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Diagnostic methods and treatment modalities of dry eye conditions

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Abstract

One may view dry eye conditions as a group of diseases in which the ocular surface is adversely affected. Tear film instability invariably leads to some degree of cellular surface damage over the cornea and conjunctiva. In turn, ocular epitheliopathy may adversely affect tear film stability. The clinical presentation of the disease may not yield a clue as to its etiology. In recent years considerable progress was made both in the diagnosis and the treatment of the disease and promising studies are planned or are underway.

The diagnostic techniques can be divided into four groups. The first is concerned with the clinical presentation. The second is concerned with the bulk properties of the aqueous tears including dynamic characteristics, composition, and colligative properties. The third is tear-film related and includes the film break-up time, evaporation rate, and lipid abnormality. The fourth is concerned with the ocular surface and includes vital staining, impression cytology, and surface microscopy. The most promising attempts are being made in the second group by attempting to elucidate the role of enzyme and enzyme activator activity and inhibitor contents as well as the tear protein profiles and correlating them with the specific disease states.

The treatment modalities belong to three major groups aside from surgical intervention; the *supplementation, preservation, and the stimulation* of tears. The modern version of tear supplementation is expected to include the topical use of efficacious aqueous formulations that typically contain film stabilizing polymers, nutrients, and/or – in the future – biochemically active ingredients such as enzyme activators and inhibitors.

Introduction

Pathophysiologically the dry eye syndrome belongs to a larger group of diseases that may be named ocular surface disease [1]. One common aspect of all dry states and of other ocular surface diseases is damaged corneal and conjunctival epithelium. Tear film insufficiency or instability invariably leads to some degree of cellular surface damage to the eye. In turn, ocular epitheliopathy adversely affects tear film stability. Figure 1 schematically represents the vicious circle of tear film in stability and ocular surface damage both leading to a pathological condition most often referred to as a 'dry eye.'

The clinical representation of the disease in the form of specific complaints and positive vital staining that may or may not be accompanied by deficient lacrimation often yields little or no clues as to the cause and effect relationship. In recent years,

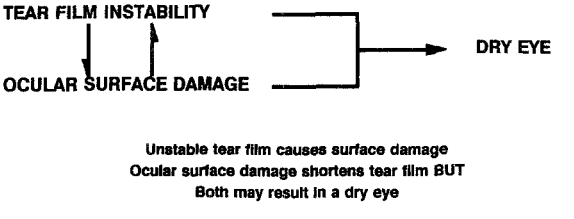

Fig. 1. The vicious circle of tear film instability and ocular surface damage.

however, considerable progress was made both in the diagnosis and treatment of the disease and additional studies are presently underway in various parts of the world.

Diagnosis

The diagnostic techniques may be divided into four groups according to type:

- clinical presentation
- tear-related
- tear-film related
- ocular-surface related

Clinical presentation

When the patient is seen at the clinic, often the first impression consists of the conveyance of his or her subjective complaints. There are several symptoms that may indicate a dry eye state. Persistent ocular discomfort such as a sandy gritty feeling which may wax and wane with time, foreign body sensation without a visible culprit, burning sensation, red, irritated eyes, excessive tearing, ocular discomfort upon awakening or in the late afternoon hours, excessive mucous discharge, or photophobia may all be a sign of ocular surface disease. It is very important to take a thorough history of the patient at this point.

Slit lamp examination is usually next, which offers an excellent opportunity to assess the quality of the tear film and the condition of the ocular surface. Debris in the tear film, the presence of threads of filaments, and an uneven, puny tear meniscus are all signs that the problem is tear film or ocular surface-related.

Tear-related diagnostic techniques

These techniques are based on the assessment of the following parameters or properties of bulk tears:

- tear secretion kinetics
- osmolality
- mucus ferning
- tear cytology
- protein content
- enzymatic activity

Tear secretion kinetics

The tear secretion rate or the tear turnover rate in the palpebral fissure may be determined by the Schirmer test, Schirmer-Holly test, and the dye-dilution test, or can be estimated by the assessment of the tear meniscus, as already mentioned.

The widely-used Schirmer test [2] is supposed to determine the amount of tears secreted in five minutes subsequent to the minor ocular irritation caused by the insertion of a dry filter paper strip in the cul-de-sac. The determined amount is usually less due to a considerable loss of tears from the strip via evaporation.

