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The Von Sallmann Lecture 1996: An Ophthalmological Explanation of REM Sleep

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The hypothesis is advanced that the purpose of the eyeball movements during REM sleep is to stir the aqueous humor behind the closed lids and so avoid the risk that its stagnation could cause corneal anoxia.

The relevance of the hypothesis to evolutionary biology and intensive care nursing is discussed.

Key words: REM sleep; corneal metabolism; lens metabolism; aqueous humor circulation; human; animal; poikilotherms; fluorometry; evolution; intensive care nursing; anoxia; exposure keratitis; convective flow.

1. Introduction

I am affiliated to a corneal discussion group on e-mail and at the beginning of this year, I received a message disseminated by Dr George Rosenwasser, of Pennsylvania State University, concerning an unfortunate young man who was involved in an accident and as a result had complete ptosis and loss of ocular motility in both eyes. What was curious was that both his corneas were becoming vascularised. This case caught my attention and made me look into the problem of REM sleep, for reasons that I will shortly make clear.

2. REM Sleep

First, let me remind you about REM sleep. It was discovered early in the 1950s (Aserinsky and Kleitman, 1953) and has aroused continuing interest; Medline identifies it as a component of some 7000 articles since 1966. Because of its implications in the functions of the central nervous system, it has been considered to be in the domain of disciplines ranging from psychology to neuropharmacology and it has not received attention from ocular physiologists. It consists of periods in which the sleep pattern changes and becomes close to arousal. Many physiological changes take place during these periods, which are also when dreaming is most active, but the most obvious signs, are the rapid jerky movements of the eyes in all directions and a characteristic change in the pattern of the electroencephalograph. These periods of rapid eye movement initially last about 20 minutes but become more prolonged as sleep continues, and they recur 3 or 4 times throughout the night. In babies, the total time spent in REM sleep is greater, being about 8 hr a day in neonates, and it is even more in the womb (Roffwarg, Muzio and Dement, 1966) as well as in animals born with sealed eyelids (Zepelin, 1989).

It is curious that REM sleep appeared very early in evolution, perhaps even before normal sleep, and is initiated in a primitive region of the brain, the pons. The opossum, evolutionarily a very ancient mammal, spends an unusual amount of time asleep and a great proportion of it in REM sleep, just as the human baby (Snyder, 1966).

The prevailing explanation of REM sleep is that it is needed for processing and efficient storage of information that is acquired while we are awake, (Crick and Mitchison, 1983; Hobson, 1990) which I see as being rather like a store closing for business during its taking inventory. Not only are these hypotheses very difficult to test experimentally, but they do not explain why the fetus in the womb, which is unlikely to receive a great deal of sensory information, or why the opossum, who only wakes up for a couple of hours to do whatever an opossum does, gathering leaves or something, would take 2 or 3 times longer to process this information than an adult human. This and other difficulties has led to the suggestion that REM was originally only a transitional phase between two other stages of sleep and it acquired further specific purposes during evolution (Lavie, 1996).

I am proposing a completely different hypothesis: thermal circulation of the aqueous humor is needed for adequate corneal respiration, this circulation is suppressed when the lids are closed, and REM is required to stir the anterior chamber and thus prevent corneal anoxia during sleep.

An advantage of this hypothesis is that it can readily be tested. It contains three components that need to be examined: first, that closing the lids suppresses the normal thermal circulation in the anterior chamber, second, that the oxygen supply to the cornea is insufficient when the aqueous humor is stagnant, and third, that movement of the eyes results in stirring of the stagnant aqueous.

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3. Aqueous Circulation in the Open and Closed Eye

The evidence in support of the first and last requirements of the hypothesis, that the aqueous humor is stagnant behind closed lids and can be mixed by eye movements, is experimental. Ehrlich (1882) showed that when fluorescein was given systematically to a rabbit a sharply defined vertical fluorescent line appeared in the anterior chamber, just behind the cornea. Türk (1906) showed that the phenomenon could be elicited in a model in vitro system and determined that it was caused by thermal convection in the anterior chamber resulting from the corneal surface of the open eye being cooled by the air.

