

ACETYLCYSTEINE IN KERATO-CONJUNCTIVITIS SICCA*†

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KERATO-CONJUNCTIVITIS sicca is the condition which follows a reduction of secretion by the main and accessory lacrimal glands, and is characterized by interpalpebral staining of the bulbar conjunctiva with rose Bengal, punctate corneal staining with punctate opacities in Bowman's zone, the presence of thick stringy mucous strands in the lower fornices, and corneal filaments, the latter being neither invariable nor pathognomonic.

Kerato-conjunctivitis sicca occurs most commonly as a manifestation of Sjögren's syndrome; it is occasionally seen in sarcoidosis due to infiltration of the lacrimal gland, and is rarely due to congenital absence of tears (*e.g.* the Riley-Day syndrome) or acquired neurogenic lesions of the secretomotor pathways.

Sjögren (1933) described the triad of clinical features (rheumatoid arthritis, xerostomia, and kerato-conjunctivitis sicca) and stated that two of the three should be present. It is now recognized that any of the collagen diseases, but particularly disseminated lupus erythematosus (DLE), may replace rheumatoid arthritis in the triad, and that Sjögren's syndrome forms part of the range of connective tissue disorders associated with the presence of autoantibodies (Morgan and Castleman, 1953; Bain, 1960; Robinson, 1963).

The frequent poor response to treatment of this disorder is indicated by the variety of methods which have been used, including various artificial tear preparations, local steroids, anticoagulants (Stark, 1961), fibrinolysin (Weve, 1928), debridement of the epithelium, radiation (Winters and Asbury, 1956), systemic hydroxychloroquine (Heaton, 1963), tarsorrhaphy, and contact lenses, while occlusion of the puncta certainly helps to conserve any lacrimal secretion which may be formed. Duke-Elder and Leigh (1965) have concluded that "in the majority of such cases the ophthalmologist is reduced to the expedient of judicious but impotent expectancy".

The best available artificial tear preparation appears to be a solution of carboxymethyl-cellulose at pH 8.5, with added sodium bicarbonate and sodium chloride as devised by Jones and Coop (1965), and this is the standard tear substitute used here.

Jones and Coop also reported encouraging results in fifteen patients with kerato-conjunctivitis sicca treated with the mucolytic agent acetylcysteine.

N-acetyl-L-cysteine is a derivative of the amino-acid L-cysteine and is widely used to reduce the viscosity of mucus in a variety of broncho-pulmonary disorders (Webb, 1962).

This reduction in viscosity is achieved by the reducing action of the free sulphhydryl group in the molecule on the disulphide bonds of the mucoproteins present in mucus.

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This paper describes a double-blind cross-over trial comparing acetylcysteine with artificial tears, and the results are discussed in the context of the pathogenesis of the corneal changes.

Material and Methods

At a preliminary examination 37 patients with the diagnosis of keratoconjunctivitis sicca were seen. Four patients had a Schirmer's test result greater than 10 mm. in 5 minutes in each eye, and one had no conjunctival or corneal staining despite evidence of diminished lacrimal secretion. These patients were therefore excluded from the trial, as were two who were unable to attend, leaving thirty patients to be studied. There were 29 women (96 per cent.) and one man (4 per cent.), and their ages ranged from 43 to 77 years (mean 64).

The distribution of systemic disease in these patients is shown in the Table. The duration of the rheumatoid arthritis in the 22 patients with this disease (73 per cent.) ranged from 6 months to 44 years (mean 21). Eighteen of these (82 per cent.) had a dry mouth, which had preceded the ocular symptoms in three cases, followed the ocular symptoms in ten cases, and occurred simultaneously in five cases.

TABLE
DISTRIBUTION OF SYSTEMIC DISEASE IN THIRTY PATIENTS WITH KERATO-CONJUNCTIVITIS SICCA

	Systemic Disease	No. of Cases
Rheumatoid Arthritis	Rheumatoid arthritis alone	18
	Rheumatoid arthritis + DLE	2
	Rheumatoid arthritis + Myasthenia gravis	1
	Felty's syndrome	1
	Total	22
Anaemia and xerostomia		1
Nil apparent except xerostomia		4
Total with Sjögren's syndrome		27
Psoriasis (no xerostomia or arthritis)		1
Nil apparent and no xerostomia		1
Sarcoidosis of salivary and lacrimal glands		1
Total other than Sjögren's syndrome		3

The duration of ocular symptoms ranged from 1½ to 20 years (mean 7.2); the three commonest symptoms were burning, grittiness, irritation or soreness, present in all but one of the patients (96 per cent.), dryness present in 22 patients (73 per cent.) and photophobia present in sixteen patients (53 per cent.).

