

# The questionably dry eye

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**SUMMARY** This paper is concerned with the recognition of the dry eye when the clinical diagnosis is in doubt and other external eye diseases may be present. Papillary conjunctivitis is common to the dry eye as well as other pathological conditions and confuses the diagnosis. We have correlated the factors involved in the assessment for dryness. We have shown that particulate matter in the unstained tear film is associated with low tear lysozyme concentration. Tear flow and tear lysozyme are not necessarily interrelated, but a low lysozyme concentration (tear lysozyme ratio < 1.0) is associated with keratoconjunctivitis sicca. The Schirmer I test can produce false positive results, and we have suggested a modification to overcome this. This modified test will detect the eye with severely depleted lysozyme secretion, but it is unreliable for detecting the eye with moderately depleted secretion. We find that its lowest normal limit should be considered as 6 mm.

The diagnosis of the severely dry eye is straightforward, but the clinical signs can be confusing in the eye with moderately depleted tear production. By the questionably dry eye we mean an eye with at least one feature of dryness in a patient with symptoms that suggest this possibility.

Dry eyes commonly occur in association with systemic diseases of the autoimmune type and may be considered an indicator of such diseases, but it is probably only in systemic lupus erythematosus that they are an important indicator as an early manifestation. The question, however, as to whether an eye is dry or not is of great importance when the dry state may have been induced by a drug.

This paper is concerned with the clinical problem of diagnosing the eye with only moderate tear depletion.

## DIFFERENTIAL DIAGNOSIS

The commonest mimic of the dry eye is *chronic blepharoconjunctivitis*, which may be related to seborrhoea or other skin conditions. The causative bacterium may be *Staphylococcus aureus* or a low-grade pathogen such as coagulase-negative *Staphylococcus epidermidis*.<sup>1,2</sup> However, this latter bacterium can be shown to be present in the conjunctiva of the majority of normal eyes.<sup>3</sup> The patient may have a chronic blepharitis with crusting or ulceration.

There may be dilated vessels on the lid margins and collarettes of scales round the cilia. There is almost invariably a chronic papillary conjunctivitis which may be due to the liberation of staphylococcal toxins and these toxins may also produce a superficial punctate epitheliopathy.<sup>4</sup>

There may be a chronic meibomianitis and also a superficial punctate keratopathy, which may be related to the meibomianitis.<sup>5</sup> The signs may be predominantly in front of or behind the grey line of the lid margin.

*Rosacea keratoconjunctivitis* is the second differential diagnosis. According to Jenkins *et al.*<sup>6</sup> it is characterised by bulbar and palpebral conjunctival hyperaemia, telangiectasia of the lid margins, chalazia, and blepharitis. There are also punctate epithelial erosions, usually in the inferior half of the cornea, and there may be dystrophic epithelial signs. With progress of the disease the keratitis can be severe leading to vascularisation, stromal loss, and perforation. Although not noted as a physical sign by Jenkins *et al.*,<sup>6</sup> we have found a papillary conjunctivitis to be a constant feature of the disease. Duke-Elder points out that rosacea conjunctivitis is frequently undiagnosed.<sup>7</sup> Borrie found that in 20% of cases the first manifestations of rosacea were in the eyes,<sup>8</sup> and Goldsmith drew attention to the fact that the ocular lesions progress or diminish independently of the skin lesions,<sup>9</sup> which Jenkins *et al.* showed do vary very widely.<sup>6</sup> Rosacea keratoconjunctivitis is commonly complicated by staphy-

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lococcal conjunctival infection.<sup>10</sup> The disease shows an excellent response to tetracycline.<sup>6,11</sup>

*Allergic conjunctivitis* is the third differential diagnosis. Here the symptoms of burning and mucoid secretion, combined with the finding of a papillary conjunctival reaction, may mimic keratoconjunctivitis sicca if a pronounced reflex tear flow is not a feature. Secondary infection with staphylococci may further complicate the diagnosis. Furthermore it has been pointed out by Jones<sup>12</sup> that many inflammatory diseases, including staphylococcal blepharokeratitis, appear to have allergic components. This adds a further complication to the differential diagnosis. An allergic aetiology may be difficult to identify clinically.