By careful kinetic analysis of the paper strip wetting while evaporation was prevented, Holly et al. [3, 4] found that the kinetics of the lacrimation response elicited by the insertion of the Schirmer strip is described by fast initial tear secretion which then exponentially decreases to a lower final secretion rate. In mathematical terms;

$$F = F_f + (F_i - F_f)e^{-kt} \quad (1)$$

where F is the tear secretion rate, k is the tear secretion decay coefficient, t is time, F_i and F_f are the initial and final tear secretion rates for a given lacrimation cycle, respectively. Such a lacrimation cycle may be repeated several times during a five- or ten-minute period, with a new set of kinetic parameters for each time interval. The more lacrimation patterns occur during the time period of measurement, the artifactually higher the Schirmer test value will become even if the tear secretion rates remain the same.

The authors found that the mean values of the initial and the final tear secretion rates of the average lacrimation cycle decreased by 50% [the mode values decreased by 3 and 5-fold] in dry eye patients as compared to age and sex-matched normals [5]. The secretion decay coefficient (k) was also significantly lower and the number of cycles were considerably less in dry eye patients than in normals. Hence, one may conclude then in dry eye patients, the ability to react to minor irritation by a suddenly increasing the tear secretion rate (F_i) (flushing action) is not impaired. In such patients, however, this elevated secretion rate decays more rapidly and to a

lower final value than in normals. The low number of lacrimation cycles observed in dry eye patients will also tend to decrease the value of the classical Schirmer I test.

The dye dilution test developed by Mishima et al. [6] consists of a small volume of fluorescein solution instilled in the eye and the decay of fluorescence followed by a fluorophotometer. By simple modelling Holly and Lamberts [7] deduced that the exponential decay coefficient of fluorescence is given by the ratio of the tear secretion rate and the steady state tear volume in the eye. Since the tear volume tends to increase with increasing tear secretion rate, their ratio stays quite invariant for moderate changes in tear secretion rate. Since this 'k' value is the slope of the fluorescence decay curve in the in the fluorescence intensity versus logarithm of time plots, the decay remains quite linear over a considerable time interval in the semi-logarithmic plot.

Osmolality

A diminished tear secretion rate, decreased tear volume, and possibly enhanced tear evaporation rate all tend to increase the solute concentration in the aqueous layer of the tear film. This would result in an increased (crystalloid) osmolality. If the barrier properties of the epithelium are yet unimpaired, a hyperosmolality of the crystalloid components at least 3 mOsm/kg (a 1% increase) would overcome the imbibition pressure and extract water from the stroma that would tend to lessen such an effect. On the other hand, in the case of damaged, leaky epithelium elevated crystalloid osmolality levels will not effect water removal from the stroma and the edematous epithelium, since the semi-permeability of the epithelial membrane is no longer functional.

Gilbard and coworkers [8] using microtechniques demonstrated a modest 3–5% increase in tear osmolality in dry eye patients and suggested that at least some of the surface cellular damage results from the elevated osmolality. The authors also claim that elevated osmolality could be used as a diagnostic sign of dry eye states. Expensive instrumentation, high degree of operational skills, and the relatively small effect prohibited the widespread use of such a diagnostic technique so far. Their method is based on the principle of freezing point depression and thus may be adversely affected by the presence of tear proteins. A method based on the vapor pressure [or dew point] depression would be more appropriate but unfortunately it requires at least one order of magnitude larger tear sample volumes.

Mucus ferning

Rolando and co-workers [9] were the first to demonstrate that the extent and symmetry of the fern-like mucous deposit around the microscopic salt crystals from a tear sample dried unto a microscope slide are very much compromised in dry eye patients. They actually developed a grading method that could distinguish the tears of normal subjects from dry eye patients if three degrees of severity. The method requires a light microscope but it is easy and inexpensive to do.

Tear cytology

The cell content of a tear sample obtained from a normal and healthy eye consists of about 5–10 superficial cells per 10 microliters [10]. The cell content of a tear sample taken from a dry eye patient, on the other hand, will be much higher, 20–50 cells in the same volume and in addition to the superficial cells the sample will contain wing cells and possibly basal cells. If the eye is inflamed then it will contain different types of leukocytes. This method is presently being perfected by Orosi and co-workers [10], and it promises to become an effective technique to assist in the diagnosis of external eye diseases. This technique also requires a light microscope and some training in cytology to effectively stain and recognize cell types and conditions.

