Continuous fluorophotometric method of measuring tear turnover rate in humans and analysis of factors affecting accuracy

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Abstract—*An improved continuous reading fluorophotometer with provision for controlling the blink rate has been used to measure tear turnover rates in 14 normal healthy volunteers. A significant difference between morning and afternoon tear turnover results has been found, indicating a possible circadian rhythm in tear flow. Sources of potential systematic error in the measurement method have been identified and analysed. Fluorescence measurements using a thin film cell have confirmed predictions of nonlinearity in fluorophotometer output at high tear film concentrations. The error in tear film fluorescence due to diffusion of fluorescein into the cornea has also been investigated. Simple precautions to minimise these errors are suggested, which should make the measurement method suitable for clinical application.*

Keywords—*Tear turnover, Fluorophotometry, Ophthalmology*

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1 Introduction

DISORDERS of the tear secretory system result in symptoms that include dryness, itching, discharge and chronic conjunctival infection. Although such disorders are commonly encountered in ophthalmic practice, it is rarely possible to establish a direct association between the symptoms and tear flow because of the difficulty of measuring tear turnover rate precisely. Schirmer's method of estimating tear flow (HENDERSON and PROUGH, 1950), using filter paper strips, causes reflex lacrimation and is unsatisfactory. Methods using dyes and colorimetry (NORN, 1965; BARENDSEN *et al.*, 1979) cannot follow rapid changes in tear flow and in some cases are subjective (NORN, 1965). Fluorophotometric methods of measuring tear turnover are objective. They require the instillation of a very small drop of fluorescein dye, but thereafter there is no contact with the eye (FURUKAWA *et al.*, 1976; JONES *et al.* 1979; PUFFER *et al.*, 1980). Moreover, the continuous reading types of fluorophotometer can follow dynamic tear flow changes. Fluorophotometric methods are therefore to be preferred for the diagnosis and study of tear secretory disorders.

We describe tear turnover measurements in normal healthy volunteers using a continuous reading fluorophotometer which monitors tear flow for several minutes. Basal tear turnover rate is not easy to measure because of its variability (MISHIMA *et al.*, 1966). Environmental stimuli, e.g. draughts, psychological factors and even the effort of keeping the eyes open (DEROETTH, 1953) can all have a strong influence on tear flow. Variation in the blink rate in some individuals has been found to have a marked effect on tear turnover. We have recorded increases of as much as 50 per cent in the measured tear turnover rate when the blink rate was changed from 20 to 6 min^{-1} and in one measurement the turnover rate increased from 19 to 115 per cent min^{-1} when the blink rate was decreased from 42 to 6 min^{-1}. Although a direct correlation between blink rate and tear flow has yet to be demonstrated, we have sufficient evidence to suggest that standardisation of the blink rate would eliminate one possible source of variation. A circuit which regulates the blink rate has therefore, been incorporated into our fluorophotometer and is described below.

Potential inaccuracies in the measurement have also been investigated. There are two stages when care is needed in interpreting the results. First, just after the drop of fluorescein has been instilled into the eye, when the relatively high dye concentration can lead to extinction; and, secondly, towards the end of the measurement, when the fluorescence of the dye absorbed by the cornea begins to become significant. These effects, which can lead to serious errors in the estimated tear turnover rates, do not appear to have been considered in detail by previous authors.

2 Apparatus

The tear flow measurements were made using an improved version of our previous fluorophotometer (SMITH *et al.*, 1977; JONES *et al.*, 1979). This instrument has a measurement volume of 0·6 × 0·2 × 0·4 mm formed by the

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intersection of the slit-lamp beam and the projection of the collecting aperture of the photometric microscope. The measurement volume is positioned to intersect an area of tear film 0·2 × 0·6 mm on the central part of the cornea with the axis of the slit lamp and microscope at approximately 30° and 40°, respectively, to the optic axis of the eye; i.e. with 70° between the illumination and collection axes. The instrument output is proportional to the fluorescence in the measurement volume. The performance of the original fluorophotometer has been improved by increasing the light collecting power by a factor of five and by changing the excitation and barrier filters to optimise the rejection of scattered light (WEBBER, 1983). The optical filters currently used are Barr & Stroud LP1, Baird Atomic B4 and 47018F as the excitation filters and Ilford Yellow Gelatine 110 as the barrier filter. The stability of the instrument has also been improved by redesigning and optimising the signal processing circuits giving an output drift rate of better than 0·9 per cent h^{-1} when measuring a standard fluorescein solution (1 $\mu g\ ml^{-1}$).