The fourth differential diagnosis is that of *other external eye diseases* in their early or atypical forms, and here a papillary conjunctivitis is often a feature as a purely irritative phenomenon.

#### ASSESSMENT OF THE EYE FOR DRYNESS

*Papillary conjunctivitis.* It will be noted that a common feature of the foregoing conditions is a papillary conjunctivitis, and with longstanding disease a cellular infiltration of the conjunctiva, whereby its normal vessels are obscured, often develops. Similarly the dry eye is characteristically associated with a papillary conjunctivitis, and the conjunctiva is often infiltrated. These features have received scant attention in the literature, and they confuse the diagnosis. Furthermore, the dry eye is especially prone to infection with staphylococci,<sup>13</sup> and this is a source of further confusion in diagnosis.

*Bengal rose staining of the conjunctiva.* According to Norn<sup>14</sup> Bengal rose stains dead and dying cells. Staining is found in dry eyes, eyes with staphylococcal disease or rosacea or allergic disease, and many other external eye diseases. This staining of the conjunctiva is also found in the localised drying associated with the disease complex of pingueculae, dellen, and pterygia,<sup>15</sup> which in its subclinical forms is very common.

*Tear film.* Vanley *et al.* using a statistical approach have criticised the use of the break-up time.<sup>16</sup> They find that it is not of any conclusive value in the diagnosis of dry eye syndromes, and its reproducibility cannot be maintained within reasonable limits.

The tear film break-up time depends on the integrity of the system at the interface of the tears and the epithelium. It is therefore related to the integrity of the microvilli of the surface epithelial cells, the cell surface related components, the intervillous mucus, and the mucus layer lying on the microvilli.<sup>17</sup> These can be deranged in many external diseases and by topical medication.

*Particulate matter in the tear film.* An abundance

of stringy mucus in the fornix is classically associated with the severely dry eye, but it may not be present with disease of moderate severity. However, careful observation of a questionably dry eye *before it is stained with fluorescein* and *before the upper lid is everted* will sometimes reveal some particulate matter in the tear film which is quite mobile (Fig. 1). The particulate matter is mucus and can be shown to stain with alcian blue. Litt *et al.*<sup>18</sup> have shown that mucus has the physical property of drying rapidly and rehydrating slowly and this may explain the presence of the particulate matter.

*Tear wedge.* Examination of the volume of the tear wedge may suggest reduced tear flow<sup>13</sup> but Lambert *et al.*<sup>19</sup> have shown that no correlation exists between meniscus height and Schirmer test. With a lid margin scarred by staphylococcal disease, ocular rosacea, or allergic disease, the tear wedge can be particularly difficult to assess quantitatively. There may be redundant bulbar conjunctiva in these diseases which also adds to the problem of assessment.

*Corneal staining with fluorescein and rose Bengal.* This is a feature of the established dry eye, but it also occurs in staphylococcal disease, ocular rosacea, allergic disease, and other disease entities. It is therefore of little use in differential diagnosis, although the precise pattern and distribution of staining may be of value in determining the cause.

*Filamentary keratitis.* Wright has reviewed the many causes of filamentary keratitis.<sup>20</sup> Filamentary keratitis is typically associated with keratoconjunctivitis sicca, but it is not specific to the disease. Filaments in the presence of a dubious reduction in tear flow raise great problems in the differential diagnosis.

*Schirmer's I test.* This is one of the 2 classical tests for the dry eye and for most clinicians is often

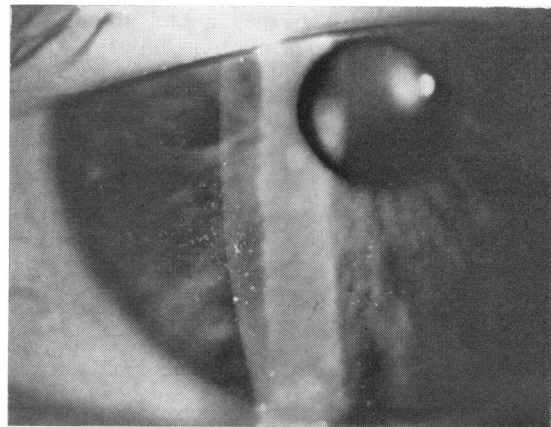


Fig. 1 *Particulate matter in the tear film.*

the crucial test which decides future management. Shapiro and Merin,<sup>21</sup> using a modified method, found the mean value for 880 healthy eyes of volunteer students to be 33.1 mm in 5 minutes with a standard deviation of 33.2! (our exclamation mark).