At the first examination, the presence or absence of conjunctival staining was noted, mucous shreds, filaments, and corneal staining, as determined by slit-lamp examination following staining with rose Bengal 1 per cent. and fluorescein 1 per cent.

Trial drops, either artificial tears or a 20 per cent. solution of acetylcysteine adjusted to pH 7.0, were dispensed in identical drop bottles for use 2-hrly in each eye. They were allocated at random by a standard method, the key being known only to the dispenser, so that neither patient nor observer knew the identity of the drops.

Although acetylcysteine reacts with rubber, there is no noticeable hardening of the rubber teat after one month, and the solution does not significantly deteriorate over this period, therefore, the drops were dispensed as usual in glass bottles with rubber teats.

The patients were seen at monthly intervals by one of us. They were asked whether their eyes felt better, worse, or the same as at the previous visit, but requested not to give any other information. The slit-lamp observations were repeated, and these subjective and objective findings were recorded on the trial card. After 2 months, each patient was issued with the alternative preparation by the dispenser, and was seen twice more at monthly intervals, the trial then being complete.

RESULTS

Seventeen patients started with artificial tears and thirteen with acetylcysteine. The subjective and objective findings in these two groups are compared in Fig. 1, which also shows the previous treatment received. When comparison is made between those patients who improved and those who were the same or worse, the objective findings in the acetylcysteine group are significantly better than those in the artificial tear group ($P = 0.028$, Fisher's exact method of probability). The subjective findings show no significant difference.

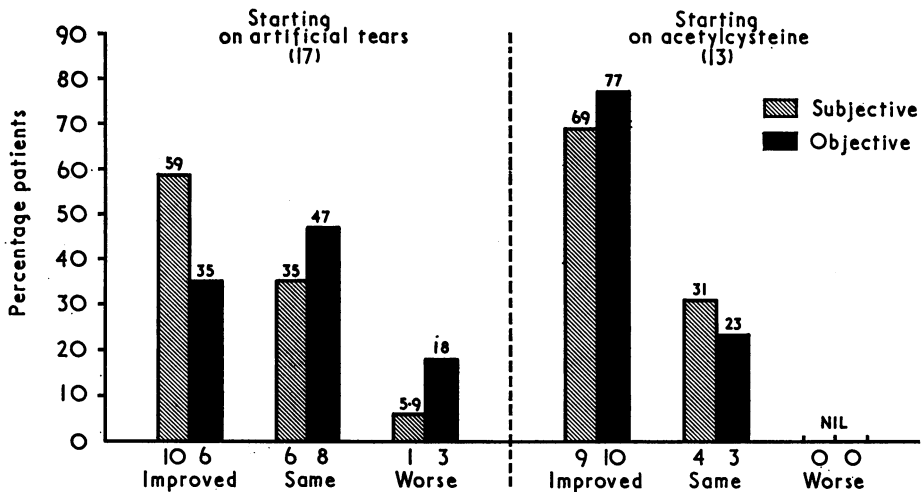


FIG 1.—Results in 30 patients.

Previous Treatment	No.	Previous Treatment	No.
Artificial tears p.r.n. four times a day	6	Artificial tears p.r.n. four times a day	7
- plus occlusion of puncta	2	- plus local steroids	3
- plus local steroids	2	- plus occlusion of puncta	2
Oc. Chloromycetin three times a day	1	Gutt. pilocarpine 2 per cent. three times a day	1
Nil	6	Nil	0

Fig. 2 (opposite) shows the results in twelve patients crossing from acetylcysteine to artificial tears and fifteen patients crossing from artificial tears to acetylcysteine. When comparison is again made between those who improved and those who were the same or worse, the objective findings show a significantly better result with acetylcysteine ($P = 0.00156$). The subjective difference between the two groups is not significant ($P = 0.182$).

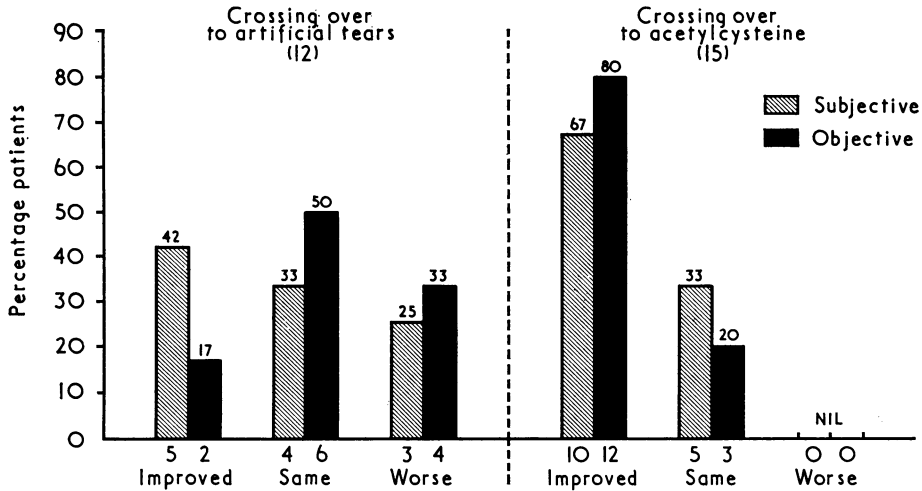


FIG. 2.—Results in 27 patients.