Protein content and enzyme activity

The total protein of normal tears is usually found to be between 7 to 9 mg/ml. In dry eye patients, when only irritation is present the total protein content may decrease by 30 to 50%. However, when the eye is also inflamed, the leakage of serum proteins could significantly increase tear protein content up to 40 mg/ml. In such tears serum albumin, practically nonexistent in normal tears, may become the major protein component.

It has been known for decades that lysozyme concentration [and activity] decreases in the tears of dry eye patients [11–13]. Interestingly, if the lysozyme content is expressed as a fraction of the total protein content, the relative concentration does not seem to differ significantly from those in normal tears [14] unless the eye is inflamed.

Lactoferrin, similarly to lysozyme, is secreted by the lacrimal gland. Its concentration is also decreased in the tears of dry eye patients if the lacrimal gland function is impaired. A relatively simple technique using Lactoplate® was developed by Janssen and van Bijsterveld [15]. These plates are now available commercially in the U.S. [Eagle Vision, Memphis, TN] to determine lactoferrin concentration in tears for diagnostic purposes.

One of the most promising attempts in developing new diagnostic techniques are made in studying the role of proteolytic enzymes in ocular surface disease especially when the risk of ulceration is present [16]. The significance of enzymes such as plasminogen activators, plasmin, and collagenase which form a cascade that may result in ulcer formation has only been recently appreciated. The tears of dry eye patients appear to contain elevated levels of plasminogen activators especially that of urokinase type [17]. Diagnostic kits capable of determining the levels of such enzymes as well as the presence and possible deficiency of inhibitors of these enzymes should prove to be useful in diagnosing and determining the progression of such potentially destructive processes in the eye.

Tear-film related diagnostic techniques

These methods are concerned with the properties of the tear film, a thin double-layered fluid film, which are controlled by surface forces. The major part of the film [99%] consists of an aqueous tear layer which is coated by a duplex lipid film approximately 50 to 80 molecules thick [100–160 nm] in the open eye. The following diagnostic techniques fall into this classification:

- tear film break-up time
- tear evaporation rate
- lipid spreading ability

Tear film break-up time

The rupture of the preocular tear film, i.e. the formation of dry spots over the cornea is basically a nonwetting phenomenon [18]. The tear film ruptures over certain areas of the ocular surface and recedes forming a finite contact angle at the boundary. The thickness of the tear film insufficiently small so that it will become unstable once the ocular surface becomes hydrophobic [18]. The time interval between the opening of the lids and the appearance of the dry spots is defined as the tear film break-up time [BUT] [19, 20]. It is incorrect to abbreviate it to tear break-up, as it is indeed the occurrence caused by the instability of the tear film and is not a bulk tear property.

It has been shown [21] that fluorescein instilled in the eye will shorten BUT, especially when the dye is contaminated with a surface active preservative, which is almost always the case [the culprit usually is benzalkonium chloride, a cationic surfactant]. Hence, it is best to use a non-invasive optical method which does not interfere with the stability of the tear film, such as the Xeroscope™ or Toposcope™ [22]. The use of dispersed light to enhance interference colors will also make the dry spots visible [23]. By non-invasive methods, BUT's as long as several minutes have been observed. Generally, if the BUT is shorter than ten seconds, one can be reasonably sure that the stability of the tear film has been compromised. To cause ocular surface damage, the BUT has to be shorter than the average blinking interval, which is usually 6–8 seconds in normals, unless the person is staring [e.g. watches television or a computer screen]. In this latter case, the blinking interval can be considerably lengthened. Unfortunately, so far no valid study has been published concerning the blinking frequency in TV viewers or computer operators.

Tear evaporation rate

What is measured here is the water evaporation rate from the aqueous layer of the tear film through the superficial lipid layer. None of the presently used methods to measure this rate is simple enough to use in the clinic. It has been found that the tear film in dry eye patients has a greater rate of evaporation than in normals [24]. The laboratory mea-

surements indicate that it would take five to ten minutes to lose all the aqueous layer completely [25]. Unfortunately, practically all the evaporation measurements so far have been conducted under non-turbulent conditions. It is well known, however, that the evaporation rate can be greatly enhanced by air turbulence adjacent to the exposed ocular surface. It is this greatly enhanced rate that would be retarded by the superficial lipid layer. Hence, it is still uncertain how much evaporation contributes to tear film instability. It seems likely, however, that only under extreme conditions such as the prolonged exposure to dry high winds or being exposed to a blast of cool, dry air from an air conditioner, would evaporation contribute significantly to tear film instability.

