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Adenovirus type 8 keratoconjunctivitis – an outbreak and its treatment with topical human fibroblast interferon

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SUMMARY

An outbreak of keratoconjunctivitis is described which involved at least 186 people; adenovirus type 8 was identified in 50 of the cases. Topical human fibroblast interferon was assessed in a double-blind, placebo-controlled study in which 34 patients participated. Seventeen of the 34 trial patients yielded adenovirus type 8; three were infected with adenovirus type 7. The outbreak was curtailed by control of infection measures: principally careful hand-washing by medical personnel between cases and by discouraging attendance of new cases at the Eye Infirmary. Consequently the trial numbers are small. In addition there was a wide interpatient variation in the severity of infection. Therefore it was not possible to make any statistically valid conclusions concerning the recovery rate of patients receiving interferon or placebo.

INTRODUCTION

In 1889 Fuchs described the clinical features of a severe keratoconjunctivitis, which was later attributed to a virus by Wright in 1930. The term 'epidemic kerato-conjunctivitis' (EKC) was coined by Hogan & Crawford (1942), who studied a large outbreak involving shipyard workers in the United States. Identification of the principal causative agent, adenovirus type 8, was achieved later by Jawetz and others in 1955 (Jawetz *et al.* 1955; Jawetz, 1959).

More recently, several outbreaks of EKC have been described in hospital ophthalmic departments, where spread has been attributed to inadequate hand-washing, inadequate disinfection of applanation tonometers and gonioscopes, and use of multidose containers of ocular preparations (Barnard *et al.* 1973; Patrick & Matthews, 1981; Anon, 1983; Richmond *et al.* 1984). Subsequent transfer of

infection has occurred to involve household contacts and patients in peripheral hospitals. The experience of the ophthalmologists and virologists in Bristol following their outbreak in 1971 was to prove invaluable in controlling a similar outbreak in Plymouth 12 years later.

Account of outbreak

On 28 November 1983 adenovirus type 8 was isolated by the Department of Virology, Bristol Public Health Laboratory, from a conjunctival swab taken on 18 November from a 65-year-old lady who had first attended the Royal Eye Infirmary (REI), Plymouth, on 4 November for removal of a concretion after which she developed a red eye. A review of the attendance register in the casualty department and discussions with the ophthalmologists disclosed that there had been an increase in November in the number of attendances at the REI due to follicular conjunctivitis. However a viral aetiology could not be established at that time. Bacterial cultures had been negative.

By the end of November 1983 at least 30 patients and one doctor had been identified as suffering from EKC. They ranged in age from 14 to 81 years. Viral cultures subsequently confirmed the aetiology as adenovirus type 8 in 15 cases and a further case of adenovirus infection was established in a patient with typical symptoms in October by a diagnostic rise in the adenovirus complement fixation titre. This was undoubtedly an underestimate of the exact number of patients involved in the early part of the outbreak, but in the absence of viral cultures the true extent could not be determined.

On 2 December 1983 two further cases of adenovirus type 8 keratoconjunctivitis were confirmed, the first in a 2-year-old girl and the second in a senior house officer at the REI who acquired the infection only 3 days after commencing her appointment in Plymouth – there had been no cases at her previous hospital.

Once the outbreak was recognized, prospective documentation of all new cases was instituted, virus isolation was attempted from all suspected cases of EKC and a double-blind, placebo-controlled trial of human fibroblast interferon eye-drops was set up from 2 December 1983. Strict attention was paid to limiting the spread of infection within the REI.

During December 1983 52 new cases of EKC were identified, from 21 of whom adenovirus type 8 was subsequently isolated. Three were infected with adenovirus type 7. A further 16 cases of EKC occurred in January 1984, of whom 5 were due to adenovirus type 8. Thirty-four of these cases were entered in the interferon study. By the end of January 1984 the outbreak appeared to be declining and the interferon study was discontinued. However a second wave of type 8 infections followed in March and April, bringing the total number of cases of EKC in the entire outbreak to 186, of whom 50 were identified as adenovirus type 8 (Table 1 and Figure 1). There were no further cases after the first week of April 1984.

Virus isolation and serology

Conjunctival swabs were taken for virus isolation from the lower fornix of each eye, placed in antibiotic-containing milk-saline transport medium and posted to the Department of Virology, Bristol Public Health Laboratory, where they usually arrived within 24 h. On receipt they were inoculated into primary or secondary

Table 1. *Monthly distributions of cases of* EKC *and method of diagnosis of those cases specifically due to adenovirus*

Month	Number of cases of EKC	Diagnosis: Adenovirus type 8 isolated	Diagnosis: By serology (rising titre) CFT	Diagnosis: By serology (rising titre) HAI
October 1983	2	0	1	0
November 1983	29	15	0	0
December 1983	52	21 (3 type 7)	9	11
January 1984	16	5	1	1
February 1984	14	0 (1 type 3)	0	0
March 1984	50	8 (2 type 7, 1 type 3)	0	0
April 1984	23	1 (2 type 3)	0	0
Total	186	50		

