THICKNESS CONTROL in the LIVING CORNEA

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The mechanisms by which the normal cornea maintains its thickness and hence its transparency in vivo are elucidated by an unsteady-state description of corneal mass transport. All modes of transport—diffusion and convection of solute, hydraulic and osmotic flow of solvent, and active transport by the corneal cells themselves—are of necessity included in the analysis. An a priori calculation of corneal dynamics based on this model shows good agreement with experiment. The physiological insights thus gained have clinical implications as well, and a number of these are mentioned briefly.

THE CORNEA IS THE TRANSPARENT PORTION of the outer coat of the eye (Fig. 1). Light enters the eye through the cornea, traverses the aqueous fluid-filled anterior chamber and pupil, passes through the lens and vitreous, and finally impinges on the retina, where it initiates the optic nerve impulses we call "sight." Because of its role in vision, the cornea must be transparent; because of its front-line position with respect to the outside world, it must be flexible and tough. The cornea protects the eye much as a football bladder protects a football from the kicker; the inflation pressure in this case is the intraocular pressure of the aqueous in the anterior chamber, amounting to some 10-20 Torr in normal eyes. Under this pressure, the cornea is curved, with a radius of curvature in man of about 8 mm; it thus refracts incident light ahead of the lens. Indeed, most of the eye's focusing power derives from the air-cornea interface at the anterior, or front, surface of the eye.

The cornea lacks blood vessels as a requirement of transparency (it may be noted that were corneal capillaries in evidence, our vision, though clouded, would at least be rose-colored). The tears which bathe the front surface of the eye lack nutrients, so the cornea must be permeable to permit the influx of these essentials from the aqueous. Similarly, the waste products of corneal metabolism must permeate out of the tissue. Only a minor contribution to material exchange can come from the capillaries at the corneal periphery (the limbus; Fig. 1), since the human cornea is 11 to 12 mm in diameter but only ¾ mm thick at the limbus.

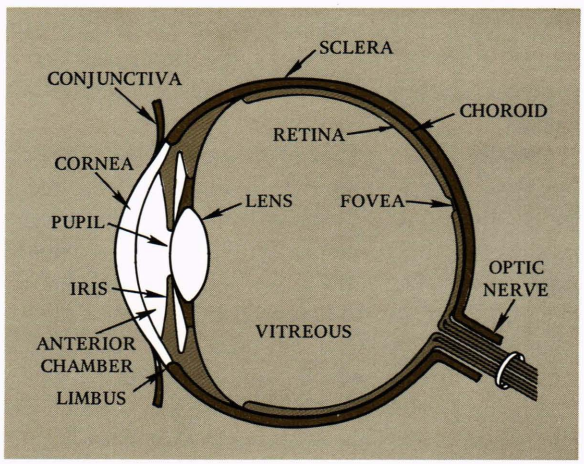

Fig. 1—Schematic diagram of the eye.

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The Major Layers of the Cornea

Before discussing the specifics of corneal thickness control, it is appropriate to review the organization of the cornea itself. This structure consists of three distinct layers, each covering the entire corneal area; from anterior to posterior, these are the epithelium, the stroma, and the endothelium plus Descemet's membrane (Fig. 2).

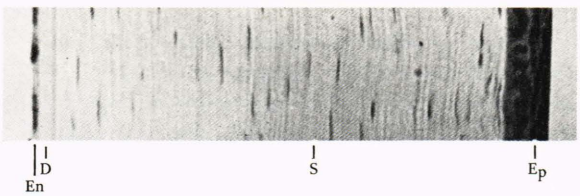

Fig. 2—Microscopic appearance of rabbit cornea showing epithelium (Ep), stroma (S), Descemet's membrane (D) and endothelium (En). Histological section; stained haemotoxylin—eosin. (Reprinted with permission of the author and publisher from *The Eye, Vol. I*, Fig. 1(a) on p. 492, Dr. D. M. Maurice. Copyright 1969 by Academic Press, Inc.)

Epithelium—The epithelium is about 50 μm thick and consists of five or six layers of closely-packed, tightly-joined, highly-interdigitated cells. Because of its close packing, the epithelium is only slightly permeable to solutes and water; indeed, if the intraocular pressure is artificially increased to a large enough value, the epithelium will separate, more-or-less intact, from the underlying stroma. Sited in the anterior layers of the epithelium is a metabolic "pump" that transports sodium ions from the tear side into the stroma. This pump, and the potential it induces, results in a continuous influx of salt into the stroma, even when there is no concentration gradient across the entire cornea. The role of the pump, as far as corneal function is concerned, has not been established.