Pinschmidt evaluated the Schirmer test.<sup>22</sup> He tested 7 normal females of ages 19 to 41 at weekly intervals for 12 weeks using standardised tear strips. In 72 out of 166 tests results were considered abnormal with less than 15 mm wetting on the strip. He concluded that 'the results were so inconsistent that the value of the test would seem to be very questionable'. There was not a single subject who, if tested once only on one given day, would not have shown deficient tear production. Earlier authors have also questioned the validity of the test.<sup>23-25</sup> The effects of higher temperature and lower humidity in reducing Schirmer values has been noted.<sup>26</sup> The test has been used as a basis for statistical analysis in a drug trial,<sup>27</sup> the results of which were later refuted.<sup>28</sup>

There is much confusion over the performance of the test. The test as described by Schirmer<sup>14,29</sup> involves an open-eye technique, but the standardised strips of Berens and Halberg (Cooper Laboratories Inc., Maine, New Jersey, 07470, USA) include instructions suggesting that the eyes may be closed. We believe that closure may result in a falsely positive result. Hypher has shown that there is no linear relationship between the wetted length of a standard Schirmer paper and the fluid weight in its 5 mm tip after a 5 minute moistening period.<sup>30</sup>

During the last 5 years while we have been working on tear lysozyme we have had referred to us patients diagnosed as having dry eyes on the basis of a positive Schirmer test. Often this test has been recorded as zero or merely a few millimetres. Frequently the test has been performed on a closed eye but, apart from this some as yet unexplained physical factor has intervened to stop the flow of tears over the lid margin into the strip proper. We have repeatedly been able to demonstrate quite copious flow in some of these patients. We have introduced a modification to the Schirmer I test to overcome this problem which we detail later.

Another technique involves the prior anaesthetisation of the eye, the Schirmer II test. However, it has been shown that the Schirmer test with anaesthesia cannot differentiate between basic and reflex tear secretion.<sup>31</sup> We believe that there is an element of reflex secretion in every Schirmer I test performed.

*Xerostomia (dry mouth).* Here again the diagnosis can be difficult. It is based on measurement of stimulated parotid gland flow (normal rate >0.1 ml/gland/minute) and labial salivary gland biopsy.<sup>32</sup>

Despite statements to the contrary,<sup>32</sup> Sjögren's syndrome can be a dry mouth and rheumatoid arthritis *without* an apparently dry eye. It can be considered to exist if any 2 of these 3 components are present clinically, although all 3 components are usually present on histological study.<sup>33</sup>

## Patients and methods

### NORMAL EYES

Schirmer's strip test was performed on 41 people with normal eyes. The 5 mm top end of the strip was folded over at 90° and placed in the lower conjunctival sac of the open eye. It was left in place for 5 minutes or until 30 mm of the strip was wetted. *If tear fluid failed to diffuse over the lid margin along the strip within 2 minutes, it was moved to another site within the sac and timing was recommenced.* This is a modification of the Schirmer I test, which we introduced to obviate false positive results. The strip was removed from the eye after 5 minutes and the wetted portion was measured.

The concentration of tear lysozyme, in units per microlitre, was measured in 255 eyes of 128 people, aged 20 to 86. Eighty-six people were tested by our direct method<sup>34</sup> and 42 by our indirect method.<sup>35</sup> The results for the 2 methods have been shown to be directly comparable.<sup>35</sup> Each result was divided by the value of the critical lower limit, to express the lysozyme concentration as the tear lysozyme ratio (TLR).

### PATIENTS

Two groups of patients were studied as detailed below. All patients were subjected to an external eye examination. Schirmer's test was performed on 69 eyes of 35 of these patients and tear lysozyme was estimated in all patients.