Lipid spreading ability

The meibomian lipids are known to form a multimolecular layer over aqueous tears constituting the tear film [26]. Non-polar lipids from only floating oil lenses in water and the water surface between the oil lenses is clean. Pure polar lipids, on the other hand, from a monomolecular layer while the excess lipid is collected in the form of lenses (autophobic behavior). Only a mixture of lipids having different polarities are capable of forming a stable multimolecular [duplex] film over water [or tears].

If the superficial lipid layer is approximately 50 molecules thick, its stability would be ensured if at least 2% of the molecules consisted of highly polar lipids [e.g. free fatty acids or fatty alcohols]. If the polar lipid fraction becomes much greater in the meibomian secretion [possibly due to the hydrolysis of fatty and cholesteryl esters effected by lipase secreted by bacteria] the stability of the whole tear film would be jeopardized [27]. Sebum, which has three-fold higher spreading film pressure than meibum (meibomian gland secretion), will immediately rupture the tear film in vivo [28].

The spreading tendency of meibomian lipids can be assessed in vitro using a Langmuir trough and a surface tensiometer [e.g. Wilhelmy-blade type] by determining the equilibrium film pressure. This parameter is obtained by spreading more and more lipid on the water surface until its surface tension no longer decreases. The lowering of the surface tension is equivalent to the lipid film pressure [26].

Based on some preliminary data (Holly FJ: unpublished) we believe that when inflammatory processes liberate free fatty acids in meibum, the meibomian glands respond by increasing the secretion of the nonpolar lipids even as much as ten- or twenty-fold thereby keeping the magnitude of the relative polar fraction more or less invariant. The spreading characteristics of such lipids will thus remain the same. For this reason and due to the complexity of the time-consuming measurement, it is unlikely that the determination of the spreading characteristics of the meibomian lipids will become a diagnostic technique for lipid abnormality.

Ocular-surface related diagnostic techniques

The underlying common denominator for ocular surface disease including dry eye states is the damage to or pathologic changes in the superficial epithelium of the cornea and conjunctiva. The techniques assessing and quantitating this damage are:

- vital staining
- surface cytology
- impression cytology
- surface microscopy

Vital staining

Norn [29] has done pioneering work studying dyes that appear to be useful in staining damaged surface epithelium. Rose bengal and fluorescein are the most commonly used dyes today, although Norn advocated 1% lissamine green in a preserved electrolyte solution, as it has the same specificity as Rose bengal but it is not irritating to the eye.

Norn has also a developed dye mixtures for use in ocular diagnosis. He combined Rose bengal and fluorescein to be able to assess, subsequent to the instillation of one drop of combined dye into the eye, epithelial surface damage in the form of dead and dying epithelial cells and frank epithelial defects [30]. Rose bengal staining has the same specificity as Lissamine Green but it may be more sensitive. Unfortunately, this dye is quite irritating to the eye and occasionally a topical anesthetic has to be

used concurrently with it in patients with sensitive or painful eyes. Bijsterveld [12] developed a grading scale of dye staining to assess surface damage. It is important to apply the vital stain before conducting a Schirmer test since even the minor damage to the conjunctiva by the paper strip is made quite visible by the stain.

Sloughed surface cell microscopy

Norn [31] pioneered the method by which loosened surface cells of the epithelium are removed by suction using a glass pipette with a wide [4 mm in diameter] and dull-edged opening. The suction is created by a rubber bulb and the cells are rinsed off the internal walls of the pipette with saline onto a glass slide. The cells the are stained by the appropriate dyes, counted, and classified. Due to the possibly large variation caused by differences in the skill of individuals doing the sample taking, the method has not become popular.

Impression cytology

This method was pioneered by Egbert et al. [32] in 1977, and further developed by Adam [33], Nelson [34], and Götz et al. [35]. By impression cytology the number and the surface density of conjunctival goblet cells can be determined to decide whether the patient suffers from mucus deficiency. In this method a disk of porous filter paper is pressed against the conjunctiva, which is then stained with the Schiff reagent and viewed under 40 × magnification. This method is much less invasive than a conjunctival biopsy and thus is used mostly in clinical studies. Attempts have been made to standardize the method by applying the same predetermined pressure [Norn, personal communication] when taking an imprint. It is important to realize that application of a topical anesthetic, if employed prior to impression taking, prior to sample taking, will loosen surface epithelium and cause pathological changes such as the loss of microridges in the surface cell morphology.