Stroma—Almost all of the rest of the cornea is stroma. This structure possesses few cells and is normally about 75% water by weight. The stroma, and hence the cornea, is provided with flexibility and toughness by the remaining 25% of the tissue. Most of the solids content of the stroma is in the form of collagen (a high molecular weight protein) fibers, which are arranged in layers (lamellae) which lie parallel to the corneal surfaces and cross the cornea from limbus to limbus. All the fibers in a single lamella are essentially parallel to one another. There is no apparent correlation between the orientation of the fibers in anteroposteriorly distant lamellae. The fibers, which are about 200 Å in diameter, are flexible and strong. Within a lamella, their axes are ordered sufficiently to allow the cornea to retain its transparency.[1]

The remaining extracellular constituent of the stroma is glycoprotein. These biopolymers are presently thought to consist of long protein chains to which are bound carbohydrate-like polymers, the acid mucopolysaccharides. The glycoproteins can be likened to a skinny protein centipede with mucopolysaccharide legs. The mucopolysaccharides are acidic; that is, they can dissociate and behave as negatively charged polyelectrolytes. As a consequence, the mucopolysaccharides can bond electrostatically to basic amino acid residues in the collagen, and it is thought that the glycoproteins may constitute a secondary array, in which the polysaccharide molecules act as "guy wires" to prevent the collagen array from becoming too highly disorganized. A review and analysis of this concept has been published.[2]

An important consequence of this molecular organization is that the stroma behaves as a polyelectrolyte gel. As such, it tends to swell. This tendency is measured by the stromal swelling pressure, the pressure necessary to hold a piece of stroma at a given thickness. Because of the collagen fibers, the stroma swells only in its thickness direction; it exerts a pressure of ca. 60 Torr at normal thickness. As the tissue swells, its swelling pressure drops; more important, it loses its transparency, apparently because the collagen fibers become disorganized and regions devoid of fibers arise. In the living eye, the stroma maintains a normal hydration of about 3 g water/g dry tissue in spite of the swelling pressure.

Endothelium and Descemet's Membrane—The endothelium is a single layer of interdigitated cells at the posterior surface of the cornea. It is 5 μm thick and is separated from the posterior stroma by Descemet's membrane, a 5 to 10 μm thick, collagenous structure. Most of the resistance to diffusion and flow possessed by this pair of distinct entities derives from the endothelium, and Desce-

[1] R. W. Hart and R. A. Farrell, "Light Scattering in the Cornea," *J. Opt. Soc. Amer.* **59**, June 1969, 766–774.

[2] R. A. Farrell and R. W. Hart, "On the Theory of the Spatial Organization of Macromolecules in Connective Tissue," *Bull. Math. Biophys.* **31**, Dec. 1969, 727–760; R. W. Hart, R. A. Farrell and M. E. Langham, "Theory of Corneal Structure," *APL Tech. Digest*, **8**, Jan.-Feb. 1969, 2–11.

met's membrane will be all but ignored in the discussion which follows.

When the cornea thins or swells as a result of the loss or imbibition of fluid by the stroma, this change in thickness is effected by endothelial motion towards or away from the epithelium which, in turn, is fixed relative to the adjacent ocular structures. Such endothelial motion accompanies the diurnal variation of corneal thickness which is induced by the corresponding variation in the solute content of the tears (see below). The facility with which the endothelium moves, along with anatomical considerations, strongly suggests that it "floats" mechanically with negligible restraint from the limbus. It then is a trivial matter to construct a force balance for this cell layer:

$$P_o = P_s + p_s \qquad (1a)$$

where P_o is the intraocular pressure, P_s is the stromal fluid pressure (termed the "imbibition pressure" by corneal physiologists), and p_s is the stromal swelling pressure corresponding to the stromal hydration, H_s. There are anteroposterior gradients of both imbibition pressure and swelling pressure in the stroma, and p_s and P_s should more correctly refer to these pressures at the interface between the stroma and endothelium. However, the pressure drop across the stroma depends on the water flow rate through this tissue and the stromal permeability to water, and the latter is sufficiently high that the stroma may be regarded as possessing a uniform imbibition pressure. Indeed, experiments[3] using a fine needle to penetrate the stroma have been unable to demonstrate any pressure gradients. The stromal hydration is quite uniform in the anteroposterior direction, suggesting that stromal swelling pressure gradients may also be neglected.

General Considerations Regarding Corneal Transport

Since all the corneal layers are permeable to water and solutes to a lesser or greater extent, there will in general be species fluxes across the entire tissue. It appears that the essential features of corneal transport can be reproduced by a model in which the geometry is one-dimensional, and the only species that are moving are sodium ion, chloride ion and water. The first of these simplifications is valid for initial considerations of the cornea because the corneal diameter is more than 15 times the corneal thickness, and the second because sodium and chloride ions make up better than ninety percent of the solute in the aqueous and tears. Then all fluxes are normal to the surface of the cornea, which is regarded as being made up of three salt and water-permeable layers in series, each of which is of infinite extent in the corneal plane. The stroma passes salt much more readily than do either the epithelium or the endothelium, so it may be regarded as uniform with respect to concentration as well as pressure.