*Groups not suspected of having dry eyes.* (a) Twenty patients with autoimmune disease and positive antinuclear factor or rheumatoid factor tests. (b) Twenty-three patients with various external eye diseases not normally associated with dryness.

*Groups suspected of having dry eyes.* (a) Thirty-eight patients with questionably dry eyes. (b) Thirty patients with keratoconjunctivitis sicca without doubt. Three patients were additionally studied who each complained of a dry mouth and sore eyes.

## Results

### NORMAL EYES

The mean TLR was 2.25 with 95% confidence limits of 2.1 to 2.4. The normal range (mean  $\pm$  2 standard deviations) for the TLR was 1.05 to 4.75.

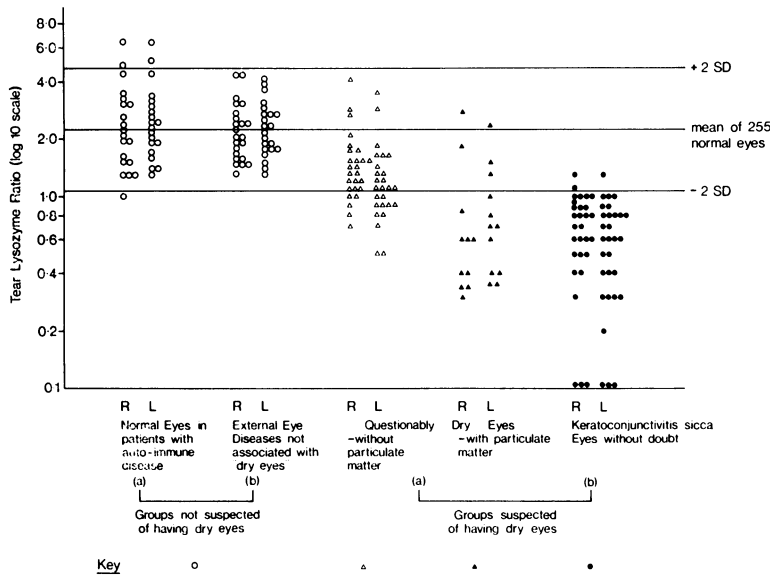


Fig. 2 Tear lysozyme concentration (TLR) results for each group of patients.

These results are shown on a logarithmic scale (base 10) in Fig. 2. Values less than 1.0 were significantly low, with a probability of  $<0.025$ . The Schirmer I test results are shown in Fig. 3. A normal range (mean  $\pm 2$  standard deviations) of 6 to  $>30$  mm was established. Values less than 6 mm were significantly low, with a probability of  $<0.025$ .

dry eyes. Its presence was associated with low lysozyme secretion (see below).

**Tear lysozyme concentration.** Patients in groups (a) and (b) not suspected of having dry eyes had normal TLRs with means of 2.37 and 2.23 and with normal ranges (Fig. 2).

Patients with questionably dry eyes had significantly reduced mean TLRs of 1.27 ( $p < 0.001$ ) for those without particulate matter and 0.77 ( $p < 0.001$ ) for those with particulate matter. The reduction in those patients with particulate matter was significantly