Novel fixation lights are used, which not only keep the subject's eye fixated but also maintain a regular blink rate during the measurement. It is important that any visible signal for controlling blink rate should not interfere with fixation, as might occur if the fixation light itself were to be switched on and off as a prompt. The measurement procedure tends to induce a relaxed state in our subjects, to the extent that their attention would sometimes wander from the original filament fixation lamp causing record artefacts. A two-colour light emitting diode is now used as a fixation and blink control light in such a way that it promotes fixation and concentration. A fixation light is attached to each side of the microscope objective, one for the left eye and the other for the right eye (only one being used at any one time). The subject looks straight ahead at one of these lights with one eye while the other eye is being measured. Each fixation light is a red/green light emitting diode which gradually appears to change from red through orange/yellow to green over an interval of 8 s and then changes rapidly back to red in 0·25 s, after which the sequence is repeated. The subject is instructed to blink once for each rapid green to red transition, i.e. each red flash.

The driving circuit for the blink/fixation lights is shown in Fig. 1. An astable multivibrator (Q1 to Q6) generates voltage pulses of reversing polarity at the red/green LED; the minimum pulse repetition rate is approximately 65 Hz which eliminates flicker. The apparent colour of the LED depends upon the mark-space ratio of the pulses, as red and green pulses are emitted during the mark and space times, respectively. During the mark time Q1 and Q6 are on while during the space time Q4 and Q5 come on and the current through the LED reverses. The red and green intensities can be set independently by *VR1* and *VR2*, respectively. The 'green' space time is determined by *C4* and *R3* and is fixed at approximately 1·5 ms; the perceived change in colour from green to red is achieved by altering only the duration of the 'red' mark time from 0·1 to 14 ms.

The required periodic variation of the mark time is achieved by means of the sawtooth current waveform generator comprising operational amplifiers X1 and X2, and transistors Q7 and Q8, and their associated components. The mark time is determined by the charging current of *C3* when Q4 is off. Some of this charging current flows through *R4* but the majority is usually supplied by the current source Q7. The relaxation oscillator based on operational amplifier X2 generates a sawtooth voltage waveform whose rise time is set by *VR3* to be 8 s and whose fall time is fixed at 0.25 s. This waveform is amplified by the noninverting amplifer based on X1 and used to modulate the current supplied to *C3* by Q7. The network *D1*, *D2*, *R5* and *R6* serves to shift the point of equal mark-space ratio to approximately the middle of the cycle thus giving a smooth transition from red to green. Transistor Q8 charges *C7* when the circuit is first switched on, but switches off after about 10 ms and plays no further part in circuit operation.

The mark and space times (maximum 14 ms) of the astable LED driver are always short compared with the duration of the rising ramp of the sawtooth, and the net effect is to cause the LED colour to appear to change gradually from red to green during the 8 s rise time and then to return rapidly (in 0·25 s) to red. The changing colours were found to be a useful aid to concentration by most subjects and gave a clear indication of the proximity of the next red flash and required blink. The circuit needs only a single 9 V supply and could be battery operated if necessary.