The fluxes of ions and water across the epithelium and endothelium may be active or passive. Active fluxes are coupled to cellular metabolism; the epithelial sodium pump noted above is an example. The passive fluxes are driven by the concentration and pressure gradients across each membrane. Both solute and solvent fluxes are influenced by these gradients. The solvent is obviously driven by hydrostatic pressure gradients, but it also tends to flow from regions of low solute concentration into more concentrated regions. This effect, termed *osmosis,* is not simply a flow of water down its own concentration gradient, but rather reflects the higher randomness of more concentrated solutions; that is, the greater number of configurations of solute and solvent molecules which are possible when more solute molecules are present. In thermodynamic terms, this randomness causes more concentrated solutions to possess a greater entropy (S), and water in such solutions has a lower free energy (A), by the thermodynamic identity, $A = E - TS$, where E is internal energy and T is absolute temperature. Thus osmosis reflects the flow of water down a free energy gradient. The solute, in turn, diffuses down its own concentration gradient, and is also carried in the water crossing the membrane. This latter "convective transport" represents an indirect coupling of the solute flow to the transmembrane pressure gradient.

The total flux of a species across either the epithelium or the endothelium is the sum of the active and passive fluxes.

Corneal Boundary Conditions

As indicated earlier, the cornea is bathed posteriorly by the aqueous and anteriorly by the tears.

[3] B. O. Hedbys, S. Mishima and D. M. Maurice, "The Imbibition Pressure of the Corneal Stroma," *Exp. Eye Res.* **2**, Apr. 1963, 99–111.

The compositions of each of these phases depend to some extent on whether the eye is open or closed,[4] but the normal variation of only the composition of the tear film appears to have a major influence on corneal behavior.

The tear fluid, as secreted by the lacrimal apparatus of the eye, is more-or-less isotonic (having the same solute concentration level) to blood serum. Serum, in turn, is isotonic to 0.9% (by weight) NaCl. Thus, when the eye is closed, the concentration of the fluid bathing the cornea is equivalent to 0.9% NaCl. The tear fluid equilibrates with the contents of the capillaries in the inside of the eyelid, but the isotonicity of the two solutions (tear and blood) would indicate that little net fluid exchange takes place across the lid during sleep.

When the eye is open, the tear film is replenished by blinking. Between blinks, the fluid becomes concentrated in salt (hypertonic) as a result of the evaporation of water from the surface of the eye. Thus the tear tonicity is greater when the eye is open than when it is closed. The difference between the closed-eye and open-eye tear tonicities becomes less as the blink frequency increases; humans blink approximately once every five seconds and their open-eye tear film concentration is 0.95% NaCl,[5] while rabbits, which blink every ten minutes, exhibit tear film concentrations of 1% NaCl[4] or above.

The Corneal Hydration Control Problem and Some Answers

The hydration control problem is simply stated in terms of the one equation we have written so far: $P_o - P_s = p_s$. The pressure difference $P_o - P_s$ represents a driving force for water flow into the stroma. Then why doesn't the stroma take up water and swell?

A large number of answers to this question have been proposed, based on numerous experiments, largely on in vitro corneal preparations. Those hypotheses most in favor at the present time are:

1. Water passively enters the stroma across the endothelium and is osmotically drawn out across the epithelium by hypertonic tears. This theory was recently reiterated.[6] But why doesn't the cornea thicken to opacity at night, when the tears are no longer hypertonic?

2. Water passively enters the stroma across the endothelium and is actively transported back across the endothelium into the aqueous. This theory has the greatest support to date, and a first experimental demonstration of the endothelial "water pump" has just appeared in the literature.[7] This result, which could be most significant, had been sought but not found by earlier experimenters.[8] Still, the pump must be highly sensitive to ambient tonicity to explain the small sensitivity of corneal thickness to the concentration of the tears.

3. There is a salt pump in the endothelium which actively transports salt out of the stroma and into the aqueous. By so doing, it causes the stroma to become hypotonic (of relatively lower tonicity) to the aqueous. Thus an osmotic driving force for posteriorly-directed passive water flow develops across the endothelium and balances the hydrostatic driving force for stromal imbibition; hence, there is no net water flow across the endothelium. But no one has yet been able to demonstrate a net salt flux across the endothelium when it is bathed by identical solutions on both sides.

The resolution of these theories has been slow in part because our ability to describe corneal transport and mechanics in physical terms has not kept pace with the immense number of experiments that have been carried out on this tissue. The analysis to follow is proposed to diminish that gap. Following the development of a model from the preceding descriptive material, we will set up the equations which describe the normal cornea, solve them, and examine the implications of their solution in the context of the hydration control problem.

Corneal Model

The model of the cornea which will serve as a framework for the analysis to follow is shown in Fig. 3. The essential features of the model, illustrated in the figure, are:

[4] S. Mishima and D. M. Maurice, "The Effect of Normal Evaporation on the Eye," *Exp. Eye Res.* **1**, Sept. 1961, 46–52.

[5] G. J. Mastman, E. J. Baldes and J. W. Henderson, "The Total Osmotic Pressure of Tears in Normal and Various Pathologic Conditions," *Arch. Ophthal.* **65**, Apr. 1961, 509–513.