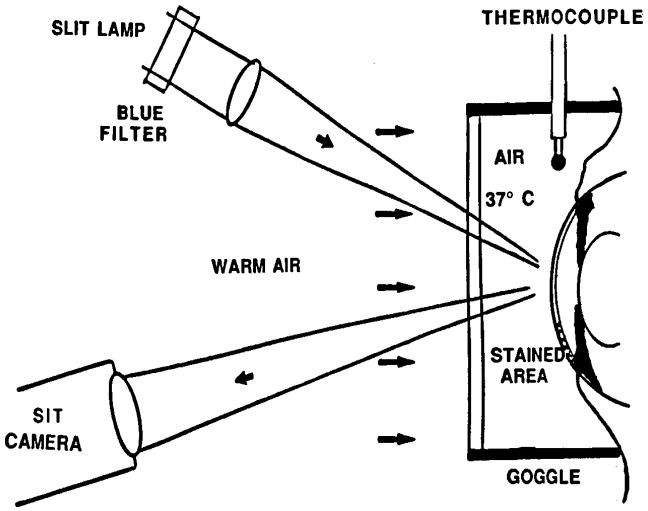

FIG. 1. View from above of the set-up for warming the surface of the open eye. Heat is provided by a hair drier and the eyes are protected by goggles from the irritation of the heated air stream. The cornea of the experimental eye is stained with fluorescein by iontophoresis two hours before the video-recording of the observations. The iontophoresis is applied at the limbus so that a clear zone of cornea remains through which the illuminating beam may pass without absorption. A bright fixation light for the opposite eye constricts the pupil by the consensual reflex.

If, instead, the anterior chamber is uniformly stained with fluorescein by the corneal route, unstained freshly secreted aqueous from the posterior chamber can be identified in the slit lamp as a dark mass silhouetted against the bright green background. The fresh fluid enters the anterior chamber from the edge of the pupil, generally in bursts lasting less than a minute and are separated from each other by a few minutes (Holm, 1968; Cunha-Vaz and Maurice, 1969).

In the course of preparing this lecture for publication, it was noted that my eye was unusually convenient in that, after it was closed for a minute or two, often a pool of fresh aqueous had accumulated in front of the pupil. If the surface of the opened eye was kept warm (Fig. 1), this pool of dark aqueous could be identified for a period of a few minutes before it fades away by diffusion of fluorescein across its surfaces (Fig. 2). Its bulk movement could be made negligible over this time by adjusting the ambient temperature to that of the blood.

When the eye was opened to the cool room air, on the other hand, the dark mass could be seen to rise in a matter of seconds and then to circulate in the anterior chamber as a result of thermal convection (Fig. 3). There was no sign of such circulation having already occurred if the anterior chamber was examined immediately after the eye is opened, so it appears that any movement behind the closed lids is minor.

Voluntary eye movements were found to stir the aqueous humor very effectively, a few rapid rotations being able to make the fluorescence of the anterior chamber nearly uniform (Fig. 4). This was previously emphasized by Holm (1968) who found, in addition,

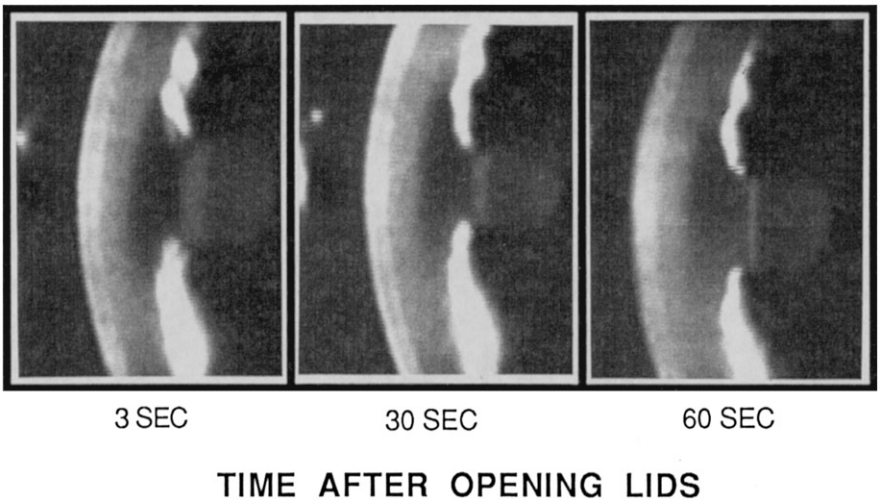

FIG. 2. Slit lamp images of stained anterior chamber at various times after opening lids in the goggles at body temperature. The dark area in front of the pupil corresponds to a volume of freshly secreted aqueous humor that entered from posterior chamber while the eye was closed. This area gradually fades out as fluorescein diffuses into it, but does not drift from its original site.