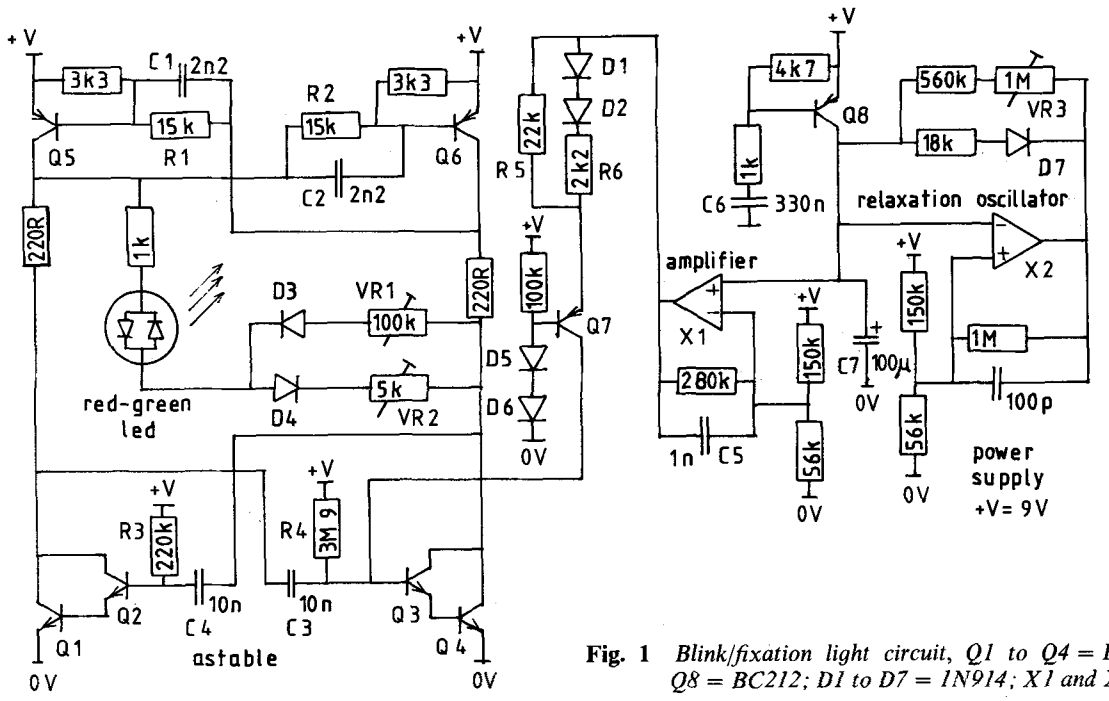

Fig. 1 *Blink/fixation light circuit, Q1 to Q4 = BC184; Q5 to Q8 = BC212; D1 to D7 = 1N914; X1 and X2 = 3140*

The fluorophotometer output for high concentrations of fluorescein in a thin film was investigated using the cell shown in Fig. 2. This cell consists of two microscope slides having a separation of the order of one tear film thickness. The microscope slides are separated by two thin strips of

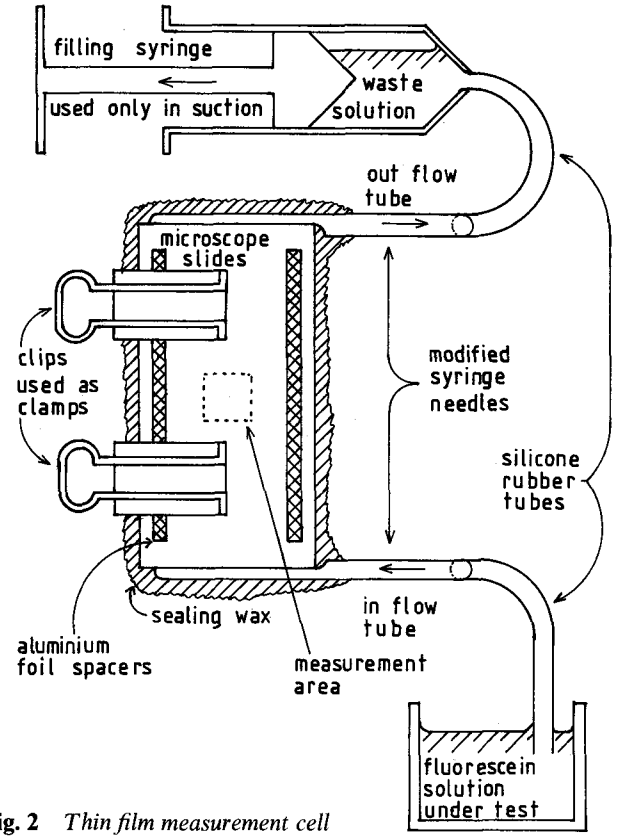

Fig. 2 *Thin film measurement cell*

aluminium foil, and to each end of the cell syringe needles which have been ground down along their lengths are fitted, as shown in Fig. 2. These needles serve as inflow and outflow tubes through which the cell can be filled with fluorescein solutions of known concentration. The cell is held together by two clips and sealed at its edges with sealing wax to form a fluid-tight joint.