[6] M. H. Friedman, "A Quantitative Description of Equilibrium and Homeostatic Thickness Regulation in the In Vivo Cornea. I. Normal Cornea," *Biophys. J.*, **12**, June 1972, 648–665.

[7] D. M. Maurice, "The Location of the Fluid Pump in the Cornea," *J. Physiol.* **221**, Feb. 1972, 43–54.

[8] K. Green and M. A. Green, "Permeability to Water of Rabbit Corneal Membranes," *Amer. J. Physiol.* **217**, 1969, 635–641.

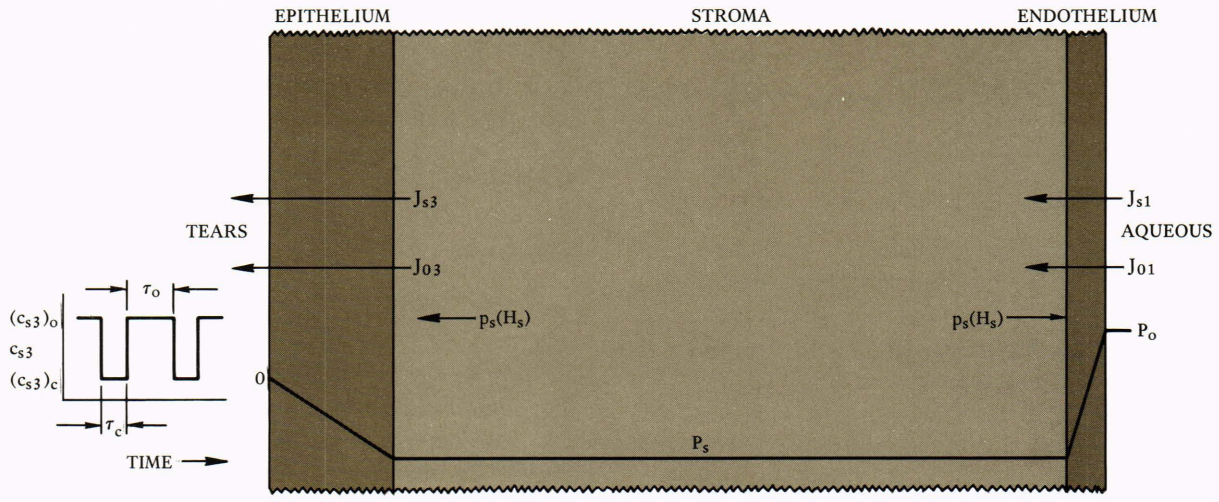

Fig. 3—Model of cornea for analysis. J_{ik} is the total flux of the i-th species ($i = s$ is salt, $i = 0$ is water) through the k-th membrane ($k = 1$ is endothelium, $k = 3$ is epithelium). Further, $J_{ik} = J_{ik}^{p} + J_{ik}^{a}$, where the superscript "p" denotes passive transport and "a" denotes active transport; $(c_{s3})_j$ is the tear tonicity in the j-th state ($j = o$ is open eye, $j = c$ is closed eye) and τ_j is the time spent in that state during the cycle period $\tau = \tau_o + \tau_c$. The statement that there is no long-term accumulation in the stroma is: $\int_{\tau} J_{s3}dt = \int_{\tau} J_{s1}dt$, $\int_{\tau} J_{03}dt = \int_{\tau} J_{01}dt$.

1. The cornea is regarded as a one-dimensional series membrane system. The limiting membranes —the epithelium and endothelium—are permeable to both salt and water. Either of these membranes may actively transport solute and/or water. The stroma is uniform in pressures and composition.

2. The stroma exerts a swelling pressure in vivo, which is the same function of hydration as is measured in vitro. The stromal fluid pressure and swelling pressure are related by $P_o = P_s + p_s$, the endothelial mechanical equilibrium condition. The pressure profile in the normal cornea is shown in the figure; since $p_s > P_o$, P_s is negative (gauge).

3. When the eyes are closed, the tears are near isotonic; when the eyes are open, the tonicity of the tears is greater than that when they are closed. Variations of tear tonicity between blinks are neglected. The period of the tear tonicity cycle is τ, and over this cycle, equal amounts of salt and water cross the epithelium and endothelium, since there is no long-term accumulation in the stroma.

Mathematical Analysis of the Living Cornea

The analysis of the cornea in the context of the model given above requires three kinds of equation: transport equations, which relate the fluxes across the membranes to the pressures and solution compositions which bound them; conservation equations, which show how the stromal salt concentration and hydration are influenced by the fluxes given by the transport equations; and a set of simple corneal boundary and periodicity conditions. These equations will now be summarized in turn.