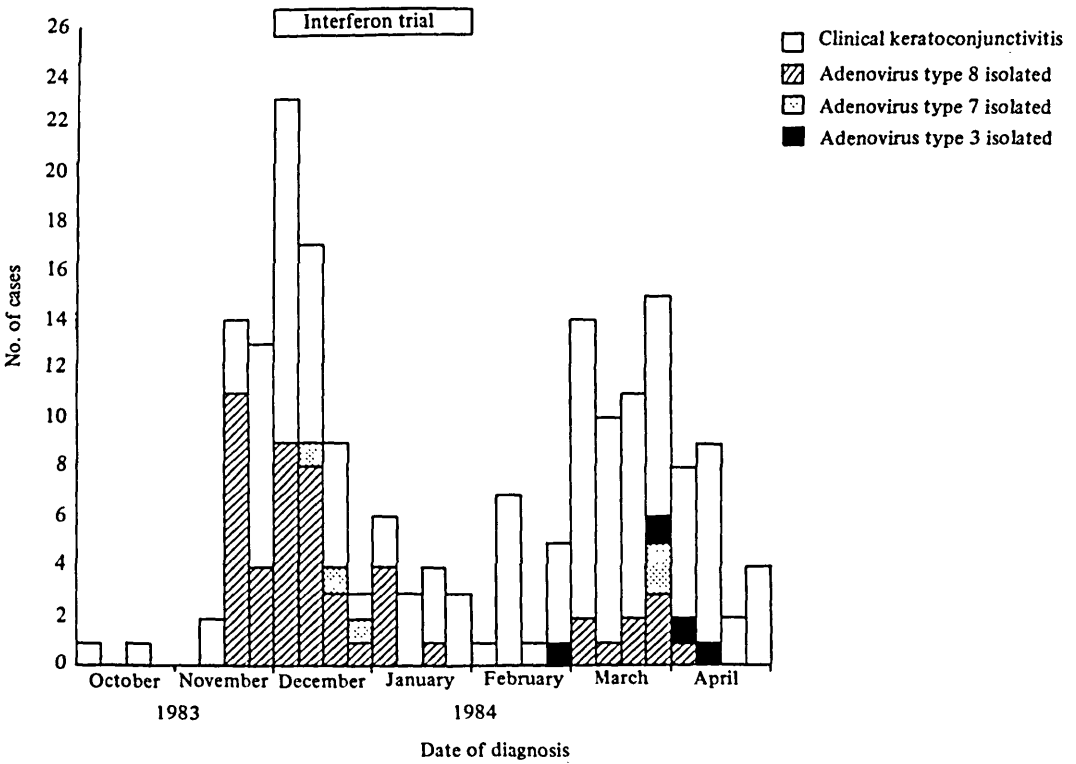

Fig. 1. Temporal analysis of the adenovirus type 8 outbreak.

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human embryo kidney cell cultures (HEK) and into the continuous human embryo kidney-derived cell line 293 (Graham *et al.* 1977), which has been shown to be sensitive to a variety of ocular adenoviruses including type 8 (Yirrell *et al.* 1983).

Identification of adenoviruses was by solid phase immune electron microscopy using the protein A capture method (SPIEM) (Svensson & von Bonsdorff, 1982). This technique does not differentiate well between types 7 and 11 and viruses typing as 7 had their identity confirmed by standard neutralization techniques.

Serological studies were not carried out on sporadic cases of EKC, but sera collected from patients in the interferon study were tested for adenovirus type 8 antibody by the type specific adenovirus haemagglutination inhibition test (Bell, Martin & Ross 1969). No additional information was gained from complement fixation test results.

Measures to control outbreak

On 30 November 1983 a meeting of ophthalmologists, microbiologists, senior nursing staff and a specialist in community medicine was convened at the REI, at which appropriate control measures were decided. It was noted that the treatment area in the casualty department comprised a small unventilated room with a single wash-hand basin. Up to that time almost all the infected patients had been examined in this room by each of the four senior house officers. Limitation of space within the REI (which is on a separate site from the other Plymouth hospitals) precluded the allocation of an examination room exclusively for new cases and follow-up of established infected cases. Nevertheless, it was agreed that where possible infected patients should be examined at the end of a session.

All medical and nursing staff were encouraged to pay particular attention to hand-washing, using either soap and water or chlorhexidine between patients. This was preferred by the ophthalmologists to wearing gloves or finger-stalls. It was noted that single-use fluorescein strips and minim preparations of mydriatics were already in regular use at the hospital. Review of earlier cases had established that in no case had tonometry been performed. This seemed to preclude applanation tonometers as a vehicle of the infection. Nevertheless, the established practice of leaving the tonometer prisms soaking for variable periods of time in 'Cetavlon' was deprecated, and all staff were instructed to soak prisms henceforth in Chloramine-T.