3 Methods

3.1 *Measurement of tear turnover rate*

The method of tear turnover measurement was evaluated on 14 normal healthy volunteers (8 male, 6 female) who had an average age of 27 ± 4 years (mean ± SD). All measurements were made in a basement darkroom where conditions were relatively stable, the temperature was in the range 20 ± 1°C. The tear flow measurements began by instilling 2 per cent fluorescein (20 mg ml^{-1}) into the eye. A syringe needle (1 μl capacity) with a 1 μl drop of fluorescein at its tip was lightly touched tangentially on the superior bulbar conjunctiva of the eye. A very small drop was used so as to cause minimal interference with the tear film. The subject then blinked three times to distribute the dye evenly through the tear film.

The tear film fluorescence was then measured continuously for 3–4 mins, with the output signal from the fluorophotometer being displayed on a chart recorder. During the measurement procedure the blink rate was regulated to once every 8 s (7·5 min^{-1}) by the blink/fixation light. This rate gave a reasonable length of trace between blink artefacts to yield a more easily interpreted record, but was high enough to be comfortable for the subjects. A 2 min rest period was next taken and the procedure was repeated. In some cases both eyes were measured on the same occasion when a similar procedure was carried out, but making measurements of each eye in turn with rest periods after every other measurement. This was continued until the tear film fluorescence was too small to measure or for 30 min after dye instillation. This latter time limit was set because of corneal staining; the dye slowly diffused from the tear film into the cornea where it contributed to the measured fluorescence. The errors due to this effect are considered below. Finally, for each eye measured there were between two and four sections of chart record of relative tear film fluorescence, each being 3–4 min long. 11 eyes were measured in the morning, before 13·00 h, and 13 in the afternoon.

The results were analysed using the equation

$$C_d = C_{do} \exp(-Q_d t)$$

where C_d is the tear film concentration, C_{do} is the value of C_d immediately after instillation of dye, and Q_d and t are the turnover rate and the time after instillation of the dye, respectively (JONES *et al.*, 1979). The turnover rate Q_d was calculated using linear regression on the plot of the natural log of the instrument output readings (i.e. relative concentration) against time for points selected from the beginning and end of each measurement interval.

3.2 *Investigation of errors due to dye extinction*

Immediately after fluorescein is instilled into the eye its concentration can be relatively high. If the dye concentration is high enough, the linear relationship between concentration and fluorescent light output, and hence instrument output, breaks down due to extinction (WEBBER, 1983). The concentration at which this becomes a significant effect for tear film measurements was estimated to be approximately 1 mg ml^{-1} by MAURICE (1967).

Measurements were carried out using the thin film cell to see if extinction was likely to affect the initial tear film measurements. The cell was filled by connecting a syringe to the outlet and a reservoir of fluorescein to the inlet via silicone rubber tubes, see Fig. 2. Once the cell was mounted on the instrument, it was simple to change solutions; the fresh solution was drawn through by suction until the instrument reading was steady. All the measurements were made with the excitation beam normal to the plane of the thin film. Readings were taken using fluorescein concentrations in the range 1 μg ml^{-1}–100 mg ml^{-1}.

The dimensions of an ordinary calibration cell are all much greater than those of the measurement volume. Hence readings from the thin film measurement cell and from an ordinary calibration cell are in the ratio of the thickness of the thin cell to the known length of the measurement volume along the direction of the excitation beam. The thickness of the film at the point of measurement can thus be deduced by measuring a standard 1 μg ml^{-1} solution in both cells. Using this method, the cell thickness was found to be 5 ± 0·5 μm which is close to the estimated tear film thickness of 7 μm obtained by EHLERS (1965).

To investigate the effect of a high initial concentration on the fluorophotometer readings, some tear turnover measurements were made using 1 μl of 100 mg ml^{-1} (10 per cent) fluorescein instead of the usual 2 per cent solution.

3.3 *Investigation of errors due to corneal absorption of fluorescein*

There are two possible sources of error associated with the cornea. First, the rate of diffusion of fluorescein through the cornea into the eye might be sufficient to significantly reduce the fluorescence readings in the tear flow measurement; and, secondly, after a long measurement sufficient fluorescein might accumulate in the cornea to cause an appreciable increase in the apparent tear film reading. This latter error arises because the measurement aperture in the photometric microscope is larger than the tear film image so that a significant portion of the cornea is always included in the measurement volume. Until about 30–40 min after dye instillation the tear film appears as a well demarcated green line in the field of view and no corneal fluorescence is observable when a piece of OG515 barrier filter glass is placed in the viewing optical train. Later, the corneal fluorescence begins to appear and the fluorophotometric readings show a much lower rate of decrease than is characteristic of tear flow. Because of this phenomenon our tear film measurements are usually terminated at 30 min, but to investigate the effect of corneal fluorescence some of the measurements were continued for up to 130 min.