Transport Equations—The frictional formulation of irreversible thermodynamics is a convenient vehicle for describing flows through membranes. This formulation can be regarded as a force balance, in which the driving force for flow of the j-th species through the membrane is its electrochemical potential gradient, $-\triangle\tilde{\mu}_j/\triangle x_k$, where $\triangle x_k$ is the thickness of the k-th membrane. The species flux assumes a value such that this driving force is balanced by the "frictional" interactions of the species with all other species and the membrane itself, these interaction forces being proportional to the pairwise relative velocities. The coupled flow equations which follow from this approach are given below; the interested reader is referred to Ref. 6 for a detailed development.

$$-\frac{4RT\,(c_{ss}-c_{so})}{(c_{ss}+c_{so})\triangle x_1} = (K_{s1}J_{s1} - J_{+1}^{a})\cdot\frac{2f_{T1}}{c_{ss}+c_{so}} - K_{s1}f_{+1}\overline{V}_0(J_{01} - J_{01}^{a}) \quad (2a)$$

$$-\frac{4RT\,(c_{s3}-c_{ss})}{(c_{s3}+c_{ss})\triangle x_3} = (K_{s3}J_{s3} - J_{+3}^{a})\cdot\frac{2f_{T3}}{c_{s3}+c_{ss}} - K_{s3}f_{+3}\overline{V}_0(J_{03} - J_{03}^{a}) \quad (2b)$$

$$-\frac{P_s - P_o}{\triangle x_1} = (f_{T1} - f_{+1}) \cdot (K_{s1}J_{s1} - J^a_{+1}) + f_{01}(J_{01} - J^a_{01}) \quad (2c)$$

$$\frac{P_s}{\triangle x_3} = (f_{T3} - f_{+3}) \cdot (K_{s3}J_{s3} - J^a_{+3}) + f_{03}(J_{03} - J^a_{03}) \quad (2d)$$

where R is the gas constant, T is absolute temperature, c_{ss} is the salt concentration in the stromal fluid, c_{so} measures the solute content of the aqueous, J^a_{jk} is the active flux of the j-th species ($j = +$ is sodium ion) through the k-th membrane, f_{Tk} is the frictional coefficient measuring solvent and membrane drag on sodium ion in the k-th membrane, f_{+k} is the frictional coefficient measuring solvent drag on sodium ion in the k-th membrane, $\overline{V}_0$ is the specific volume of water, and f_{0k} is the frictional coefficient measuring membrane drag on solvent in the k-th membrane. The assumptions and justifiable simplifications made in the derivation of Eqs. (2) are: the effect of hydrostatic pressure on ionic activities is negligible; the velocity of the endothelium during changes in corneal thickness is negligible; the frictional coefficients are related by Onsager's[9] reciprocity condition (in physical terms) the drag on species a by species b is equal and opposite to that on b by a); direct ion-ion interactions are negligible;[10] and the frictional coefficients for solvent and membrane drag on chloride ion are proportional to those for sodium ion, with a proportionality constant $(K_{sk}-1)$ in the k-th membrane.

Equations (2) give J_{s1}, J_{01}, J_{s3} and J_{03} as functions of the temperature, the corneal properties and boundary conditions, and the (time-dependent) values of c_{ss} and P_s. The stromal fluid pressure can be related to the stromal hydration through Eq. (1a) and an experimental swelling pressure-hydration curve. This last relation is well represented in the physiologic range by $p_s = \gamma \exp(-\beta H_s)$, where γ and β are empirical, species-dependent constants. Thus an auxiliary equation is

$$P_s = P_o - \gamma \exp(-\beta H_s). \quad (1b)$$

Conservation Equations—Two equations are needed to describe the accumulation of salt or water in the stroma. They are based on the simple conservation relation $dn_j/dt = J_{j1} - J_{j3}$, where n_j is the mols of j in the stroma per cm² corneal area. The water content of the stroma is related to stromal hydration by $n_0 = H_s\psi_2/(E\overline{V}_0)$, where ψ_2 is the thickness of dry stroma and E is the ratio of the density of the stromal fluid to that of the stromal dry tissue. Thus

$$\frac{dH_s}{dt} = \frac{E\overline{V}_0}{\psi_2}(J_{01} - J_{03}). \quad (3a)$$

For the dilute solutions under consideration here, the volume of stromal fluid is close enough to $n_0\overline{V}_0$ cc/cm² corneal area. Thus $c_{ss} = n_s/(n_0\overline{V}_0) = n_sE/(H_s\psi_2)$. Differentiating with respect to time, and using Eq. (3a)

$$\frac{dc_{ss}}{dt} = \frac{E}{H_s\psi_2}(J_{s1} - J_{s3}) - \frac{c_{ss}}{H_s} \cdot \frac{E\overline{V}_0}{\psi_2}(J_{01} - J_{03}). \quad (3b)$$

The general procedure of solution is iterative. One begins with a pair of values of c_{ss} and H_s. Equations (1b) and (2) are solved for P_s and the fluxes. Using these fluxes, the difference forms of Eqs. (3) are used to advance H_s and c_{ss} in time, after which a new P_s and a new set of fluxes are found.