The Medical Officer of Environmental Health circulated a letter to all GPs served by the REI informing them of the outbreak and summarizing the clinical details of EKC. Basic principles to limit spread of infection in the home were outlined. It was anticipated that such guidance would limit the attendance of new uncomplicated cases to the REI, but no attempt was made to close the casualty department, lest this might deter patients from attending for the removal of coincidental foreign bodies or for other serious ophthalmological complications. Nevertheless, it had the effect of limiting the number of entrants to the interferon trial.

The consultant in charge of the contact lens clinic deferred all further attenders to his clinic for the duration of the outbreak.

Interferon trial

Patients and methods

From 2 December 1983 all patients presenting with a follicular conjunctivitis of recent onset (symptoms for less than 7 days) were included in the trial. Patients were excluded if they were under 16 years of age, pregnant, currently receiving steroids, antiviral agents or oral antibiotics, or if they had other viral or systemic diseases. Those patients who had been applying topical ocular antibiotic preparations for more than 7 days were also excluded.

All patients included in the trial were required to give their informed consent in writing. Pertinent clinical details were recorded including occupation, contact with other cases of 'red eyes', ocular trauma, previous attendance at the REI and drug treatment. The date of onset and severity of the following symptoms were recorded using a subjective scale from 0 to 5: soreness, epiphora, stickiness, grittiness (conjunctival symptoms) and photophobia as evidence of corneal involvement. Slit-lamp examination of the affected eyes was performed in the casualty department by B.J.D., K.M.N., A.M.D.'S. or N.T. The following signs and their severity were recorded on an objective scale from 0 to 5: injection, follicles on upper lid, follicles on lower lid, papillae and haemorrhages (conjunctival signs) and the presence of corneal opacities and staining was similarly scored. Visual acuity was recorded for each eye.

Conjunctival swabs were taken from each eye, venous blood collected for adenovirus serology (at Bristol) and standard toxicological tests (at Plymouth), and a mid-stream urine specimen was tested for the presence of glucose and protein.

Treatment packs comprising either interferon or placebo and labelled according to a random code were provided by Serono Laboratories, Welwyn Garden City, UK. Each pack consisted of eight vials; four contained the freeze-dried interferon or placebo and the other four vials contained diluent. Each of the 'active' vials contained 1×10^6 i.u. human fibroblast interferon, which was reconstituted with 2 ml diluent. The placebo consisted of the excipients only and was reconstituted in an identical manner. The freeze-dried preparations were stored at 4 °C prior to use. As each patient was entered into the trial, the preparations were reconstituted by either the hospital pharmacist or the attending clinician. Each patient was instructed to instil two drops, every 6 h, into the lower fornix of the affected eye – giving a daily dosage of 2×10^5 i.u. Patients were requested to store the reconstituted vials in their domestic refrigerator. Treatment was continued for 10–14 days.

All patients were followed up in the casualty department at twice-weekly intervals, specifically on Monday and Friday afternoons. More frequent visits would have compromised infection control measures. At each attendance, symptoms and signs were scored and visual acuity checked. Conjunctival swabs were repeated. Enquiries were made regarding any local irritation attributed to the drops. If, during treatment for a uniocular infection, a patient developed bilateral keratoconjunctivitis, drops were subsequently instilled into both eyes. Patients who discontinued the treatment prematurely were withdrawn from the trial.

When treatment was completed, a final conjunctival swab was taken and blood

Table 2. *Comparison between adenovirus type 8 isolation and serology*

		Adenovirus type 8 HAI rise*	No HAI rise	Single serum only (or no serum) received
Adenovirus type 8 isolated	17	12	1†	4
Adenovirus type 8 not isolated	14	0	9	5
Adenovirus type 7 isolated	3	0	1	2
Totals	34	12	11	11

* Range of convalescent titres 12–192.
† Only 10 days between acute and convalescent specimens.

collected for toxicological studies and convalescent adenovirus antibody titres. A urine sample was tested for glucose and protein.

An independant observer (F.I.K.F.) undertook detailed slit-lamp examination of 13 patients who successfully completed the trial (7 had received interferon, 6 placebo) on 12 March 1984 to assess residual ocular pathology. Adenovirus serology was repeated at this visit.

Results of interferon trial

Virology and serology

Between 2 December 1983 and 31 January 1984, 34 patients were entered into the study, from 20 of whom adenoviruses were recovered. Subsequent typing showed that 17 belonged to type 8, 3 to type 7; an isolation rate of adenovirus type 8 in the study patients of 50%.