4 Results and discussion

4.1 *Tear turnover results*

A typical section of chart recording obtained from a tear flow measurement is shown in Fig. 3. The large downward excursions in the trace are caused by blinks as the subject's

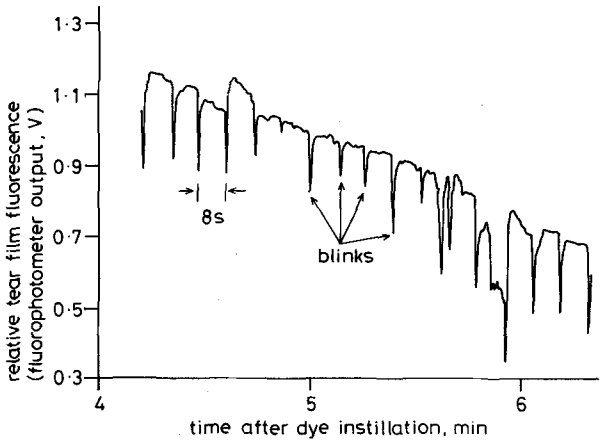

Fig. 3 *Fluorophotometer output against time for a typical decay of tear film fluorescence in a normal male volunteer*

eyelid momentarily obscures the tear film; the regular intervals ensured by the blink/fixation circuit are clearly evident. An interesting feature in Fig. 3 is the decrease in fluorophotometer output immediately after several of the blinks. This was almost certainly due to the thinning of the tear film after the blink as, for a given concentration, the output signal is proportional to the tear film thickness. EHLERS (1965) observed the same effect by measuring the tear film thickness at different times after a blink. In his method round disks of compressed paper were pressed against the cornea to soak up the tear film under them. The tear film thickness was calculated from the change in weight and surface area of the disk.

The tear film concentration can show large discontinuous jumps after a blink, and these are thought to be due to the fluorescein not being completely mixed in those parts of the tear film behind the eyelids. Despite this possibility

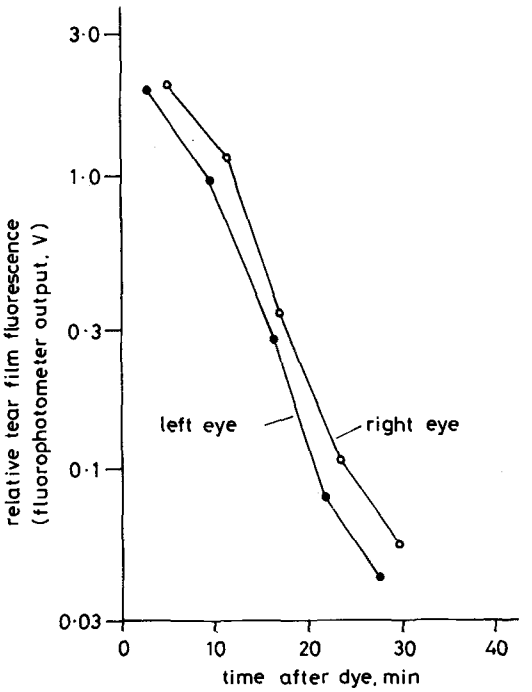

Fig. 4 *Semilog plot showing relative tear film fluorescence against time for the right and left eyes of a normal male volunteer. The points were selected from the beginning and end of measurement intervals similar to that of Fig. 3*