Corneal Boundary and Periodicity Conditions—All corneal boundary conditions are held constant, with the exception of c_{s3}. This property takes the closed-eye value $(c_{s3})_c$ for a time τ_c, followed by the open-eye value $(c_{s3})_o$ for a time τ_o. This cycle repeats indefinitely. Experiments on laboratory rabbits, performed in cooperation with Dr. Keith Green of the Wilmer Institute of The Johns Hopkins University School of Medicine, showed that, for this population, appropriate values of τ_c and τ_o are 1¼ and 4¾ hours, respectively. That is, the average rabbit naps four times a day, and has his eyes closed about twenty percent of the time.

The integration of Eqs. (3) is begun with arbitrary values of c_{ss} and H_s, and is continued until the following periodicity condition is satisfied to a desired accuracy: $c_{ss}(t) = c_{ss}(t - \tau_o - \tau_c)$, $H_s(t) = H_s(t - \tau_o - \tau_c)$.

Input Parameters

As has already been intimated, the cornea simulated here belongs to the rabbit. The rabbit has long been the animal of choice for mammalian corneal physiology experiments and, as a result, it

[9] L. Onsager, "Reciprocal Relations in Irreversible Processes," *Phys. Rev.* **37**, Feb. 15, 1931, 405–426; *Phys. Rev.* **38**, Dec. 15, 1931, 2265–2279.

[10] M. H. Friedman, "Mass Transfer in the Cornea. II. Ion Transport and Electrical Properties of a Series Membrane Tissue," *Biophys. J.* **12**, 1972, 325–350.

is the only species for which sufficient property data are available. Each of the properties called for in the foregoing equations has been measured independently by at least one of the numerous experimental physiologists active in corneal research. As a consequence, it is possible to use the formulas presented above to effect an a priori prediction of corneal behavior, which must cast some light on the hydration control problem.

As noted earlier, most of the recent hydration control theories invoke metabolically-coupled water or salt pumps in the endothelium to explain how the cornea maintains its normal thickness. In view of the difficulties that have been encountered in trying to demonstrate directly the existence of these pumps, no active transport system is sited in the endothelium in the a priori calculation given below. The well-documented epithelial sodium pump is included, however.

A Priori Calculation of Corneal Behavior

The calculated periodic behavior of the normal rabbit cornea is shown in Fig. 4. The figure covers one 6-hour cycle; from the beginning of one nap to the beginning of the next one. When the animal goes to sleep, the tear tonicity is regarded as undergoing a step change from $(c_{s3})_o$ to $(c_{s3})_c$. The fluxes across the epithelium change discontinuously in response to this discontinuous change in boundary conditions, but the endothelial fluxes, stromal salt content, and corneal thickness remain continuous, though their derivatives are not. Since c_{ss} changes slowly, the tears are initially hypotonic to the stromal fluid, and there is a brief time during which fluid flows *posteriorly* across the epithelium ($J_{03} < 0$). The epithelial salt flux contains a large constant component due to the sodium pump in this membrane, and the influence of c_{s3} on J_{s3} is relatively small. Water continues to enter the stroma across the endothelium, and since it is no longer extracted to any extent across the epithelium, the tissue swells. This swelling causes c_{ss} to fall towards the aqueous salt concentration, and the magnitude of the transendothelial salt flux diminishes as the driving force $c_{ss} - c_{so}$ becomes less. At the same time, the driving force $c_{s3} - c_{ss}$ for passive salt flow across the epithelium becomes larger, leading to a gradual increase in $|J_{s3}|$. As c_{ss} falls, an osmotic driving force for anteriorly directed transepithelial flow develops and that for osmotic flow across the endothelium becomes less; accordingly, J_{03} eventually becomes positive and J_{01} slowly diminishes as the rabbit sleeps.

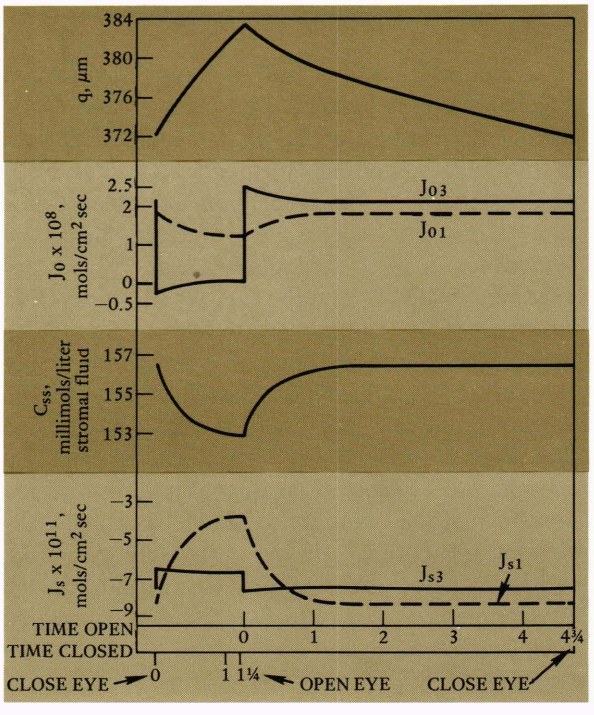

Fig. 4—Calculated periodic behavior of normal rabbit cornea; q = corneal thickness.