Fig. 3 shows the results in Figs 1 and 2 added together. The superior effect of acetylcysteine is highly significant for the objective findings ($P = 0.00013$). The subjective difference between the two groups is not significant ($P = 0.166$).

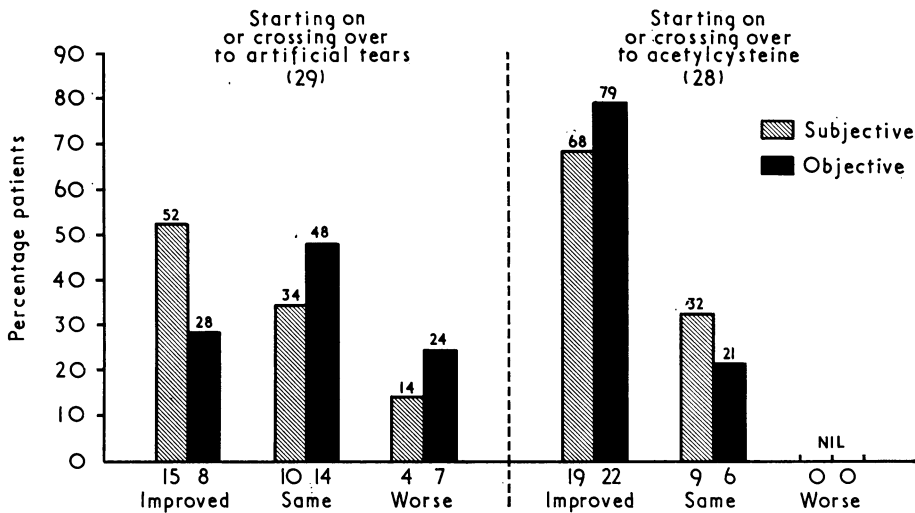


FIG. 3.—Results in 57 patients

Filaments

21 patients had filaments at some time during the trial, and none had filaments without the presence of mucous shreds. Nine patients had no filaments at any time during the trial, and three of these had no mucous shreds either.

The mean Schirmer's test result (mm. in 5 min.) for the nine patients with no filaments was R.5 L.4, and for the 21 patients with filaments it was R.4 L.3, showing no significant difference.

In all, ten patients commencing treatment with artificial tears had filaments (nine initially and one on crossing over from acetylcysteine); the filaments disappeared in three of these ten patients.

Sixteen patients commencing treatment with acetylcysteine had filaments (eight initially and eight on crossing over from artificial tears); the filaments disappeared in fifteen of these sixteen patients.

Eleven patients commencing treatment with artificial tears had no filaments (three initially and eight on crossing over from acetylcysteine); six of the eleven developed filaments while on artificial tears.

Four patients commencing treatment with acetylcysteine had no filaments (one initially and three on crossing over from artificial tears); two of them developed filaments while on acetylcysteine (noted on one occasion and in one eye only).

Discussion

Analysis of Figures

The trial was designed to compare the response to artificial tears and acetylcysteine, and Fig. 2 shows the direct comparison. The objective findings show a significantly better performance by acetylcysteine. The non-significance of the subjective findings was not unexpected, and is explained by analysis of the individual patients. Thus, five patients were subjectively better on crossing to artificial tears (Fig. 2), but four of them were in fact the same objectively, and one was actually worse objectively.

It is believed that this poor correlation between subjective and objective assessments is due to the fact that the artificial tears sting less on instillation into the conjunctival sac than acetylcysteine, and although the patients were asked specifically whether their eyes felt better, worse, or the same, *not* which drops were most comfortable to use, some were unable to separate these two aspects.

The reverse effect is found on examining the cross-over to acetylcysteine. Thus ten patients were subjectively better on crossing to acetylcysteine (Fig. 2) and seven of these were objectively better, three being objectively the same. But all of the five patients who were the same subjectively on crossing to acetylcysteine were in fact better objectively. Here again, the patients were probably unable to separate comfort in using the drops from the overall state of their eyes.