Paired sera were obtained from 13 of the 17 adenovirus type 8 positive patients, from 1 of the 3 adenovirus type 7 patients and from 9 virus culture negative patients. In 12 cases where paired sera were available separated by an adequate time interval (>2 weeks), there was complete concordance between the results of serology and virus isolation (Table 2). All 12 cases from whom adenovirus type 8 was isolated had serological evidence of infection as determined by antibody rise to significant titres by HAI (haemagglutination inhibition). Convalescent titres ranged from 12 to 192. These may be considered significant titres (Richmond *et al.* 1984) since any patient seroconverting to a titre of 8 or more may be regarded as definitely infected. None of the patients in whom virus isolation was negative had such serological evidence. Detailed aspects of virus isolation and serology will be published separately.

A further patient from whom virus was isolated from both eyes had blood taken only once 9 days after the first positive swab. She had a significant HAI titre of 12.

Comparison of treatment groups

Of 34 patients entered into the study, 16 received interferon drops, 18 placebo. The two groups were well matched with regard to age, sex and ocular involvement (Table 3).

Table 3. *Details of patients entered into interferon trial*

	Interferon	Placebo
No. of patients entered into trial	16	18
Age (y)		
Range	18–64	17–59
Mean	31·1	31·9
Sex		
Male	11	11
Female	5	7
Ocular involvement at presentation		
Unilateral	15	15
Bilateral	1	3
Culture positive		
Adenovirus 8	9	8
Adenovirus 7	2	1
Excluded from analysis	5	5
No. patients available for analysis	11	13
Culture positive		
Adenovirus 8	7 (63·6%)	6 (46·1%)
Adenovirus 7	2	1

Five patients in each group were subsequently excluded from the study for the following reasons: lack of compliance (5 cases), presence of symptoms for more than 7 days (4 cases) and development of dendritic ulcer (1 case). This left 11 patients in the interferon group, 13 in the placebo group. Adenovirus was isolated from 9 of the 11 interferon recipients and from 7 of the 13 placebo recipients, but subsequent typing showed a higher isolation rate of type 8 in the interferon group (63·6%) compared with the control group (46·1%). Three patients had adenovirus type 7 keratoconjunctivitis. These were excluded from further analysis in order to eliminate another variable.

Table 4 gives a detailed comparison of the adenovirus type 8 positive patients on presentation in the two treatment groups. As one patient in each group had bilateral infections from the outset, each eye has been assessed separately. Patients in the interferon group had poorer visual acuity on presentation than those receiving placebo: range 6/4 – 6/24 compared with 6/5 for all placebo patients. Imbalance between the two treatment groups was largely due to one patient, a 25-year-old woman who presented with infection of her right eye of 4 days duration. She had the highest scores of all the patients for conjunctival symptoms (15 out of a possible 20), conjunctival signs (18 out of 25) and photophobia (4 out of 5), and the most impaired visual acuity (6/24). Despite receiving interferon, swabs taken on day 5 showed that the left eye had become infected as well as the right. Cultures were negative on day 8, but she continued to have quite severe conjunctival symptoms and signs. With the small number of patients available for analysis, the presence of one patient with such extreme ocular involvement in one of the treatment groups made a valid comparison difficult, but it was not considered justified to exclude her.

Tables 5 and 6 summarize the changes in conjunctival symptoms and signs, and corneal symptoms and signs over 2 weeks of treatment with either interferon or placebo. Patients' conjunctival scores were high at presentation and the response

Table 4. *Comparison between adenovirus type 8 positive treatment groups*

	Interferon	Placebo
No. of eyes treated	8	7
Mean age (y)	27·0	28·2
Sex		
Male	4	3
Female	3	3
Severity scores at presentation		
Conjunctival symptoms (maximum possible = 20)		
Median	9·5	10
Range	5–15	5–11
Conjunctival signs (maximum = 25)		
Median	10·5	10
Range	5–18	5–13
Corneal symptoms (maximum = 5)		
Median	0	1
Range	0–4	0–2
Corneal signs (maximum = 10)		
Median	0	0
Range	0	0
Visual acuity		
Median	6/10·5	6/5
Range	6/4–6/24	all 6/5
Virus shedding	100%	100%

to treatment has been calculated as percentage changes from day 0. In contrast corneal scores were very low at the outset (see Table 4) and therefore response to treatment is more appropriately tabulated as absolute changes in score from day 0. After their initial presentation, patients were seen at the REI only on Mondays and Fridays to limit the spread of infection within the hospital, and it follows that patients were not all seen the same number of days after presentation (day 0). Therefore observations have been grouped by 3-day-time intervals to present the maximum information with the minimum duplication of data.

By chance a few patients in the placebo group were seen 13–15 days after onset, which meant that this group was followed up for a longer time than the interferon group. However the results show that both groups should have been examined for more than 2 weeks to assess fully the clinical response to treatment.

The patients showed a wide range of response of both conjunctival symptons and signs with time after presentation. Taking the median value for each group, patients in the interferon group after initial deterioration appeared to show some clinical improvement in both conjunctival symptoms and signs 7 days after commencing treatment. In contrast, there appeared to be some abatement of symptoms and signs in the placebo group during the first week of their attendance, followed by some deterioration 7–9 days after presentation, although there was a marked improvement by the end of the second week.