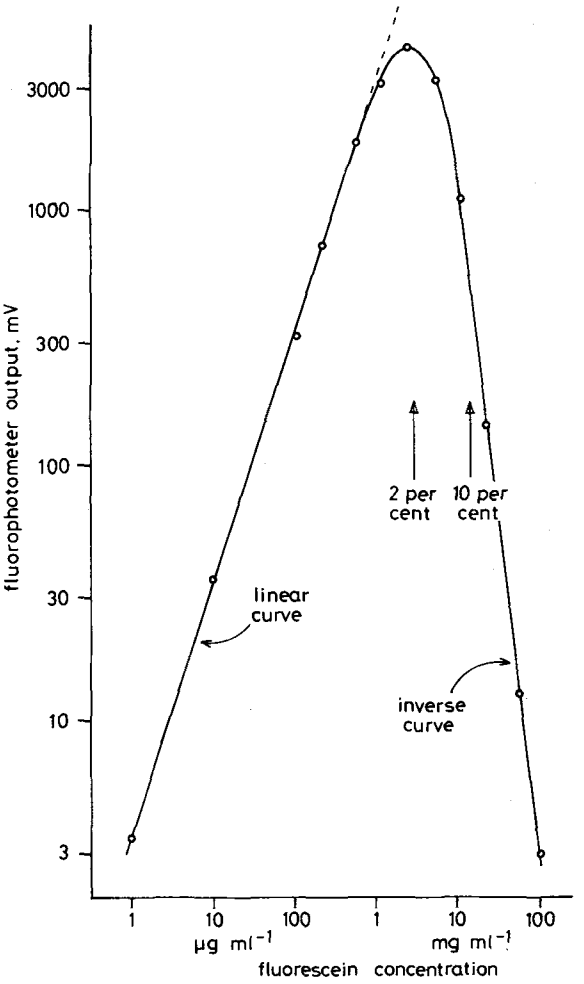

Fig. 5 *Fluorophotometer output against fluorescein concentration for the thin film cell (thickness approximately 5 μm). The arrows marked 2 and 10 per cent indicate estimated initial tear film concentrations when 20 and 100 mg ml^{-1} drops of 1 μl volume are instilled, respectively*

of large variations, consistent results were obtained for almost all of the subjects measured. The points selected from the chart recordings for one subject are shown on the semilog plot in Fig. 4. These data are typical and show an approximately linear variation compatible with a constant-volume and constant-flow model of tear turnover (JONES *et al.*, 1979). Two-sample *t*-tests were used to compare the tear turnover data. No statistically significant differences in tear turnover rates were found between right and left eyes, males and females, and between light and dark irises. However, the mean tear turnover rate Q_d for morning measurements was $15{\cdot}5 \pm 5{\cdot}3\%$ min^{-1} (mean $\pm$ SD, $n = 11$) and for afternoon measurements the corresponding mean was $11{\cdot}8 \pm 3{\cdot}8\%$ min^{-1} ($n = 13$). The difference between these values was statistically significant ($p < 0{\cdot}05$) (WEBBER *et al.*, 1984). The reason for this is at present obscure and is under investigation.

4.2 *Sources of error and misinterpretation: extinction*

The results of readings from the thin film cell are shown in Fig. 5, where they are plotted on a log-log graph. The instrument output is linear with concentration up to 1 mg ml^{-1}. Above this value the output becomes nonlinear due to dye extinction and then exhibits a sharp decrease as the concentration increases, probably due to the absorption of the fluorescent light by the highly concentrated fluorescein solutions. If the tear volume is taken as 7 μl (MISHIMA *et al.*, 1966) then adding 1 μl of 20 mg ml^{-1} and 100 mg ml^{-1} fluorescein will produce concentrations of 2·5 mg ml^{-1} and 12·5 mg ml^{-1} in the tear film, respectively. Both these initial concentrations are higher than can be measured accurately, see Fig. 5, however, there is usually a high tear turnover rate immediately after the drop is instilled into the eye (MISHIMA *et al.*, 1966) and a delay of a minute or two before recordings of tear film fluorescence are started. These two factors are assumed to reduce the tear film concentration to below 1 mg ml^{-1} by the time recording starts.