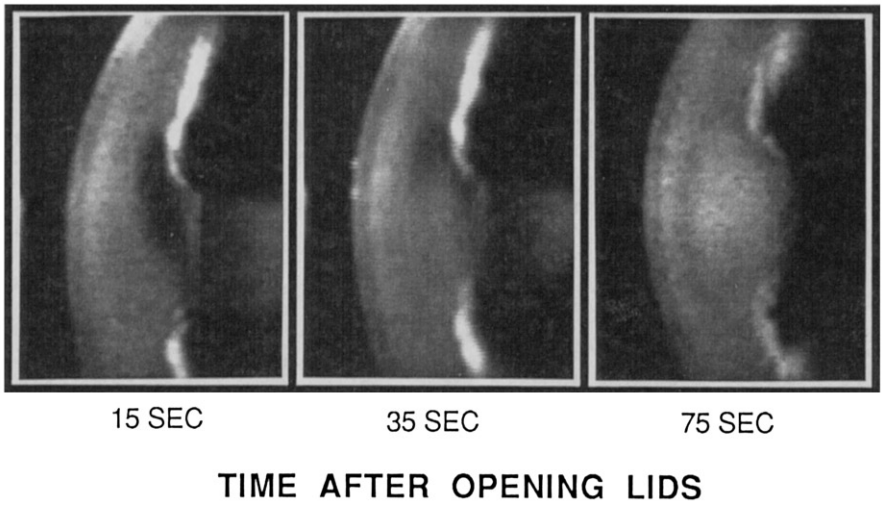

FIG. 3. As Fig. 2 but with the eye opened at room temperature. After a few seconds, a thermal current is established that causes the freshly secreted fluid to rise and then circulate around the anterior chamber. Because the dark volume is extended, it fades away more rapidly.

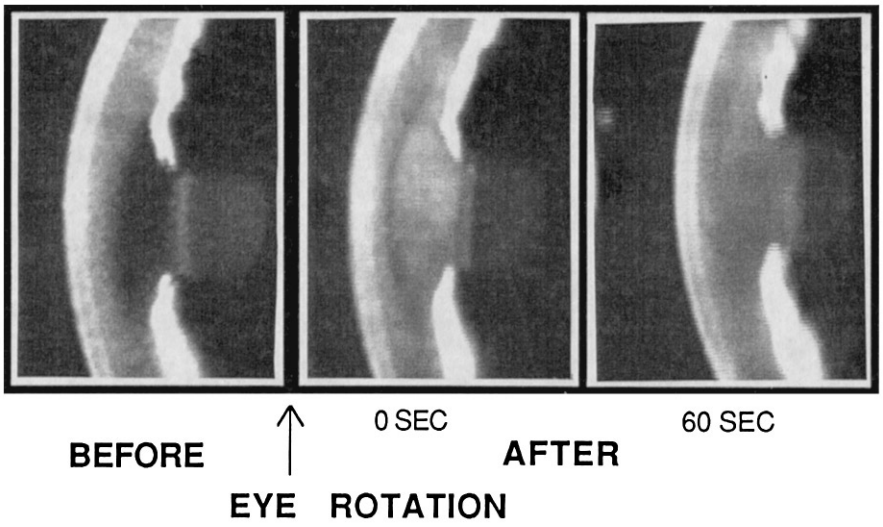

FIG. 4. As Fig. 2 but the eye makes six rapid side to side rotations shortly after opening the eye. The freshly secreted aqueous appears to be dispersed through the anterior chamber almost immediately.

that shaking the head of a rabbit similarly stirred its anterior chamber.

If closing the lids could totally suppress the thermal circulation of the anterior chamber, the freshly secreted aqueous humor that pools in front of the pupil might be expected to stream in all directions to the angle where it would be lost by bulk flow. Simple calculation shows that such a stream would be very slow, of the order of 0·1 mm min^{-1}, over most of its course. It is more probable, however, that the flow of blood through the lids is not sufficient to warm the corneal surface to body temperature, so that a residual thermal circulation would persist in the closed eye. The rate of this movement would depend on the thickness of the lids and the density of their vasculature as well as whether the face is covered or exposed; in the latter case, the ambient temperature and air flow will be important factors. Wyatt (1996) was able to demonstrate changes in aqueous circulation as a result of applying hot or cold packs to the closed lids of the human eye.