The wide range of values for corneal symptoms and signs also made comparison

Table 5. *Interferon trial – scoring of conjunctival symptoms and signs with time*

Treatment group...	Interferon				Placebo				
Total eyes in group...	8				7				
Time interval (from day 0)...	1–3	4–6	7–9	10–12	1–3	4–6	7–9	10–12	13–15
Conjunctival symptoms: % change from day 0*									
Median	+17	+20	−47	−50	−27	−9	+15·5	−55	−100
Range	+83 to 0	+100 to −20	+120 to −92	+40 to −92	+129 to −60	+100 to −40	+22 to −100	−29 to −80	−55 to −100
No. of eyes assessed	6	7	7	5	4	5	4	6	3
Conjunctival signs: % change from day 0*									
Median	+8·5	+2	−30	−22·5	−31	−15	−11	+4	−40
Range	+73 to 0	+112 to −10	+60 to −42	+40 to −50	+20 to −40	+12 to −20	+120 to −29	+240 to −38	−29 to −100
No. of eyes assessed	6	6	7	4	4	5	4	6	3

* Calculated from the formula:

$$\frac{\text{score at time t} - \text{score at time 0}}{\text{score at time 0}} \times 100$$

0, no change; −100%, cure; +100%, twice as bad as original score

Table 6. *Interferon trial – scoring of corneal symptoms and signs with time*

Treatment group...	Interferon				Placebo				
Total eyes in group...	8				7				
Time interval (from day 0)...	1–3	4–6	7–9	10–12	1–3	4–6	7–9	10–12	13–15
Corneal symptoms*: absolute change from day 0									
Median	+0·5	+1	+1	+1	0	+1	0	+2	−0·5
Range	+4 to −3	+3 to −3	+4 to −3	+4 to −1	+1 to 0	+2 to 0	+1 to −1	+4 to 0	+1 to −1
No. of eyes assessed	6	7	7	5	4	5	4	6	4
Corneal signs†: absolute change from day 0									
Median	+1	+1·5	+4	+3·5	0	+1	+2	+3	+3
Range	+4 to 0	+6 to 0	+6 to 0	+8 to 0	all 0	+3 to 0	+4 to 0	+8 to +2	+4 to +2
No. of eyes assessed	6	6	7	4	4	5	4	6	3

0, no change; +, worsening; −, improving.
* Maximum score 5.
† Maximum score 10.

between the groups difficult. As expected corneal pathology became more apparent with time. The long-term sequelae were assessed for some of the trial patients at the follow-up in March.

Analysis of visual acuity was complicated by the unexpected finding of considerable inter-patient variation in visual acuity in the interferon group on presentation. All patients in the placebo group had a visual acuity of 6/5 on presentation. Interferon did not lead to any noticeable improvement compared with placebo.

Table 7 provides a comparison between the duration of viral shedding in both groups. As interferon would be expected to be effective against all types of adenovirus, the adenovirus type 7 patients have been included. Of the 9 patients in the interferon group, 8 presented with unilateral conjunctivitis, 1 had bilateral involvement. In 5 cases the left eye was infected, in 3 the right eye. Three of the unilateral infections subsequently became bilateral. Conjunctival swabs from two patients continued to yield adenovirus type 8 9 days after presentation. Each was negative by day 13.

In comparison 6 patients in the placebo group had uniocular infections on presentation, 1 was bilateral. The right eye was infected in 3, the left eye in 3. Only one of the uniocular infections subsequently became bilateral, although a further patient (F) developed typical symptoms in the right eye 9 days after onset in the left eye, but this could not be virologically confirmed. One patient continued to shed adenovirus type 8 until day 9. He was clear by day 12.

Allowing for the fact that the interferon group contained more seriously affected patients, treatment with interferon did not appear to curtail viral shedding.

Assessment of study patients in March 1984

On 12 March 1984, approximately 3 months since their admission to the study, 13 patients re-attended for follow-up. Seven had received interferon, six placebo. The number of residual corneal opacities was recorded (Table 8). For those patients who had received treatment within 7 days of the onset of their symptoms, there was no correlation between the clinical severity of their symptoms and the number of corneal opacities. Indeed, patient III, who was noted for her extreme symptoms and signs during the study, was left with only scanty fading opacities at 3 months. One patient in each treatment group had been excluded from the study assessment because their symptoms had already been present for more than 7 days. Nevertheless they had each completed the appropriate course of treatment and it is interesting that both had corneal opacities or staining at presentation and that the corneal opacities persisted at 3 months.

In all cases with bilateral involvement in the interferon group, residual corneal damage was more severe in the presenting eye than in the secondarily infected eye. This was in agreement with the lower severity scores of second eyes recorded during the study.