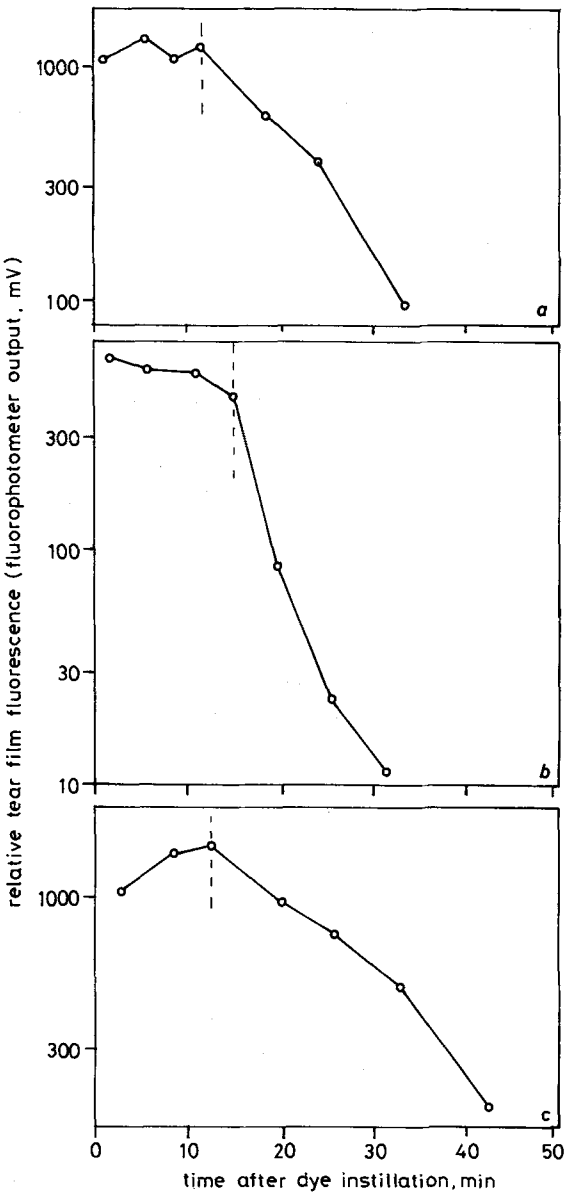

Fig. 6 *Semilog plots of fluorophotometer output against time illustrating the initial behaviour after instillation of 1 μl of dye. Fluorescein concentrations: (a) and (b), 20 mg ml^{-1}; (c), 100 mg ml^{-1}. Data to the left of the broken lines are not used for tear turnover estimates*

The implications of the results in Fig. 5 are that if the tear turnover rate is low and readings are started immediately after instillation of fluorescein (i.e. the concentration has not decreased appreciably before the measurements begin) then the instrument readings might even increase initially with time, particularly with the 100 mg ml^{-1} drops. In the case of the 20 mg ml^{-1} drops near-stationary initial readings might be expected. Both these effects have been observed. Traces *a* and *b* in Fig. 6 show such stationary behaviour for 20 mg ml^{-1} drops and trace *c* for 100 mg ml^{-1} drops, shows an initial rise before the decreasing part of the curve is reached. The early readings are clearly unreliable as measures of concentration and are ignored for the purpose of tear turnover calculations (i.e. those points to the left of the dotted lines in Fig. 6). At least four points, each lower in value than its predecessor, and all within a period of 30 min after dye instillation are required for a valid tear turnover calculation. All our results were calculated on this basis.

In general, it would be better to use 1 μl drops of fluorescein of concentration 8 mg ml^{-1} or less as this would result in an initial concentration of 1 mg ml^{-1} in the tear film (assuming a 7 μl tear volume) which is safely on the linear part of the calibration curve of Fig. 5. For the above measurements 20 mg ml^{-1} fluorescein was used as this was readily available in sterile form and 8 mg ml^{-1} was not.

PUFFER *et al.* (1980) also estimated tear turnover rate fluorophotometrically but by a method relying on a series of discrete measurements. They used a 1 μl drop of high concentration fluorescein, i.e. 100 mg ml^{-1}, and reported that five of their 52 subjects had a very low initial tear turnover rate with the tear film fluorescence showing no change for up to 30 min after dye instillation. They also observed in one of their subjects a steady increase in fluorescence from the tear film during the initial part of the measurement. These observations might be better explained by nonlinearity at high dye concentration rather than by a virtually zero tear turnover rate as the authors suggest.

FURUKAWA *et al.* (1976) performed thin film measurements using a cell constructed from glass plates separated by 7 μm. Their results gave a straight line on a log-log plot over the range 10 μg ml^{-1}–10 mg ml^{-1}. However, the slope of their line suggests a weak power law dependence of signal voltage on concentration and there is no evidence of extinction even at 10 mg ml^{-1}. These results are in contrast to those of Fig. 5, especially as their measurement cell, being slightly thicker than the present one, should have exhibited nonlinearity due to extinction at a lower fluorescein concentration (MAURICE, 1967). It is possible that the overlap in the transmissivity of their excitation

and barrier filters at about 380 nm accounts for the differences.