PATIENTS

**Particulate matter in the tear film.** Particulate matter in the tear film was seen in 23 out of 75 questionably

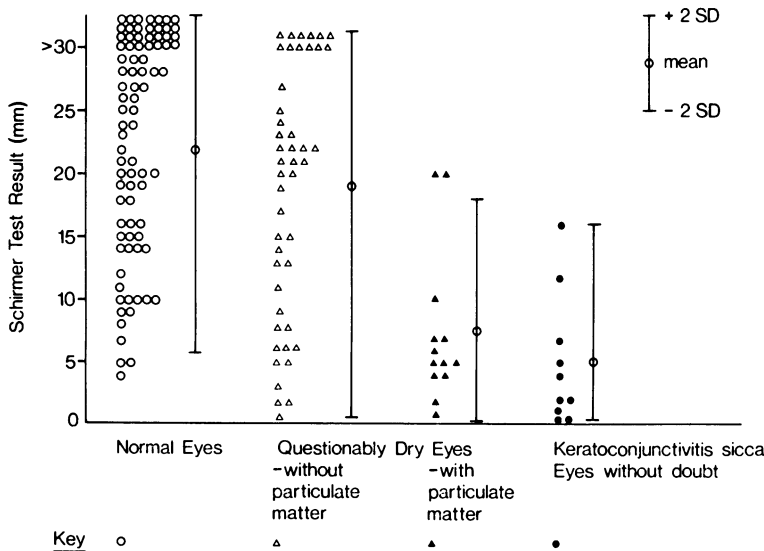
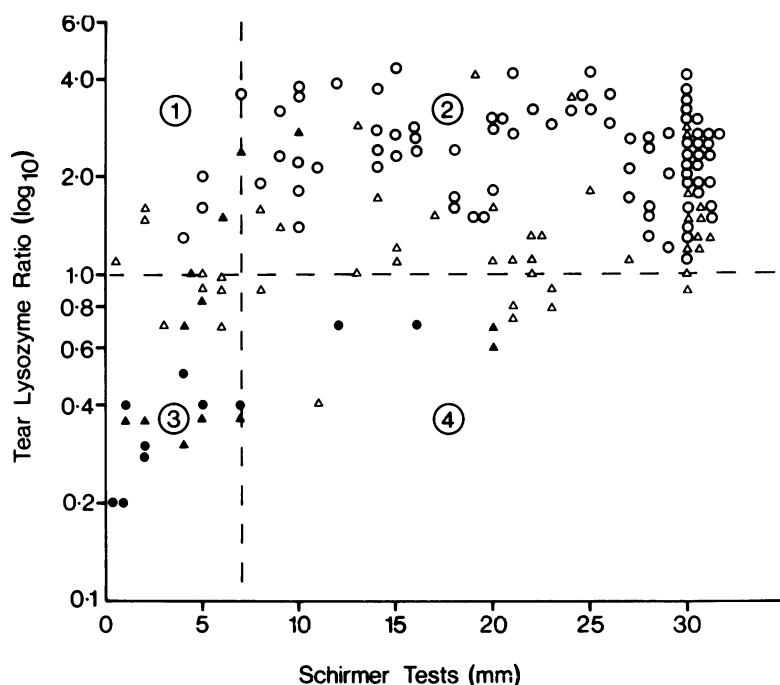


Fig. 3 Schirmer test results for each group of patients.

Fig. 4 Comparison between tear lysozyme concentration and Schirmer test results.



**Key**      ○ = Normal eye                      △ = Questionably dry eye without particulate matter  
              ● = Keratoconjunctivitis sicca eye      ▲ = Questionably dry eye with particulate matter

① Normal Lysozyme - Low Schirmer      ③ Low Lysozyme - Low Schirmer  
 ② Normal " - Normal "                      ④ Low " - Normal "

greater than in those patients without ( $p < 0.001$ ).

Patients with keratoconjunctivitis sicca without doubt had a significantly reduced mean TLR value of 0.52 ( $p < 0.001$ ).

**Schirmer tests.** Patients with questionably dry eyes without particulate matter had a mean value of 19 mm, which was not significantly reduced. Such patients with particulate matter had a mean value of 7 mm, which was significantly low ( $p < 0.001$ ). The results are given in Fig. 3.

Patients with keratoconjunctivitis sicca without doubt had a significantly reduced mean value of 5 mm ( $p < 0.001$ ).

**Correlation between tear lysozyme concentration and Schirmer test.** Comparison of tear lysozyme concentrations and Schirmer tests performed at the same examination are shown in Fig. 4, both for the normal eyes and for the dry or questionably dry eyes. The statistics are given in Table 1.

There was no significant correlation between the Schirmer test and the tear lysozyme concentration

in normal eyes, while there was good correlation ( $p < 0.01$ ) for undoubted keratoconjunctivitis sicca. Correlation thus occurs when the tear fluid has diffused not further than 15 mm along the Schirmer strip.