The response of the cornea when the animal awakes can be viewed similarly. The tear tonicity rises suddenly, and the epithelial water flow is suddenly greater than the inward flux across the endothelium. The tissue thins, causing c_{ss} to rise, this increase being augmented by the discontinuous rise in transepithelial salt flux driven by $(c_{s3})_o - c_{ss}$. The steady increase in c_{ss} causes $|J_{s1}|$ to increase with time and $|J_{s3}|$ to decrease slowly after its initial jump; similarly, the changing osmotic driving force causes J_{01} to rise gradually, and J_{03} becomes less positive during the open-eye phase. As the eye remains open, the fluxes assume nearly constant, *but unequal*, values. Thus more water leaves the stroma across the epithelium than enters across the endothelium ($J_{03} > J_{01}$) and more salt leaves the stroma across the endothelium than enters across the epithelium ($-J_{s1} > -J_{s3}$). The stroma thins slowly owing to the inequality of water fluxes; however, the rate of salt loss is such that c_{ss} changes only slightly with time. The difference between the nearly constant flux values after the eye has been open for some time is such

that, over a cycle, the algebraic area between the J_{01} and J_{03} curves, and the J_{s1} and J_{s3} curves, is zero.

Comparison of Theory with Experiment and Concluding Remarks

Most important, the calculated corneal thickness ranges from 372 to 384 μm, and these values are within the experimental range for rabbit. The periodic variation in thickness, 12 μm, agrees with the degree of thinning observed[4] when rabbit eyes are held open after a period of closure. Good agreement is also found between the calculated and experimental values of stromal salt concentration.

What does this tell us about corneal hydration control? Most important, the analysis shows that the in vivo cornea is never in the steady state, with continuously identical salt and water fluxes through all its layers. Rather, owing to the cyclic variation in tear tonicity which accompanies the animal's sleep-wake cycle, and the difficulty with which solute and solvent enter or depart the stroma across the limiting corneal layers, the cornea never attains the steady-state thickness that would result from continued exposure to either the open eye or closed eye tear tonicity. Rather, its thickness oscillates with a relatively small amplitude about the steady-state thickness corresponding to an intermediate tonicity.

The corneal hydration control problem looks different when the unsteady character of the corneal fluxes is recognized. The only requirements that must be satisfied if corneal thickness is to be maintained solely by the osmotic withdrawal of stromal fluid by hypertonic tears are (a) the *time-average* tear tonicity must be greater than that of the aqueous, and (b) the tear tonicity must be *sufficiently* hypertonic to "draw out" of the stroma as much water as enters across the endothelium. The first requirement is met because the tear film is near isotonic to the aqueous when the eye is closed, and it is hypertonic when the eye is open; satisfaction of the second requirement is illustrated by Fig. 4.

It must be emphasized that the analysis presented here does not *prove* the absence of a pump in the corneal endothelium, but it does provide a framework for understanding corneal behavior which does not require the presence of such a transport mechanism. Nonetheless, a pump may yet exist. Figure 4 is based on the published values of numerous corneal properties. If any are in substantial error, it may be that when corrected values are used, the calculated corneal thickness will oscillate about a value which is greater than those found experimentally. Then an active dehydration system would be implied, rather than denied, by the analysis set forth here. In any event, the fundamentally unsteady character of corneal hydration must be taken into account.

Finally a few words are in order regarding the extension of this work to the human eye. There is no reason to expect that the human cornea does not behave in a fashion *qualitatively* identical to that exhibited by the rabbit. There will be quantitative differences in nearly every corneal parameter, however, and these will be manifest in the human analog of Fig. 4. It is unlikely that the required properties of human cornea will be available in the reasonable future, for obvious reasons, and a quantitative description of this tissue will have to rely on reasoned extrapolation and intelligent guesswork. Such an exercise is to be undertaken shortly.

Even in the absence of a rigorous quantitative description of human corneal behavior, the qualitative insights developed by studying the rabbit in detail have important clinical applications. Two such are:

1. Epithelial edema and bullous keratopathy. This condition is characterized by distortion of the epithelium, rupture of the epithelial cells adjacent to the stroma, and the formation of water blebs (bullae) between the epithelium and stroma. Vision is impaired because the anterior surface of the cornea is no longer smooth, and pain is not uncommon. This condition can result either from stromal swelling subsequent to endothelial deterioration, or when the intraocular pressure is highly elevated, as in glaucoma. The description of the cornea developed here has been used[11] to describe the origins and physical character of epithelial edema, and to indicate in quantitative terms how current therapies operate to relieve it. This extension of the corneal analysis to pathologic states provides a physically sound foundation for the development of more effective means of managing such conditions.

