medication (if nonirritating) may well be more effective therapeutically and that volumes of 1 to 5μl are ideal.[4] Using the method described here, a 13μl drop can be from 80 to 90+ % retained on the eye for five minutes regardless of head position (Tables V, VI, VII). While we do not know the optimum size drop, current commercial drops are not ideal. Also, directions on the containers recommend giving 1 to 2 drops; whereas, one drop

TABLE IX: SUMMARY OF METHODS WHICH GIVES THE GREATEST PERCENT RETENTION OF A 13μL DROP TO A GIVEN AREA

Ocular Location	Area and Method of Application	N	A.M.	S.E.	A.M.	S.E.
Temporal half	Supine—Inferior temporal Lids closed	4	87.0%	7.7	76.0%	4.1
	Side—Lower eye Lids closed	7	88.0%	4.5	72.0%	5.0
	Face—Inferior temporal Lids closed	9	96.0%	1.0	70.0%	8.1
Nasal half	Supine—Superior nasal Lids closed	4	94.0%	1.2	72.0%	11.5
	Supine—Inferior nasal Lids closed	5	83.0%	4.3	71.0%	9.3
	Side—Upper eye Lids closed	5	85.0%	11.9	62.4%	15.0
Superior half	Supine—Superior temporal Lids closed	4	94.0%	1.7	26.0%	2.7
	Supine—Superior nasal Lids open	4	53.0%	10.6	61.0%	8.4
	Supine—Inferior nasal Lids open	4	36.0%	1.2	43.0%	1.9
Inferior half	Vertical—Pressure on sac Inferior temporal—Lids open	4	94.0%	1.6	87.0%	3.8
	Vertical—Pressure on sac Inferior temporal—Lids closed	7	93.0%	3.0	86.0%	2.3
	Face—Eyes closed	9	96.0%	1.0	79.0%	8.2
	Supine—Inferior temporal Lids closed	4	87.0%	7.7	74.0%	3.9
	Vertical—Inferior temporal Lids closed	4	81.0%	6.1	63.0%	9.9
Cornea	Face—Eyes closed	9	52.0%	8.3	54.0%	5.1
	Vertical—Inferior temporal Lids closed	4	50.0%	10.5	61.0%	8.7
	Vertical—Inferior nasal Lids closed	4	46.0%	2.4	55.0%	3.1

N = number of samples, A.M. = arithmetic mean, S.E. = standard error of mean.

is 50 to 75μl and is 2 to 7 times more than the eye can hold.[6] This excess solution on the conjunctiva and especially the cornea probably increases reflex lacrimal secretion which washes away and further dilutes the medication. Equally detrimental to ocular contact times is the associated blink-

ing and squeezing which occurs with wiping away the excess fluid from the lids.

The ocular drug delivery device, Mistura®, sprays medications on the eye. This method can only get medication into the tear film and, therefore, would very rapidly be released from the eye (Table III). Also, the reflex lacrimal secretion from the spray effect hitting the cornea and reflex blinking favors poor corneal and ocular contact times. It has been suggested that the medication is sprayed onto the lids and lashes and in time through capillary action or gravity gets into the ocular tear film.[28] If the mechanism of secondary ocular contact of drugs from the skin and lashes is confirmed by others, this may totally revolutionize the thinking of the application of topical ocular medication.

While the overall data presented here point out some aspects to increase ocular contact time, they also raise an equal number of questions. Further work in this area is essential to improve topical ocular medical therapy.

SUMMARY

Using recently developed radioactive techniques, the patterns of ocular tear flow in the palpebral aperture and under the eyelids were studied. The flow patterns are dictated by many factors, including the tarsal plate, fornix, gravity, reflex lacrimal secretion, lid margin, lid closure, and lid movement. From this data, various methods were tested to see their effect on increasing ocular and corneal contact times. A simple method of topical ocular application utilizing an area under the eyelid to entrap solution is described which markedly improved corneal and ocular contact times. In this manner more solution is contained on the eye and is released at a slower rate from this "depot" application. The importance of gravity, blinking, lid closure, head position, and area of drug application on ocular contact time was investigated. These data were then used to design the optimum methods to apply medication to a given area.

With the patient's head tilted back and looking at the ceiling, gently grasp the lower outer eyelid below the lashes and pull the eyelid away from the globe. In the space between the lid and the eye apply one drop of solution without touching the lashes or the lids. It is preferable to have another person with clean hands apply the medication. Continue to hold the lid in this position for a moment to allow the solution to gravitate into the base of the cul-de-sac. Have the patient look down so as to increase the volume of the cul-de-sac while lifting the lid upward until it touches the globe while slowly and gently closing the eyes (Fig. 3).

The patient should keep his eyes closed for 1 to 2+ minutes. For self medication, tilt the head back, grasp the lower outer lid with clean hands, and pull the lid away from the globe. Place the dropper over the eye by looking directly at it. Just before applying a drop look upward. After applicaiton of the drop look down for a moment and then lift the lid up toward the globe while slowly and gently closing the eyes.

GENERAL CONSIDERATIONS

1. Blinking markedly increases outflow of solutions. During initial drug application, try to prevent squeezing or fluttering of the eyelids since this can cause a fourfold increase in lacrimal outflow. "Half blinks" or incomplete closure of a blink has significantly less effect in removal of fluid from the eye while squeeze blinks may cause solution spillage onto the lids.
2. Closure of the lids prevents loss of solutions by inhibiting flow into the lacrimal outflow system, enhances entrapment of fluid under the lid, and increases the volume of extraocular fluid.
3. The conjunctival sac is a potential space which holds and releases medication as much as three times slower than compared to solutions just applied to the globe.
4. Avoid mechanical or psychic factors which will increase secondary lacrimal secretion. Do not apply drops that initially hit the cornea. Do not hit the cilia, pinch the skin, flood eye with excess solutions, or encourage anyone whom the patient has little confidence in to apply the ocular medication. Preferably, drops should be near body temperature.
5. Apply the drug to the main area of pathology and put the head in a position where gravity will have the greatest tendency to keep the drug where medically indicated. If a significant corneal defect is present, place the patient in a position where gravity will allow filling of the defect with medication and gently close the lids. How long to keep the lids closed depends on severity of underlying disease, but they should be closed for at least 1 to 2+ minutes.
6. Pressure on the lacrimal sac, especially with lids closed, is a most effective method to increase ocular contact times.
7. Theoretically, for drugs which must have a high corneal contact time to achieve intraocular penetration, the best method is inferior temporal application with eyelids closed in either the face down or the head vertical position.

8. Theoretically, current commercial drop sizes of 50 to 75μl are larger than necessary and may not be as effective therapeutically if drug equivalents can be given in a 15μl range.

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