4.3 *Sources of error: corneal absorption*

At about 30–40 min after dye is instilled sufficient fluorescein will usually have diffused into the cornea to give a measurable signal. The effect of corneal fluorescence on tear film measurements can be seen in Fig. 7, where the relative tear film fluorescence for three subjects is shown on a semilog plot. By about 40 min after instillation of dye the readings no longer decrease steadily. They begin to increase as the corneal fluorescence rises, reaching a peak at between 60 and 120 min, as shown in the example in Fig. 7. The image observed in our instrument is an oblique cross-section of the tear film and cornea, thus the relative contributions to the fluorescence from each can be observed qualitatively although not measured. The change of image appearance is indicated in Fig. 7.

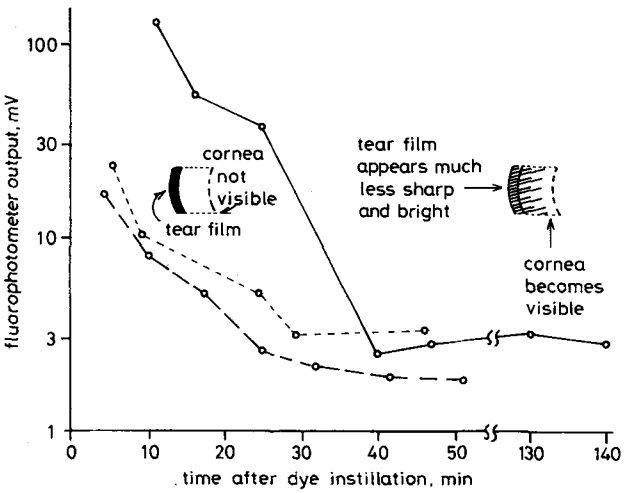

Fig. 7 *Semilog plot of fluorophotometer output against time showing the effect of corneal fluorescence on the measured tear film fluorescence. The change in the tear film image in the field of view as seen through OG515 filter glass is also illustrated; the initial bright sharp line becomes very diffuse after about 30 min. Instilled dye concentration in each case was 20 mg ml^{-1}*

PUFFER *et al.* (1980) who used a relatively high concentration of fluorescein (100 mg ml^{-1}), did not observe any effects due to corneal fluorescence, although their measurements extended up to between 45 and 60 min after dye instillation. Their instrument viewed an area of cornea 5 mm in diameter at near normal incidence and not in cross-section, and they were thus unable to observe the separate contributions of the tear film and cornea to the total fluorescence. A possible reason why these authors did not see the effects of corneal staining shown in Fig. 7 is that the time at which the corneal concentration becomes significant can be longer than 30 min, depending on tear turnover rate. In some cases we did not observe corneal fluorescence until 60 min after dye instillation.

Errors in the measurement of tear turnover rate due to the direct loss of fluorescein into the cornea are likely to be very small. This is because the corneal epithelial permeability normalised with respect to tear volume is low, being of the order of 10^{-3} min^{-1} (MAURICE, 1967; WEBBER 1983) and the rate of loss of fluorescein from the tear volume via the cornea is thus much less than that due to tear flow which is of the order 10^{-1} min^{-1} as a fraction of the tear volume. The fluorescence contribution of the total quantity of dye within the cornea begins to become comparable with the tear film fluorescence after about 30 min, but by this time the tear film fluorescence is only of the order of 1 per cent of its initial value. It is tear flow that removes about 99 per cent of the fluorescein from the tear film, the rest leaving by the cornea. In our studies the tear film fluorescence measurements are abandoned after 30 min to minimise the risk of error due to corneal fluorescence.

5 Conclusions

We have shown that by using an improved fluorophotometer which controls blink rate, it is possible to make continuous and consistent measurements of tear turnover rates in normal healthy volunteers. A possible circadian rhythm in turnover rate has been identified in our results. Sources of systematic error, namely the nonlinearity in output at high fluorescein concentrations and the corneal absorption of fluorescein, have been investigated and criteria established for the maximum fluorescein concentration for instillation into the eye and the maximum duration of the measurements to minimise the effect of these errors. The methods described should prove of clinical value in the study and quantitative assessment of disorders of the tear secretory system.

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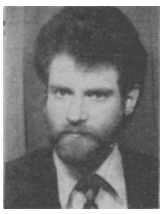

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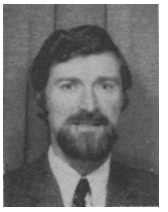

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