4. Corneal Respiration in Closed Eye

The second component of the hypothesis, that there would be a metabolic problem when the aqueous humor is stagnant, can be established by semi-theoretical considerations. It has been shown that the aqueous humor is the main source of nutrients to the cornea; the direct supply from the blood at the limbus is negligible (Maurice, 1967, 1984). Solutes enter the anterior chamber by two routes which are of comparable magnitude in most cases that have been studied. One is by inflow through the pupil of freshly secreted aqueous from the posterior chamber and the other is by diffusion from the iris surface (Fig. 5).

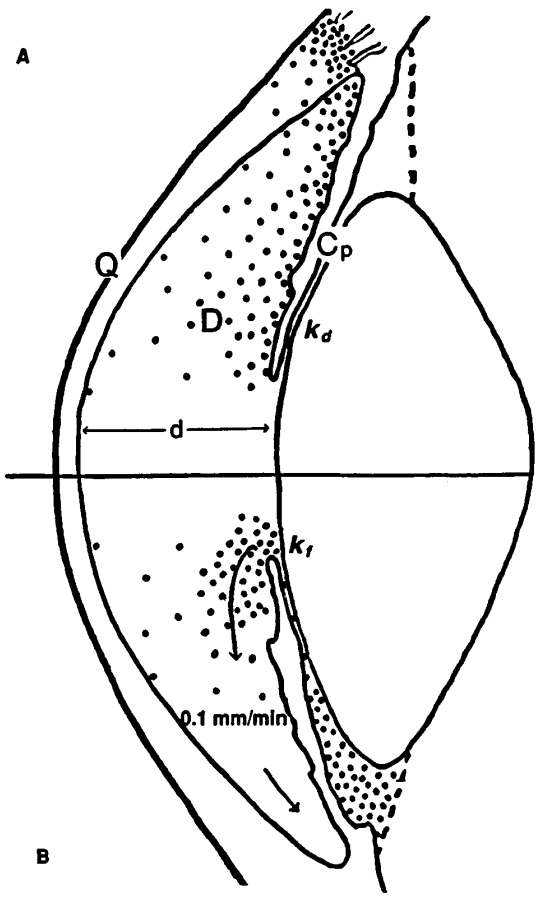

FIG. 5. Diagram illustrating the supply of nutrients to the cornea by, (A) diffusion from the iris and circumferential blood vessels, (B) flow from the posterior chamber through the iris margin. Q, represents the utilization of the nutrient per unit area of the cornea, D, its rate of diffusion across a stagnant aqueous humor, and C_p, its concentration in the plasma, assumed to be that in the aqueous at the iris surface. The depth of the anterior chamber is shown by d, and k_d and k_f, the conventional diffusional and flow exchange coefficients of anterior chamber, correspond to the routes A and B.

When the normal thermal circulation in the anterior chamber is suppressed behind the closed lids, the freshly secreted aqueous will come into contact with the cornea in a limited zone near the pupil or possibly over a diffuse band as a result of a slow residual circulation. In either case, some corneal areas would not be effectively irrigated and would receive nourishment only by the second route, diffusion across the stagnant anterior chamber from the adjacent iris.

It is possible to calculate the adequacy of the diffusional supply, when information on the metabolic activity of the cornea is available, as in the case of the rabbit and to some extent of the human. If a nutrient such as glucose or an amino acid that penetrates the cornea only from the aqueous side is considered, the maximum supply can be estimated to be $C_p D/d$, where C_p is the concentration of the nutrient in the plasma, D is its free diffusion coefficient in aqueous solution, and d is the depth of the anterior chamber. For glucose, a value for C_p of 5 μmol ml^{-1}, for D of 3×10^{-2} cm^2 hr^{-1}, and for d of 0·2 cm, leads to a maximum supply of 0·75 μmol cm^{-2} hr^{-1}. This figure is comparable to the measured aerobic metabolic usage, Q, of the cornea, 0·6 μmol cm^{-2} hr^{-1}, which suggests the supply would be just adequate. (A similar conclusion was recently arrived at by Wyatt, 1996.) With the appropriate changes, the same calculations show that the supply of amino acids also should be sufficient, except, perhaps, in the case of aspartic acid (Maurice, 1967).