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[11] M. H. Friedman, "A Physical Description of the Pathogenesis, Histopathology and Treatment of Corneal Epithelial Edema," *Amer. J. Ophthal.*, submitted for publication.

2. Design criteria for artificial epithelia (epikeratoprostheses, EKP's). In conditions where the epithelium has deteriorated irreversibly to the point that vision is significantly impaired, one possible course of action is to remove this layer entirely and replace it with a contact lens glued permanently to the anterior stroma. In doing so, one would like to design the prosthesis to mimic as faithfully as possible the function performed by normal epithelium. Since the materials of which such a prosthesis may be constructed are limited, the frictional properties of the epithelium cannot be reproduced exactly, and of course the EKP has no sodium pump. The present analysis can serve as a guide to the development of prostheses and prosthetic materials which maintain the corneal milieu in spite of their unnatural transport properties.

PUBLICATIONS

Compilation of recently published books and technical articles written by APL staff members.

R. B. McDowell, "The APL Technical Approach to Real-Time, Interactive Multiple-Computer Simulation Systems," *Simulation* **17**, No. 1, Jul. 1971, 3–18.

A. G. Witte, "Hardware Implementation of Three Computer Links to the IBM 360/91 Digital Computer," *Simulation* **17**, No. 1, Jul. 1971, 19–31.

N. K. Brown, "Software Considerations for Simulation Hardware in the Supercomputer Environment," *Simulation* **17**, No. 1, Jul. 1971, 33–38.

P. F. Bohn, "Interactive Simulation Terminals to the IBM 360/91 Computer," *Simulation* **17**, No. 1, Jul. 1971, 39–44.

D. M. White, "A Real-Time Radar Simulation Using the APL Digital Computer Links," *Simulation* **17**, No. 1, Jul. 1971, 45–51.

J. A. Schetz and S. Favin, "Numerical Calculation of Turbulent Boundary Layers Including Suction or Injection with Binary Diffusion," *Astronautica Acta* **16**, No. 6, Dec. 1971, 339–352.

A. L. Burns (Univ. of Iowa) and S. M. Krimigis, "Changes in the Distribution of Low-Energy Trapped Protons Associated with the April 17, 1965 Magnetic Storm," *J. Geophys. Res.* **77**, No. 1, Jan. 1, 1972, 112–130.

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W. G. Spohn, "On the Integral Cuboid," *Am. Math. Monthly* **79**, No. 1, Jan. 1972, 57–59.

R. E. Walker and T. L. Litovitz, "An Experimental and Theoretical Study of the Pneumatic Tonometer," *Exp. Eye Res.* **13**, No. 1, Jan. 1972, 14–23.

T. A. Potemra and A. J. Zmuda, "Nightglow Evidence of Precipitating Energetic Electrons in the Midlatitude Nighttime *D* Region," *Radio Sci.* **7**, No. 1, Jan. 1972, 63–66.

M. H. Friedman and R. L. McCally, "Sieving Behavior of a Series Membrane System," *Science* **175**, No. 4021, Feb. 4, 1972, 556–557.

T. O. Poehler and C. H. Wang, "Low Temperature Scattering in InSb Measured by Infrared Faraday Rotation," *Phys. Rev. B* **5**, No. 4, Feb. 15, 1972, 1483–1489.

APL COLLOQUIA

Jan. 7—"Tunable Raman Lasers," by C. K. Patel, Bell Telephone Laboratories.

Jan. 14—"Adelie Penguins and Whistling Swans: A Study of Gregarious Individuals," by W. Sladen, The Johns Hopkins University.

Jan. 28—"Is the World Livable?" by M. G. Wolman, The Johns Hopkins University.

Feb. 4—"Our Understanding of the Cometary Phenomena," by A. H. Delsemme, University of Toledo.

Feb. 11—"The Measurement of the Gravitational Constant," by J. Beams, University of Virginia.

Feb. 18—"A Physician's Report on His Visit to China," by S. Rosen, Mt. Sinai Hospital Medical School.

Feb. 25—"Surface Chemistry and Practical Adhesion," by H. Schonhorn, Bell Telephone Laboratories.

ADDRESSES

Principal recent addresses made by APL staff members to groups and organizations outside the Laboratory.

Jane Olmer, "INFO 360, The Applied Physics Laboratory Information Package," *University of North Carolina School of Medicine,* Chapel Hill, January 19, 1972.

W. H. Avery, "Practical Requirements for Advanced Public Transportation Systems," *Highway Research Board Transportation Meeting,* Washington, D.C., January 20, 1972.

The following four addresses were presented at the Annual Meeting of the *American Physical Society,* January 31 to February 3, 1972, at San Francisco:

N. A. Blum, C. Feldman, and K. Moorjani, "Optical Properties of Amorphous Silicon Films;"

K. Moorjani (APL), T. Tanaka (Catholic U. of America), M. M.