Table 1 Correlation between tear lysozyme ratios and Schirmer tests for clinical groups

Clinical group	Total numbers	Correlation coefficient (r)	Significance level
Normal eyes	82	0.14	NS
Keratoconjunctivitis sicca without doubt	10	0.86	0.01
Questionably dry eyes: without particulate matter	46	0.27	NS
with particulate matter	11*	0.70	0.02
All groups with Schirmer values:			
between 0 and 15 mm	59	0.63	0.001
between 16 and 30 mm	92	0.13	NS

\*2 aberrant points of (0.7/20) and (0.6/20) omitted. NS = Not significant.

The correlation coefficient for all eyes within the Schirmer strip range of 0 to 15 mm was 0.63 ( $p < 0.001$ ). By linear regression within this range the Schirmer result of 7 mm was equivalent to the TLR of 1.0. Since a TLR of 1.0 was the lowest limit of normality, this supported our previous findings that the *lowest normal limit of the Schirmer test (with our modification) should be considered as 6 mm*.

Schirmer tests of 0 to 6 mm were associated with low TLRs; they occurred in patients with known or suspected sicca. However, 3 normal eyes and 4 questionably dry eyes, of which one had particulate matter, gave low Schirmer results ( $< 6$  mm) and normal TLRs. In some instances where there is a reduced tear flow a reduced secretion of lysozyme may produce an apparently 'normal' concentration, indicating that *tear flow and tear lysozyme are not necessarily interrelated*.

Schirmer tests of 16 to 30 mm did not correlate with the tear lysozyme concentration. They reflected a normal flow of tear fluid with a normal or moderately low lysozyme concentration. A low tear lysozyme result in the presence of adequate tear flow occurred in 1 eye of a patient with keratoconjunctivitis sicca, 2 eyes of patients with questionable dryness and particulate matter, and 5 eyes of similar patients without particulate matter. These results were probably due to reduced secretion of lysozyme in a normal tear flow and represent an early sign of lacrimal gland dysfunction in the patient with

objective signs of a dry eye. This accords with our findings in patients on practolol.<sup>36</sup>

Table 2 shows the results of Schirmer tests in patients with moderate and severe tear lysozyme depletion. TLRs of 0.5 or less (severely depleted) were associated with low Schirmer tests of less than 7 mm. TLRs of 0.9–0.6 (moderately depleted) were associated with Schirmer tests of 0 to  $> 30$  mm; 11 out of 17 patients had values  $> 7$  mm. Normal lysozyme results were associated with Schirmer tests of 3 to  $> 30$  mm confirming that while the Schirmer test is of value in *detecting the eye with severely depleted lysozyme secretion, it is unreliable for detecting the eye with moderately depleted lysozyme secretion*.

*Xerostomia*. Table 3 shows the laboratory results obtained. All 3 patients had unequivocal evidence of xerostomia, but had a normal tear lysozyme concentration. All 3 patients had normal eyes on external examination, with no evidence of keratoconjunctivitis sicca. *These findings confirm that patients can have xerostomia in the absence of dry eyes*.

## Discussion

The description of an ocular adverse reaction to practolol<sup>37</sup> was followed by sporadic reports of eye symptoms and signs in response to beta blocker and other drugs, and an increased interest in the effects of drugs generally upon the lacrimal gland.

Table 2 Values of Schirmer tests for tear lysozyme concentrations

Tear lysozyme concentration (TLR)	Total numbers	Schirmer I test (modified)			
		Mean value	Standard deviation	95% Confidence limits	
				Mean	Range
4.7–1.0 (normal)	120	21	9.1	19–23	3– $> 30$
0.9–0.6 (moderately depleted)	18	13	8.7	9–17	0– $> 30$
0.5–0.2 (severely depleted)	12*	3	2.4	2–4	0–6

\*1 aberrant point of (0.4/11) omitted.

Table 3 Results of patients investigated for xerostomia and dry eyes

	Parotid gland flow (ml/gland/min)	Labial salivary gland biopsy	TLR	
			Right	Left
Patient 1	0.06	Chronic inflammatory cell infiltrate—grade 4	1.3	1.6
Patient 2	0.04	Chronic inflammatory cell infiltrate—grade 4	2.4	2.6
Patient 3	$< 0.01$	Chronic inflammatory cell infiltrate—grade 4	3.3	3.4
Normal range	$> 0.10$	Grade 1 and 2	4.8 to 1.0	

The questionably dry eye is by implication not a severely dry eye, but it is an eye which may have a moderately reduced tear flow and there may be a moderately reduced tear lysozyme content. There is doubt about the diagnosis. It was shown by McEwen and Kimura that lysozyme deficiency preceded tear depletion.<sup>38</sup> This may be too simplistic a view. We have attempted to assess the association of tear lysozyme and tear flow volume. Our results for the latter depend on our modified Schirmer I test.