Oxygen is so poorly soluble that the freshly secreted aqueous can supply less than 10% of that required for the corneal respiration. Oxygen is also unusual in that it penetrates the cornea across the epithelial surface as well as from the aqueous, so that the balance between its supply and consumption is more complex than for other nutrients. Fatt and his colleagues (Fatt, Freeman and Lin, 1974; Fatt and Weissman, 1992) computed the profile of the O_2 tension in the three cellular layers of the cornea from the experimentally determined values of their metabolic rates and how fast O_2 diffuses through them. They found that, in the closed eye, a tension dropping at its minimum to a little below 40 mm Hg was to be expected in the stroma as a result of the tissue respiration. I have extended these calculations (Fig. 6) to include a layer of stagnant fluid adjacent to the endothelial surface and have made the assumption that the aqueous between this layer and the iris is well mixed and contains O_2 at a tension equal to that in the arterial blood, 95 mm Hg, rather than that assumed by Fatt, 55 mm Hg. Even under these favorable conditions the least thickness of the stagnant layer required to cause anoxia within the cornea is found to be 0·4 mm. Evidently, the formation of such a layer is physically possible over much of the surface of the human cornea where the depth of the anterior chamber at its center is about 3 mm.

Under anaerobic conditions the corneal metabolism becomes completely glycolytic (Riley and Winkler, 1990) and the glycogen store is depleted in a few hours (Smelser and Ozanics, 1953), suggesting that the glucose supply is inadequate for the anoxic demand. If the corneal glycogen becomes exhausted after a prolonged period of hypoxia, the absence of both an adequate glucose and oxygen supply could lead to cellular dysfunction or death.

5. A Test of the Hypothesis

An overall test of the hypothesis would be to look for corneal disturbances after permanently closing the lids over an eye that is not capable of making movements, either voluntarily while awake or by REM while asleep, and preferably in a situation where head movements are also suppressed. By good fortune, it seemed that such experiments had already been carried out, in which the lid margins of rabbits were surgically fused together. As a result, small corneal

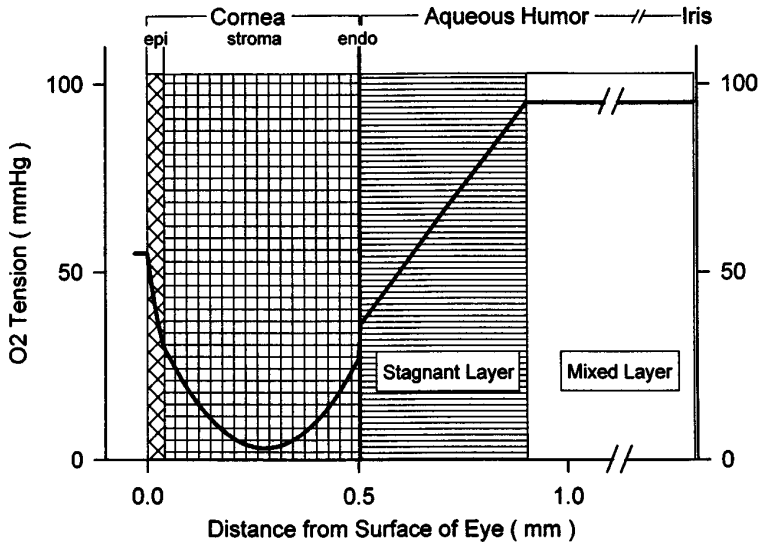

FIG. 6. Profile of O_2 tension in the anterior segment of the closed human eye with a stagnant layer of aqueous humor in contact with the cornea, calculated as described by Fatt and Weissman (1992), taking the O_2 consumption to be independent of its level. The aqueous between the stagnant layer and the iris is assumed to be well mixed and to have the O_2 tension of arterial blood, about 95 mm Hg. The thickness of the stagnant layer was adjusted until the calculated tension in the cornea fell to zero. Disturbance to the cornea resulting from asphyxia is to be expected if it is separated from the iris by more than this distance, 0·4 mm.

erosions appeared in 3 days and the tissue became edematous and vascularised after 10 days (Koch et al., 1989).