Epidemiology of outbreak

At least 186 patients suffered from EKC in the entire outbreak. Their ages ranged from 6 months to 81 years. The 50 virologically confirmed adenovirus type 8 cases comprised 27 males and 23 females, with a mean age of 34·6 years.

Several of the patients early in the outbreak (November to December 1983) had

Table 7. *Comparison between viral shedding in (a) interferon and (b) placebo groups*

Patient	Days 0	1	2	3	4	5	6	7	8	9	10	11	12	13	Adenovirus type (type 8 except where indicated) Adenovirus
							(*a*) Interferon group								
I	+R	·	+R	·	·	·	·	·	·	·	·	·	·	·	type 7
II	+R	·	·	+R	·	·	·	·	·	·	−R	·	·	·	·
III	+R	+R	·	·	·	+R	·	·	−R	·	−R	·	·	·	·
						+L			−L		−L				
IV	+R	+R	·	·	·	−R	·	·	−R	·	·	·	·	·	·
	+L	+L				−L			−L						
V	+L	·	−L	·	·	−L	·	·	·	−L	·	·	−L	·	·
VI	+L	·	·	−L	·	·	·	·	·	·	·	−L	·	·	type 7
VII	+L	·	·	·	·	+L	·	·	·	+R	·	·	−R	·	·
										−L			−L		
VIII	+L	+L	·	·	·	+R	·	·	−R	·	·	·	·	·	·
						+L			−L						
IX	+L	·	+L	·	·	·	+R	·	·	+R	·	·	·	−R	·
							+L			−L				−L	
							(*b*) Placebo group								
A	+R	·	·	+R	·	·	·	−R	·	·	−R	·	·	−R	·
				+L				−L			−L			−L	
B	+R	·	·	·	−R	·	·	−R	·	·	·	−R	·	−R	·
C	+R	·	·	·	+R	·	·	·	+R	·	·	·	·	·	Adenovirus type 7
D	+R	·	·	+R	·	·	−R	·	·	·	·	·	·	−R	·
	+L			+L			+L							−L	
E	+L	·	·	+L	·	·	·	·	·	·	·	·	·	·	·
F	+L	·	·	·	+L	·	·	−L	·	·	−R	·	·	·	·
											−L				
G	+L	·	+L	·	·	·	+L	·	·	+L	·	·	−L	·	·

R, right eye
L, left eye

Table 8. *Corneal changes at final assessment on 12 March 1984*

Patient sex, age	Presenting eye: Right or left	Onset to presentation (days)	Corneal signs at presentation (max score = 10)	No. opacities at 3 months	Secondary eye: Right or left	Days after first eye	Corneal signs at presentation	No. opacities at 3 months
			(*a*) Patients from original interferon group					
III F 25y	R	4	0	2 f	L	5	1	1 f
V M 64y	L	6	0	3	—	—	N/A	—
VI M 51y	L	1	0	0	—	—	N/A	—
VII M 18y	L	2	0	2 f	R	8	0	0
VIII M 22y	L	1	0	3 f	R	5	0	0
IX F 19y	L	2	0	⩾ 4 f	R	6	0	1
X F 39y	R	8*	4	⩾ 4	—	—	N/A	—
			(*b*) Patients from original placebo group					
A F 19y	R	4	0	2	L	6	0	2
B M 24y	R	1	0	1	—	—	N/A	—
F M 39y	L	3	0	1	R	9†	0	1
G M 42y	L	0	0	⩾ 4	—	—	N/A	—
X M 23y	Both	8*	2 L 1 R	3 L N.R. R	—	—	N/A	—
Y[Δ] M 29y	R	3	1	0	—	—	N/A	—

f, Fading opacities. * Excluded from earlier analysis (symptoms > 7 days' duration). † Clinically infected but culture negative. N.R., Not recorded