Microscopic observation of epithelial surface

There are several methods capable of direct examination of the ocular surface cells in vivo. Specular microscopy [36] is a method where the direct incident light beam is split and the beam reflected from the corneal surface [or from various interface of the medium] is examined. The latest technique employs a wide-field color specular microscope of the Keeler-Konan type and utilizes vital stains [37]. This technique allows scanning of large areas of the corneal surface and provides clear images of the individual cells. The cells can appear darker or brighter, pathological cells are colored due to dye uptake. Their sizes can also be estimated. Smaller cells are usually younger, immature and readily stain with Rose bengal or fluorescein. A high density of such cells indicates more rapid cellular turnover. As the cells mature they increase in size prior to exfoliation.

In dry eye patients, the mucus layer appears to be deficient and discontinuous frequently exposing the hydrophobic epithelial surface to tears. The mucous filaments and plaques, hydrophobic due to their lipid content, can also be visualized by specular microscopy [37]. They appear to be bound tightly to mucus-free epithelial surface most likely through hydrophobic bonding. Shear forces created by blinking will pull the filaments and thus exert stress on the cells creating the painful condition known as filamentary keratitis.

Treatment

Even after decades of intensive research, the dry eye states, i.e. the majority of the ocular surface disease states still cannot be cured today. Still, there are several ways the symptoms can be alleviated and the patients' condition ameliorated. If we exclude surgery, the treatment applied usually falls in one of three categories:

- supplementation of tears
- conservation of tears
- stimulation of tear secretion

Supplementation of tears

Existing tears can be supplemented most readily by topical instillation of artificial tear formulations in the eye. The conventional tear substitutes contain various electrolytes, mostly sodium chloride, to

achieve the proper tonicity, some polymers to enhance viscosity, and preservatives to maintain sterility of the preparation. Modern tear substitutes are formulated according to the guidelines provided by tear film physiology [38, 39]. They contain polymers that enhance film stability without enhancing viscosity. They may contain elevated contents of a non-viscous polymeric component to provide high oncotic pressure [40] which is thought to be beneficial for irritated eyes by reversing epitheliopathy [1, 38].

Retention time

Tear substitutes also act as lid lubricants so their viscosity cannot be increased with impunity. At first, it was thought that increased viscosity will increase the retention time of the drop. Later, it was shown [42] that there is no correlation between retention time and viscosity, especially in a lower viscosity range suitable for eye drops. Still the idea, that increased viscosity is an advantage for an eye drop, lingers on.

Continuous supplementation

Tears can also be supplemented more or less continuously by attaching a small reservoir containing a tear substitute to the spectacle frames which will feed tears to the interpalpebral fissure due to gravity [43]. Small specially designed tear pumps can also be placed at some suitable location on the person which are capable of pumping the fluid at a low rate [1-2 microliters per minute] through a small plastic tube leading to the canthus [44]. Such heroic measures are justified in severe dry eyes with greatly compromised tear secreting ability.

Tonicity of artificial tears

Initially isotonic tear substitute formulations were prepared to avoid an osmotic shock to the eye. When it was found that the tear tonicity was slightly elevated in dry eye patients, it was thought that hypotonic [215–260 mOsm/kg] tear substitutes would be more effective because they would dilute the slightly hypertonic tear layer in the eye for several minutes subsequent to instillation [7, 45]. A recent publication [46] advocates the use of an even more hypotonic formulation claiming that other commercially available collyria are toxic to the epithelium. Unfortunately, the study was found to be invalid as an unpreserved and nonbuffered formulation was compared to a preserved commercial formulation [47]. The first hypotonic formulation on the market was HypoTears® with a tonicity almost one-third lower than normal [214 mOsm/kg] [IOLAB, Claremont, CA]. Several other solution manufacturers followed suit and lowered the tonicity of their preparations by at least 10% regardless of the fact that careful, quantitative analysis of existing results including kinetic studies [7] does not support the advantage of such a deviation from isotonicity.

Oncotic pressure of artificial tears

This colligative property is effected by colloidal molecules at high concentration especially if the particles are electrically charged [Gibbs-Donnan potential] [40, 48]. Unlike blood plasma which has an oncotic pressure of about 25 mmHg due to its relatively high protein concentration, normal tears have a low oncotic pressure [approximately 2 mmHg] but still higher than that of aqueous humor [0.1 mmHg] [40]. However, an oncotic pressure higher than that of the imbibition pressure of the deturgescent stroma [40–50 mmHg] is needed to dehydrate diseased, leaky epithelium and the interfacial region at the basement membrane [41]. Such a solution will even dehydrate denuded edematous stroma. Solutions with elevated oncotic pressure have been found effective in increasing epithelial adhesiveness, healing recurrent corneal erosion, and diminishing Rose bengal staining in ocular surface disease [1, 38, 49].