Significantly, the degenerative process was prevented or reversed if the lids became separated by a space as little as 2 mm. The investigators attributed this to an improvement in the oxygen supply, but this should only affect the tissue immediately below the separation and the area opened up to the air would seem to be too small to assist the respiration of the cornea under the lids at a distance from their margins. It is more likely that the corneal exposure provided by the lid separation is sufficient to promote an adequate thermal circulation in the anterior chamber.

When I first came across this paper during a literature survey, I believed it argued against the hypothesis, since rabbits were on record as having episodes of REM sleep (Weiss and Roldan, 1964). A further search revealed, however, that the eye movements during these episodes are infrequent, occurring only about once per minute on the average, and are apparently quite restricted in amplitude (Narebski, Tymicz and Lewosz, 1969; Pivik, Bylsma and Cooper, 1986). Moreover, when the animal is awake, it is unlikely that the aqueous in the closed eye is stirred because observation of an open eye under the slit lamp shows that its movements, as well as head movements, are normally rare (Maurice, 1995).

Thus the breakdown of the cornea after prolonged lid closure is in accordance with the stagnant aqueous humor hypothesis and could be considered to support it, if one accepts the validity of Fatt's calculations that show that the oxygen supply under the closed lid would be adequate if the anterior chamber is stirred. However, a more convincing test would be to provide mixing of the aqueous humor under the closed lid, for example, by stimulation of the extraocular muscles with an implanted electrode, and to check whether corneal erosion is prevented.

6. Biological Issues

The new hypothesis could explain why longer periods of eye movements are required when sleep is prolonged, since the metabolic embarrassment would be greater under these circumstances. It must be assumed that intermittent periods of mechanical stirring will supply enough nutrition to replace the deficits that build up during stagnation. Furthermore, the absence of thermal gradients in the womb would explain the more urgent need for mechanical stirring in the fetus. It is interesting that Zepelin (1989) suggested that REM sleep in mature animals is a carryover from fetal life so that a correlation with eye size should, perhaps, be sought for at the time of birth.

It should be emphasized that any large piece of metabolizing tissue at a distance from a vascular system is liable to have a problem in obtaining an adequate supply of metabolites, and for many animals the nutrition of the cornea is precarious, This must be evaluated on a species by species basis. The problem is not likely to be important in animals with small eyes, such as rodents, or in prey animals, which sleep only fitfully. There may be a range of larger eyes, possibly including the human, where the suppression of convective flow in the aqueous does not inevitably result in corneal ulceration but only creates a risk. On the other hand it could be particularly acute in large poikilotherms such as the giant squid, as well as in fishes which often have a viscous aqueous humor, up

to 130 centistokes in the trout, for example (Hoffert and Fromm, 1969). It is perhaps relevant that goldfish make frequent saccadic movements when their head movements are restrained, not only in light but in darkness, when no visual function can be served (Easter, 1971). It is also possible that frequent accommodative changes, which involve forward and backward displacements of the lens, can occur, which would ensure mixing of the aqueous fluid.

The situation of two other ocular tissues can be remarked upon, where potential nutritional problems arise because the need for optical clarity has resulted in them being devoid of blood vessels. The first is the lens which has a low metabolic rate that can doubtless be satisfied by it being bathed in freshly secreted aqueous at its equator and probably, for much of the time, over its anterior surface (Figs 2 and 5). Of more interest, because it presents parallels with the cornea, is the situation of the avian retina, which unlike that of the mammal lacks a direct blood supply. However, the primary source of nutrition for the inner retina appears to be the pecten, a well vascularised projection from the retinal surface. Although it is commonly believed that avian eyes cannot rotate (Duke-Elder, 1958), they can in fact, make frequent saccadic movements that are accompanied by rapid oscillatory rotations about the optic axis. It has been shown by Pettigrew, Wallman and Wildsoet (1990) that these rotations cause the pecten to agitate the vitreous humor and drive nearby fluid over the retinal surface, thus supplying it with nutrition. Little seems to have been published about the sleep patterns of birds, so that I do not know whether these rotatory movements could serve a useful purpose in the respiration of the cornea.

