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Sir,

We were interested to read Diaper's report (Eye 1994;8:448) confirming our original proposal that the severe form of granular corneal dystrophy represents the homozygous state. With the exception of some of Sajjadi's and Javadi's cases all reports to date of this syndrome can be explained on a simple Mendelian basis. We ourselves have two separate pedigrees under observation, both propositi being the products of consanguineous marriages. The high concentration of abnormal material in the affected corneas of presumed homozygotes has allowed us to make new observations concerning the ultrastructural changes which are shortly to be reported.

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Sir,

I was interested to read the recent paper by Aylward et al. in the journal[1] and agree with the authors that the role of acyclovir in the management of the immunocompetent patient remains controversial. The authors give the opinion that the only two prospective, randomised, controlled clinical studies of oral acyclovir given early in herpes zoster ophthalmicus (HZO)[2,3] have serious methodological and statistical flaws. They then go on to present evidence from a retrospective, case–control study and conclude that oral acyclovir has little or no preventive effect on the ocular complications of the disease. It is indeed true that the two previous studies give conflicting results but this may have been due to the suboptimal dose of 600 mg acyclovir used in the first.

Their main criticism of the two studies is based on the the bias introduced when a large number of outcome measures are investigated with a probability of a null hypothesis being accepted in the first study[2] of only 0.40. By the same argument, however, this probability rises to 0.70 in the second study[3] in which seven different measures were used. In addition, this study found a statistically significant drug benefit for three of the seven (active ocular disease at 6 months, frequency of pain at 2 and 3 months, severity of pain at 2, 3 and 6 months), not one as stated by Aylward et al. In this study sample size was calculated in accordance with normal statistical practice to give an 80% chance of showing a treatment effect at the 5% level, assuming an effect for treatment of 15% and for placebo of 50%.

Aylward et al. report results which are different to previous studies on the subject and this may be due to a number of reasons. The population studied is from a tertiary referral clinic. The frequency of ocular complications is higher at 81% than in previous reports[4–6] and their patients were more likely to be on treatment at 6 months. This suggests that their patients had more severe disease than other series. Seventy-two per cent of patients received topical steroid therapy. Although the evidence is incomplete, previous work has suggested that topical steroids can enhance ocular involvement.[7]

It would be interesting to know how many patients were referred from outside in each group. With only 10% of patients receiving adequate treatment with acyclovir one might expect that it is not the authors' drug of choice in HZO, so presumably the acyclovir group were commenced on the drug elsewhere and presented with more severe ocular disease. Since acyclovir does not prevent all ocular disease this would not be surprising but, if so, means that the case-control nature of the study is suspect.

Conclusions are based on a subset of 42 patients who received adequate treatment with acyclovir and their age-matched controls rather than on 419 patients as implied in the abstract. In their final paragraph Aylward et al. conclude that doubt has been cast on claims of efficacy for oral acyclovir and to some extent this is true, but this does not lead one to the conclusion in the abstract that the drug has little or no preventive effect on ocular complications. No power analysis is presented to support the authors' failure to find a treatment benefit and argue against a type 2 statistical error. It must not be forgotten that pain is also influenced by oral acyclovir[2,3,8–10] although, once again, results of published studies do differ.

Evidence on the preventive efficacy of oral acyclovir in HZO remains conflicting and clinicians face the difficulty of deciding whether to use the drug in their patients. Acyclovir is certainly not the complete answer but its use has become widespread

and while we await something better I believe that its use in all cases of HZO remains justified.

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Sir,

We are grateful for Harding's comments on our paper,[1] and we are pleased that he agrees that the role of acyclovir in immunocompetent patients with HZO remains controversial. In our paper we drew attention to serious flaws in the analysis of data presented in two previous randomised, controlled trials, including the problem with multiple outcome measures.[2–4] We were addressing the specific issue of whether acyclovir has a beneficial effect on ocular complications. Therefore the second study did have only one relevant positive outcome measure (active ocular disease at 6 months) supporting the conclusion. One accepted method of dealing with the problem of multiple outcome measures is to employ the Bonferoni inequality.[5] In order to obtain an overall alpha risk of 0.05, the alpha risk for each of the individual significance tests is simply divided by the number of outcome measures. When this is applied to the data from the aforementioned trials, *all* the treatment effects become non-significant. For this reason, and others mentioned in our paper,[1] we do not believe that the results in either study support the conclusion that acyclovir reduces the incidence or severity of ocular complications. Therefore, we do not agree with Harding that we reported *results* which are different to previous studies, but rather that our results are the same. It is the *analysis* and *conclusions* which are different.

It is incorrect to state that our population came from a tertiary referral clinic, since patients in the Zoster Clinic come from a variety of sources. The source of referral for the treated patients was given in our paper, the vast majority (86%) being referred by their general practitioners, who are generally the only ones with the opportunity to begin treatment rapidly. The question of selection bias was fully addressed in our discussion. In brief we found no evidence to suggest that patients on acyclovir had more severe initial disease than controls.

We are aware of the previous publication suggesting that topical steroids can enhance ocular involvement, but are unaware of any independent verification of this interesting and challenging hypothesis. In any event the number of patients in our study receiving topical steroids was not different between cases and controls.

Our abstract states clearly that we studied 77 matched pairs from an overall pool of 419 patients with HZO. Forty-two pairs were considered to have received adequate treatment and separate analysis was carried out for this subset, with identical results.

Harding is correct in saying that we presented no power analysis. In fact we chose to present the data using the alternative and much preferred method of confidence intervals, consistent with modern statistical practice.[6] Such analysis does indeed allow us to conclude from our data that the drug has little or no preventive effect on ocular complications in our patients. For example, the upper limit of the confidence interval for the difference in ocular involvement score (OIS) was 0.49. This is very low using a scoring system with which episcleritis scores 1. Therefore, a clinically significant treatment effect should have been detected by our study.

We did not address the issue of pain being influenced by acyclovir, but we agree with Harding that the results of published studies differ. Harding concludes his letter by pointing out that the use of acyclovir has become widespread, and that its use in all cases of HZO remains justified. We suggest that in the current financial climate, the use of an expensive drug should be justified by sound clinical evidence of its efficacy, regardless of its popularity. We believe that such evidence is currently lacking.