Nutrition of ocular surface epithelium

It is widely known that poor nutrition, especially lack of vitamin A and protein in a diet, will lead to the devastating conditions known as xerophthalmia and keratomalacia. Tears are also known to contain retinol complexed by tear specific prealbumin, one of the tear proteins secreted by the lacrimal gland. Since adequate nutrition may not be provided for the ocular surface, especially when the stability of the tear film is jeopardized, the topical application of some forms of vitamin A (retinoids) has been considered. Ointments containing trans-retinoic

acid were found to be efficacious in patients suffering from ocular pemphigoid or Stevens-Johnson syndrome [50]. In a recent, well controlled clinical study, retinyl palmitate complexed by a water-soluble polymer in an aqueous formulation was found to be significantly more efficacious in moderately severe sicca and Sjögren patients than the leading commercial artificial tear [Tears Naturale®, Alcon, Forth Worth, TX] and another artificial tear with similar biophysical properties that contains no vitamin A [Dwelle®, Dakryon Pharmaceuticals, Lubbock, TX] [51].

An artificial tear formulation that contains vitamin B_{12} [cyanocobalamine] has become available in late 1989 under the trade name NutraTear® [Dakryon Pharmaceuticals, Lubbock, TX 79423]. The effect of this nutrient has not been studied well. Vitamin B_{12} is essential for life and normal cell growth, cannot be synthesized by the body, and may protect the eye from oxidative-free radicals. This nutrient has been found to increase the healing rate of epithelium over denuded rabbit cornea about threefold when the limbal area was included in the defect. The ability of the tear proteins to bind Vitamin B_{12} is much greater than that of blood plasma proteins. Vitamin B_{12} is absorbed poorly in the elderly. In an open clinical trial, NutraTear® was found to be beneficial by 95% of the patients. After using the formula for one week, the majority of the participants stated that their eyes felt more comfortable and looked better [1].

Preservation of tears

The existing tear pool in the interpalpebral fissure (the tear meniscus and the tear film) can be diminished through drainage via the puncta and through evaporation of water. It is believed that by supplying a polymeric solute in the form of an ocular insert can also retain some of the moisture in the eye. Thus, the following methods are aimed at the preservation of tears in the hope of ameliorating dry eye conditions by impeding tear loss:

- obstruction of the puncta
- elimination of evaporation
- supplementation of polymeric solute

Obstruction of the puncta (or canaliculi)

The obstruction of lacrimal drainage can be achieved several ways [52]. By sealing them surgically (thermal cautery) tear drainage is eliminated permanently. This is not the best method to use because it permanently disfigures the puncta and causes thermal damage to the surrounding tissue. The procedure could also cause, on occasion, irreversible iatrogenic epiphora. Argon laser Canaliculoplasty, another technique to effect long-term canalicular occlusion, offers clinicians the flexibility to close the tear drains fully or partially. The greatest drawback of this method has been the high cost of the argon laser. Another alternative, the punctum plug, was introduced in 1983 as a non-surgical, readily reversible means of canalicular occlusion. The molded inert silicone plug was designed to be partially inserted into the punctum for easy removal.

The punctum plug still had some drawbacks. The punctum had to be dilated prior to plug insertion. Topical anesthetic had to be used for the insertion. The relatively large diameter of the plug made them difficult to insert. The head of the plug has the potential to cause microabrasion of the cornea. Nearly a third of the patients experience the expulsion of the plug.

Another temporary, self-limiting obstruction of the tear canaliculi can be achieved by inserting a collagen rod through the inferior puncta. This thin collagen rod dissolves in about three weeks restoring lacrimal drainage. This is an ideal method to find out whether the obstruction of lacrimal drainage is useful for the patient without having to remove the obstruction later on.

A lacrimal plug was invented by R.S. Herrick in 1990 for long-term occlusion of the tear drainage ducts. The 'golf-tee' shaped molded silicone implant is designed to be inserted past the punctum, down the vertical canaliculus and into the horizontal canaliculus. Here the plug becomes lodged just in front of the common canaliculus.

Unlike the punctum plug, the Herrick Lacrimal Plug does not stick out of the punctum eliminating the potential for corneal abrasion. Its expulsion rate is practically zero. Due to its small size, the Herrick Plug is extremely well tolerated by patients and re-

quires no topical anesthetic or dilation of the punctum for insertion. If patients experience irritation or epiphora, the Herrick Plug can be readily removed through saline irrigation or probing of the canaliculus (R.S. Herrick, personal communication).