Finally, I will allow myself to offer some unverifiable speculations. In the first place, the early appearance of REM sleep in evolutionary history may signify that some of the most primitive forms had large eyes and periods of sleep or at least general inertia. REM would be particularly important if they were cold blooded. In its minimal form the new hypothesis need propose that REM was necessary only in the earliest evolutionary stages and is now a vestigial function, although it is more interesting to consider that it might be still of importance in species with largish eyes, particularly humans. Furthermore, it may be noted that eyes of even very primitive vertebrates have extraocular muscles (Duke–Elder, 1958), and it could be that their original purpose was more to shake the eye than to guide it.

It also seems quite possible that REM sleep evolved with the primary purpose of protecting the cornea. It is not evident why the functions ascribed to it, for example by Crick and Mitchison (1983), cannot be carried out by non-REM sleep. I cannot deny that there is a periodic set of phenomena associated with REM that include changes in the EEG, dreams, a rise in brain temperature, penile erections, and so on; even congenitally anophthalmic children share several of these events, that are still referred to as rapid eye movement sleep (Okawa et al., 1987). Nevertheless, none of these events have any clear physiological function and it may be that they result from a partial arousal necessary for eye movements to occur. I would, of course, modify my view if any such physiological function was clearly demonstrated. In any case, my interests are in the plumbing and I am happy to leave dreams to others.

7. Clinical Significance

I must confess that I first conceived of the stagnant aqueous humor hypothesis ten or more years ago but never followed it up because I thought it was so obvious that it must already have been proposed and, presumably, rejected[1]. Although this does not seem to be the case, it took Dr Rosenwasser's patient to spur me into action.

The corneas of humans, unlike those of rabbits, are not harmed by lid closure created by tarsorraphy or by paralysis of the lid muscles with botulinum toxin (Dutton, 1996), but rather this is employed to ameliorate ulceration. This paradoxical result is understandable because, at least in tarsorraphy, the lid closure is usually not complete and also because we differ from rabbits in making large and frequent eye movements during REM sleep and both eye and head movements while awake. However, there may exist rare cases such as Dr Rosenwasser's patient where head and eye movements are absent and total lid closure could lead to stagnation of the aqueous humor and corneal anoxia and degeneration. He was inspired to give the name 'closure keratopathy' to this situation. Such a condition could be mistaken for an exposure keratopathy or a neuropathy if the ophthalmologist was not aware of the alternative explanation, and it might be treated by ensuring that the eye was covered by the lids. However, this procedure might further the process of corneal suffocation.

It must be admitted that there is virtually no published evidence that suggests that this mechanism is operating in humans. The abolition of head and eye movements is most likely to be found in deeply comatose patients or those administered paralytics. I cannot find any reports of corneal ulceration under these conditions that were not attributed to poor lid closure and consequent corneal drying, and it is unlikely that there would be a uniform failure to report other cases because they could not be so classified. Factors that might generate some circulation in the anterior chamber could be residual REM, the ministrations of nurses carrying out routine ocular hygiene (Wincek and Ruttum, 1989) and, above all,

[1] It is not so obvious, however, to the sleep community. An article, similar in content to this one but more sober in tone, was rejected outright by the Journal *Sleep*, and a poster was refused for the annual meeting of the Associated Professional Sleep Societies.

cooling of the cornea through the closed lids. Humans often sleep in a supine position (especially in intensive care) so that the iris is in a horizontal plane, whereas in most animals it is in a vertical plane. This difference might result in any residual thermal convection providing a more uniform irrigation of the cornea with aqueous which has picked up oxygen by circulating over the surface of the iris. This is not a question that can be answered by superficial speculation, however.

There are some clinical situations where it is to be expected that a stagnant fluid layer adjacent to the corneal endothelium would be created that is insensitive to eye or head movements and could cause metabolic problems for the tissue. One such situation is when the anterior hyaloid membrane of the vitreous touches the cornea, and this is known to lead to corneal ulceration in the contact area. Another is a hypopyon, where the hypoxia caused by the lack of aqueous circulation should be compounded by the respiratory uptake of the white cells. However, corneal decompensation is rare in this condition. Perhaps displacement of the cells from the lower angle as a result of the change of eye position during sleep, combined with REM, is enough to protect the tissue.

Just as the basis of the new hypothesis can be tested by laboratory investigation, these clinical issues should be capable of experimental elucidation by ingenious ophthalmologists. Apart from the one instance noted earlier, I would rather not diminish the satisfaction of future investigators by suggesting which direction these researches should take.

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