Table 9. *Details of all adenovirus type 8 positive cases*

	Patient sex, age		Previous attendance at REI (reason)	Family contact	Incubation period	Eye infected
				(*a*) November 1983		
(1)	M	32y	+(conjunctivitis)	—	13 days	Right
(2)	M	43y	+(hit in eye)	—	8 days	Left
(3)	F	29y	—	—	8 days	Left
(4)	F	17y	+(eye injury)	—	14 days	Right
(5)	M	16y	+('stinging' eye)	—	13 days	Both
(6)	M	62y	+(loss of vision)	—	12 days	Left
(7)	M	43y	+(foreign body removed)	—	10 days	Left
(8)	M	36y	+(foreign body removed)	—	10 days	Right
(9)	F	65y	+(Sjögren's syndrome, removal of concretion)	Husband subsequently (case 10)	14 days	Both
(10)	M	70y	—	Wife (case 9)	7 days after wife	Both
(11)	M	16y	+(foreign body removed)	Girlfriend subsequently (case 19)	14 days	Both
(12)	M	22y	+(foreign body removed)	—	10 days	Left
(13)	F	81y	+(ectropion, epiphora)	—	13 days	Right
(14)	M	23y	+(eye injury)	—	7 days	Both
(15)	F	18y	—	—	N.K.	Right
				(*b*) December 1983		
(16)	F	2y	+(spectacles fitted 24 August)	—	N.K.	Both
(17)	F	31y	+(S.H.O.)	—	3 days	Left
(18)	F*	19y	+(conjunctivitis)	—	12 days	Right, then both
(19)	F*	19y	—	Boyfriend (case 11)	14 days	Both
(20)	M*	22y	—	Father-in-law	N.K.	Left, then both
(21)	F*	21y	—	Husband	N.K.	Both
(22)	F*	23y	—	Boyfriend	N.K.	Left
(23)	M*	18y	+(foreign body removed)	—	5 days	Left, then right
(24)	M	80y	+(sticky eye)	—	$\geqslant$ 3 weeks	Left
(25)	M	20y	+(glue in eye)	—	15 days	Both
(26)	F	24y	+	Child	9 days	Right

* Interferon trial participants.

(27)	M	32y	N.K.	N.K.	N.K.	Right
(28)	M*	64y	—	Wife subsequently (case 34)	N.K.	Left
(29)	M*	43y	—	—	N.K.	Left
(30)	F*	19y	—	—	N.K.	Left, then both
(31)	F*	25y	—	Husband subsequently (case 40)	N.K.	Right, then both
(32)	F	6/12	N.K.	N.K.	N.K.	Left
(33)	F*	39y	—	—	N.K.	Right
(34)	F*	56y	—	Husband (case 28)	9 days after husband	Right
(35)	M*	22y	—	—	N.K.	Right
(36)	M	50y	+(old dendritic ulcer)	—	9 days	Right
				(*c*) January 1984		
(37)	F	46y	—	—	N.K.	Left
(38)	M*	23y	—	—	N.K.	Both
(39)	M*	39y	—	—	N.K.	Left, then both
(40)	M*	24y	—	Wife (case 31)	3 weeks after wife	Right
(41)	M*	33y	—	—	N.K.	Right
* Interferon trial participants.						
				(*d*) March and April 1984		
(42)	M	41y	—	—	N.K.	Right
(43)	F	52y	—	Grandson and daughter	N.K.	Left
(44)	M	21y	+(metal in eye)	—	8 days	Both
(45)	M	13y	+(graphite in eye)	Father and mother subsequently	9 days	Left
(46)	M	43y	+(with son)	Son	7 days after son	Both
(47)	F	41y‡	+(with son)	Son	9 days after son	Right, then left
(48)	F	46y	N.K.	N.K.	N.K.	Both
(49)	F	77y	†	—	N.K.	Both
(50)	M	30y	+(steel in eye)	—	11 days	Right

N.K., Not known.
‡ Left corneal laceration 1972, aphakic, contact lens worn.
† Keratoconjunctivitis sicca.

attended the REI for a variety of reasons prior to the development of symptoms and signs of EKC (Table 9). In no case had tonometry been performed. Some had been examined at the REI on several occasions, in which case it was not possible to define the date on which their infection was acquired. One patient, a 25-year-old male, had made repeated visits to the casualty department since 28 July 1983 for persistent follicular conjunctivitis. A clinical diagnosis of viral keratoconjunctivitis was made on 6 October, but unfortunately viral swabs were not taken. The course of his infection was subsequently identical to the virologically confirmed adenovirus type 8 cases.

Staff at the REI were also affected. A male senior house officer developed conjunctivitis on 20 November. His infection cleared up within a week and without virological confirmation, it may not have been due to adenovirus type 8. However at least nine of the early cases had been examined by him at some time (range 2–25 days) prior to their onset of definite symptoms and signs of EKC. A second member of staff at the REI, a 31-year-old female SHO, acquired virologically confirmed adenovirus type 8 keratoconjunctivitis only 3 days after her arrival at the hospital. As there had been no cases at her previous hospital, it must be assumed that she was infected by one of the Plymouth cases. A 48-year-old nursing sister developed a unilateral conjunctivitis in December, but viral cultures were negative.

There was evidence of household spread of infection from early on in the outbreak. The 70-year-old husband of the lady with Sjögren's syndrome from whom adenovirus type 8 was first isolated, developed bilateral culture positive follicular conjunctivitis 7 days after his wife. He had not been examined previously at the REI. A 39-year-old man who presented to the REI with established EKC on 9 November, reported that his wife and children had identical symptoms 2 weeks later. Unfortunately viral cultures were not obtained. This was typical of the anecdotal reports received throughout the outbreak of spread of infection to other household members.

From December 1983 fewer new cases of EKC gave a history of prior attendance at the REI. Indeed only 4 of the 34 interferon trial participants had attended previously – for removal of foreign bodies (2), conjunctivitis (1), and removal of diesel oil from the eye (1). Only two of these cases were infected with adenovirus type 8. Consequently in many cases the incubation periods could not be determined.