Elimination of evaporation

The simplest means to drastically reduce evaporation from the ocular surface is to use ointments. Since this method interferes with tear film formation and thus results in obscured vision, this method is used only at night in moderate to severe dry eye patients [50]. Another way of reducing evaporation is the use of shielded goggles [43]. Since such devices are not attractive and they are mentally associated with danger [eye protecting gear], only patients with severe dry eyes are willing to wear them. The advantage of such goggles are that they can be combined with artificial tear reservoirs and the collyria can be gravity-fed or pumped to the eye as we have seen previously [44].

Supplementation of polymeric solute

Instilling artificial tears into the eye every two to four hours is inconvenient and the benefit of the drop wanes rather quickly. Hence, a method consisting of the placement of a small piece of solid, water-soluble polymer in the fornix has been developed [54]. Lacrisert®, consisting of hydroxypropyl methyl cellulose [Merck, Sharp and Dohme, Philadelphia, PA], is a small cylindrical object weighing a few milligrams that lasts in the inferior fornix several hours or most of a day [55]. It can be inserted dry but that may prove to be uncomfortable especially when the tear meniscus is scanty. It can be wetted by sterile saline prior to insertion, but then the insert becomes slippery and hard to handle. The best method is to place the insert in the fornix dry and then immediately instill a drop of saline or artificial tear into the eye to alleviate the discomfort. Bausch & Lomb [Rochester, NY] has been testing clinically a collagen mini-shield, Bio-Cor®, a small, oval shaped, wafer-like collagen sheet to serve as an ocular insert (Lamberts, D.W. personal communication). Approximately one half of dry eye patients, among those who try ocular inserts, appear to be helped by them. The greatest shortcoming of this type of dry eye aids is that they do not supply water to the eye but that they themselves need moisture.

The use of highly viscous tear substitutes or even gel-like substances should perhaps be mentioned here. Vidisic gel [56] has a viscosity three orders of magnitude higher than tears. It is made of a polyacrylic acid polymer and exhibits drastic shear-thinning. Viscosity of tear substitutes should be no higher than 20 centipoises. To act as effective ocular lubricants, the viscosity should be even lower, between 1–6 centipoises. Viscosities higher than 50 centipoises are poor lubricants. Eye drops with even higher viscosities have been tested and were found to cause epithelial damage.

Fortunately, gels or drops with very higher viscosities do not mix well with the tear film and hence, do not interfere with lubrication. Such substances may collect in the fornix and act as an ocular insert. This may be the mechanism of action of a carboxymethyl cellulose containing formulation that has been recently marketed under the trade name Celluvisc®, which has a dynamic viscosity of nearly 300 centipoises and exhibits no appreciable shear-thinning [57]. Recently a more dilute version of Celluvisc®, Cellufresh™ with one hundredfold less viscosity (3 centipoises) was placed on the market to answer this criticism.

Stimulation of tear secretion

As late as the sixties the dry eye states were still thought to result exclusively from diminished tear secreting capability. It is now recognized that diminished lacrimating ability is not a necessary condition for the dry eye states to develop [58]. There are well defined disease states, however, where the lacrimal gland's secreting capacity has been damaged but some secretory parts are still functional, e.g. Sjögren's syndrome. Hence, at least in some of the dry eye states, the stimulation of the lacrimal gland appears to remain an attractive way to treat the condition.

Adverse systemic drug effects

Topically applied or systemically administered

drugs can alter tear secretion rate [53]. Systemic atropine is well known for its effect of diminishing tear production. Timolol® can also decrease tear production but apparently this side effect is only temporary. Topically instilled Timolol® also shortens the tear film break-up time. This effect, however, may originate from its preservative content.

Beneficial drug effects

Systemic pilocarpine is known to enhance tear production but not sufficiently to justify the use of this rather toxic drug for the treatment of keratoconjunctivitis sicca [53, 59]. Bromhexine hydrochloride [Bisolvan®], which is basically a bronchial mucolytic agent can apparently double as a secretagogue. When administered three times daily, Bisolvan® apparently improves the result of the Schirmer I test, BUT, and the vital staining score of van Bijsterveld as demonstrated by Manthorpe et al. [60]. Others failed to demonstrate such an improvement [53].