It has always been assumed that the 2 eyes were equally involved in the sicca process and our results for lysozyme concentration have shown correlation between one eye and the other, as in normals.<sup>34</sup> However, occasional cases do occur where there can be a normal lysozyme concentration in one eye and a low, abnormal concentration in the other.

The real problem in the clinical assessment of the questionably dry eye is the differential diagnosis from other conditions. In clinical practice the assessment is not so often between a *dry eye* and *not a dry eye* but between a dry eye and some other ocular pathology, and there is always the possibility that two conditions may coexist.

At the present time the laboratory assessment of the questionably dry eye is best made by the tear lysozyme test. This would appear to relate to lacrimal gland function. Recent work has shown that there is no functional or qualitative difference between the main and accessory lacrimal glands<sup>39</sup> refuting previously expressed ideas of Jones,<sup>40</sup> and supporting the conclusions of Jordan and Baum<sup>31</sup> that there is really no such phenomenon as a basic tear flow. Further work needs to be done on the relationship of the speed of reflex tear production and tear lysozyme concentration.

There are 2 aspects to our results. Firstly, there is the interpretation involved in group studies, and, secondly, the interpretation in the individual patient.

#### GROUP STUDIES

In group studies we compare mean values statistically with those of a normal population. From our present studies a group of patients may be considered to have abnormally low tear lysozyme concentration if their mean tear lysozyme ratio value is less than 2.1 (the mean of normal eyes at its lower 95% confidence limit). It should be noted that our method involves the use of calibrated standards and is therefore independent of temporal and spatial variations. It is of interest that *in one of our group studies* (questionably dry eyes without particulate matter) *we found that the mean Schirmer I test value was normal when the mean tear lysozyme ratio was significantly reduced.*

#### THE INDIVIDUAL PATIENT

In the individual patient we compare values with the lowest expected (at the 95% confidence level) for a normal population. From our present studies we have concluded that an eye can be considered *moderately dry* if the tear lysozyme ratio result is between 0.9 and 0.6 or if the Schirmer I test, as we have modified it, is less than 6 mm.

There have been a small number of patients whose tear lysozyme concentration and Schirmer test value has not correlated. Either the tear lysozyme concentration was normal and the Schirmer test was low or vice versa. None of these patients had keratoconjunctivitis sicca without doubt.

We have also concluded that an eye can be considered *severely dry* if the tear lysozyme ratio is less than 0.5 and the modified Schirmer I test is less than 6 mm. It is of interest to note that 3 of the 23 eyes in this study, which were considered questionably dry with particulate matter on clinical examination, in fact fell within this severely dry category.

In this paper we have been concerned with lysozyme concentration. However, other proteins are present in tear fluid including secretory IgA,<sup>41</sup> other immunoglobulins,<sup>42</sup> complement components,<sup>43</sup> lactoferrin,<sup>44</sup> ceruloplasmin,<sup>45</sup> orosomucoid,<sup>46</sup> and  $\beta$ -lysin.<sup>47</sup> We have initiated an investigation of the concentration of these proteins by the ELISA (enzyme-linked immunoassay) technique. The results will reflect different aspects of lacrimal gland function, and alterations of other proteins may be a more sensitive marker of diminished activity.

We are greatly indebted to Mr Peter Wright, Moorfields Eye Hospital, London EC1. We thank Dr J. S. Greenspan, formerly of the Royal Dental Hospital, London WC1, for his investigation of the patients with xerostomia. We thank Dr D. R. Gamble, Public Health Laboratory, Epsom, for his critical advice, and Dr D. G. Fleck, St George's Hospital, London SW17, for his continued support. We are grateful to Miss P. J. Stoffell for typing the manuscript.

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