It can be argued that the five patients better subjectively on crossing to artificial tears (Fig. 2) must have been worse on acetylcysteine, and that the two patients better objectively must have been worse on acetylcysteine. This means that different results are obtained depending on whether the patient received acetylcysteine first or second. This argument has been disposed of as far as the subjective findings are concerned.

As far as the objective improvement of two patients on crossing to artificial tears is concerned, this could be due to a "carry over" effect of acetylcysteine (which may indeed occur, Jones and Coop, 1965); to natural fluctuation in the disease, or to observer error.

Fig. 1 shows an indirect comparison between artificial tears and acetylcysteine, comparing each with the patients' previous treatment. The two groups were roughly comparable as regards the clinical condition. Thus, of the 21 patients with filaments, twelve started on artificial tears and nine on acetylcysteine, while of the nine patients without filaments, five started on artificial tears and four started on acetylcysteine.

It will be noted that there is a bias in favour of artificial tears as regards the previous treatment, six patients having had none, while all the acetylcysteine group had had some previous treatment.

Despite this, the objective findings show a significantly better performance by acetylcysteine.

The subjective findings are not significant, and this may be due to two factors:

(a) Six patients who started on artificial tears had had no previous treatment, and this produced a poor correlation between subjective and objective findings in individual patients.

(b) The factor of discomfort in actual use of acetylcysteine may have been operating here too since, of the four patients who were the same subjectively on acetylcysteine (Fig. 1), three were in fact improved objectively.

It is concluded, therefore, that treatment with acetylcysteine produced on the whole significantly better objective results than treatment with artificial tears, both when making a direct comparison (Fig. 2) and when making an indirect comparison, comparing each form of treatment with that given previously (Fig. 1). These findings are combined in Fig. 3.

Pathogenesis of corneal changes

The role of mucus is important in the pathogenesis of the corneal changes in kerato-conjunctivitis sicca. There is an increased number of goblet cells in the conjunctiva, so that the amount of mucus secreted is greater than normal. Since it is unable to be dissolved in the deficient or absent lacrimal secretion, the mucus collects as shreds in the lower fornix, as well as rendering the abnormal tear film (consisting largely of Meibomian secretion and mucus) more viscous than usual (Klein, 1949).

The mucous layer of the normal tear film is firmly adherent to the cornea (Fischer, 1928), and this is accentuated under the abnormal conditions present in this disease.

Hess (1892) and Nuel (1892, 1893) stated that the filaments spring from a triangular elevation of epithelium which, as a result of elongation and torsion, evolves into a spiral of progressively more degenerate cells, enclosing a homogeneous core of mucus, while adjacent corneal epithelial cells showed degenerative changes. de Haas (1962) believed that a metabolic disturbance of the epithelial cells was an additional factor in most cases, and Weskamp (1956) described an eruption of gelatinous degenerated stromal material carrying epithelial cells with it.

Jones and Coop (1965) confirmed the findings of Norn (1962, 1963) that the filaments stained intensely with the mucin-specific dye Alcian blue, and stated that they seemed to consist largely of mucin.

There seems to be little doubt, therefore, that the corneal changes in kerato-conjunctivitis sicca are brought about by the interaction of the abnormally tenacious mucus with an already diseased cornea, a process facilitated by the frequent blinking due to the irritation and photophobia so common in this condition.

The known corneal manifestations of collagen diseases in patients with normal lacrimal secretion suggest that the epithelial and stromal degenerative changes are due at least in part to the systemic disease and not entirely to the lack of tears *per se*.

The importance of mucus in the pathogenesis of filaments is borne out by the fact that, although six patients in this study had mucous shreds but no filaments, not one patient had filaments in the absence of mucous shreds.

Further evidence for this important role of mucus is provided by the encouraging results of treatment with the specific mucolytic agent acetylcysteine. On the whole, acetylcysteine achieved a significantly greater improvement objectively than artificial tears, as judged by conjunctival and corneal staining, mucous shreds, and filaments. The fact that different results were obtained depending on whether acetylcysteine was given first or second could be attributed to a carry-over effect of acetylcysteine.

Investigations are now being carried out to decide the best composition of the solution of acetylcysteine in an effort to find a preparation which is more comfortable for the patient to use.

Summary

A comparison has been made of the treatment with artificial tears and N-acetyl-L-cysteine of thirty patients with kerato-conjunctivitis sicca by means of a double-blind cross-over trial. The features of the disease and methods of treatment are briefly described, and the pathogenesis of the corneal changes is discussed. The conclusion that treatment with the mucolytic agent acetylcysteine on the whole produced significantly better objective results than treatment with artificial tears, emphasizes the importance of the role of mucus in the production of the corneal changes.

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