There was no evidence of geographical clustering of cases. Most came from different areas of Plymouth or from surrounding towns. The 25-year-old female patient who had the most severe infection of the trial participants was a doctors' receptionist in a town 25 miles away. The source of her infection was not known. However she wore contact lenses and continued use of these may have exacerbated her infection. She subsequently spread the infection to her husband.

This was one of two instances of household spread of infection among study patients (Table 10.) In both cases the index case had marked epiphora which would have facilitated the transmission of virus-laden ocular secretions to the spouse via fingers and fomites such as pillow-cases, towels and handkerchiefs. This occurred in spite of the fact that all patients were warned at each attendance against sharing face-flannels and towels, to use disposable handkerchiefs and to launder pillow-cases

Table 10. *Details of spread of infection within households – interferon trial participants*

Patient sex,	age	First eye infected date	Second eye infected date	Comments	Spouse sex,	age	Eye infected date	Comments
V		L	—	Marked epiphora	*		R	Much less severe
M	64 years	1 Dec 83	—	Culture negative by 9 Dec R_x interferon	F	56 years	10 Dec 83	Culture positive 19 Dec Culture negative by 22 Dec R_x placebo
III		R	L	Severe symptoms until Christmas	B		R	Much less severe
F	25 years	7 Dec 83	12 Dec 83	Culture negative by 19 Dec R_x interferon	M	24 years	1 Jan 84	Culture negative by 6 Jan R_x placebo

* Excluded from trial analysis (onset of symptoms > 7 days before presentation).

regularly. Several female patients chose to sleep in separate bedrooms to reduce the risk of transmission to their partners. It is of interest to note that the wife of the first case was infected 9 days after her husband, whereas the husband of the second case was not infected until 3 weeks after his wife. Both contacts had less severe manifestations than their spouse.

During the second wave of nine cases which occurred in March and April 1984, the REI may have been the source of infection in three instances. A 13-year-old boy who developed EKC 9 days after a piece of graphite was removed from his eye subsequently infected both his father and his mother (onset of each 7 days and 9 days after their son respectively).

Overall, where incubation periods could be ascertained, they ranged from as short as 3 days to 3 weeks, with a mean of 10·9 days.

Of the 50 adenovirus type 8 positive patients, 36 had uniocular infections – 18 involved the right eye and 18 the left eye. Of those patients who were directly questioned on this point, there was no correlation between eye involvement and handedness of the patient. Fourteen patients had bilateral infections from presentation and seven of the uniocular infections subsequently spread to the other eye.

DISCUSSION

This outbreak illustrates several of the features of previous reports (Barnard *et al.* 1973; Richmond *et al.* 1984). It had probably been in progress for 1–2 months before its extent was appreciated. In spite of detailed investigations, the source could not be identified. It is possible that it was introduced in October by one of the chronic attenders at the REI or brought from another hospital, although there was no known association with any other nosocomial outbreak occurring at about the same time.

As this was the first outbreak in Plymouth of adenovirus type 8 keratoconjunctivitis at the REI, there was a delay in initiating virological investigations and instituting appropriate control measures. The overcrowded conditions in the casualty department at the REI precluded satisfactory segregation of infected from uninfected patients. Thorough hand-washing by staff probably played a major part in controlling the outbreak (Clarke, Dean Hart & Barnard, 1972). Fomites were not identified as important factors in the spread of infection within the hospital, but within the home contaminated fingers and articles of linen were probably both responsible for secondary infection of household contacts (Richmond & Dodd, 1983).

Following a report from Israel of a favourable clinical response to human fibroblast interferon (Romano *et al.* 1980), it was decided to evaluate the same type of interferon during the Plymouth outbreak, while not allowing this to compromise infection control measures. Unfortunately the number of patients who satisfactorily completed the trial was small, thereby preventing a valid assessment of interferon. Nevertheless the preparation was without local or systemic side-effects (two patients reported a mild stinging sensation) and it would be worth evaluating interferon therapy further in a similar but larger outbreak.

The Plymouth outbreak was unusual in that a second cluster of cases of adenovirus type 8 infections occurred in March 1984 after a 5-week infection-free period. This may have been due to a lapse in careful hand-washing by the casualty

staff; some of the patients had previously attended the REI within the incubation period and the interferon trial had ceased by the end of January. The infection was probably maintained again by household spread. Sporadic cases of conjunctivitis due to adenoviruses types 7 and 3 also occurred during this period. However the fact that there have been no new isolations of adenovirus type 8 for more than a year since 4 April 1984 testifies to the ultimate success of infection control measures.

There may be residual corneal damage attributable to this virus, and it is important that cases of adenovirus type 8 keratoconjunctivitis are diagnosed more quickly in future so that such epidemics may be aborted.

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