Tachykinins

An intriguing secretagogue, eledoisin, is well known in Europe. This drug belongs to a group of pharmacologically active peptides, the so-called tachykinins. This topical drug was first isolated from the salivary gland of the Mediterranean octopus [Eledona moschata] and later was successfully synthesized. This endecapeptide was found to be an effective secretagogue by Bietti in 1973. Since then positive results were published in several publications attesting the efficacy of this drug for keratoconjunctivitis sicca and Sjögren's syndrome [61]. Unfortunately, the effect is short-acting due to the short retention time of the topically applied, water-soluble drug in the eye. The beneficial effect of eledoisin could possibly be prolonged if a proper ophthalmic drug vehicle could be designed for this drug.

Immunosuppressors

The immunosuppressive drug cyclosporin A appears to be effective in dogs with Sjögren-type dry eye condition [62] it is being presently tested in Sjögren patients. Topically administered cyclosporin A is primarily effective in controlling inflammation often present in dry eyes and probably has no direct secretagogue effect.

Treatment modalities in the U.S.

According to a survey [59] conducted by the Dry Eye Institute [Lubbock, TX] among 223 optometrists and 74 ophthalmologists, practically all the eye care professionals [99%] prescribe the use of artificial tears for their dry eye patients. Among these, 68% also prescribed at one time ocular inserts [mostly Lacrisert®] for patients. The majority [62%] now distinguishes among the different artificial formulations searching for better efficacy [mucomimetic or lacrophilic drops], hypo-allergenicity [avoidance of thimerosal or benzalkonium chloride-containing drops], or hypo-osmolality [e.g. HypoTears], and there is a clear tendency to prescribe preservative-free unit-dose drops whenever it is available. There is a growing segment of practitioners which advocates the use of nutrient-containing eye drops especially of those containing vitamin A palmitate [Dakrina®, Dakryon Pharmaceuticals, Lubbock, TX; Viva-Drops® (formerly Vit-A-Drops), Vision Pharmaceuticals, Mitchell, SD].

An overwhelming majority of the practitioners [87%] also prescribes the use of ointments for night time use. The ocular insert, Lacrisert®, however, has been regularly prescribed by only 38%.

Other treatments that are occasionally used by some practitioners include: scleral or rigid contact lenses to prevent evaporation, Healon® [hyaluronic acid] -containing formulations, and diluted autologous blood plasma.

Unfortunately, contact lenses are tolerated poorly by many dry eye patients especially if the tear secretion is diminished so this method of evaporation prevention is often not feasible. Hyaluronic acid is a hydrophilic polysaccharide that is quite costly. At the present time it is not clear whether sufficient advantage is provided by Healon® to justify the extra cost. It is well to keep in mind that all the polymers included in artificial tears play a strictly biophysical role, where the physical properties rather than the actual chemistry of the polymer is important. Autologous blood serum proteins to be used in the dry

eye appear to experience a revival and not only in the U.S. For example, it is used by dry eye patients who are deficient in lacrimal proteins in Montevideo, Uruguay [J.C. Suarez, M.D., Montevideo, Uruguay; personal communication] for treatment with some success.

Both pilocarpine hydrochloride and Bisolvan® are occasionally used in the U.S., although the latter drug is difficult to obtain. So far, no secretagogues have been approved by the U.S. Food and Drug Administration for human use in the United States.

Occasionally one hears about the application of topical steroids in dry eye patients in an attempt to control the low grade inflammation often present in such patients. While such an approach is certainly justified to control acute inflammation for several days, long term treatment in view of the grave ocular side effects [cataract, glaucoma] of such drugs, their prolonged use is clearly not advisable.

Nonsteroidal inflammatory drugs [e.g. Flurbiprofen, Allergan, Irvine, CA], for controlling inflammation in dry eye patients are now available. These drugs also appear to be effective in managing severe dry eye conditions where inflammation is usually present.

Future prospects

Intensive research effort is expended to investigate the role of various proteolytic enzymes, enzyme activators, and their inhibitors in ocular surface disease. The etiology of the tri-level enzymatic cascade involving plasminogen activators, plasmin, and collagenase is yet unknown but investigative efforts are expended toward its elucidation. Once such a role at different stages of the disease is known, then novel diagnostic techniques capable of providing differential diagnosis could be developed and formulations specific for the various conditions could be formulated. Such an approach will result in a major progress in the treatment of ocular surface disease and hopefully will avert or diminish the risk of occurrence of major corneal disasters such as corneal ulceration and the sight-threatening ocular perforation.

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