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Reply

On the potential causes of presbyopia

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1. Past work

Weale (1998) states that the suggestions of changes in lens power with decapsulation, geometric factors, lenticular shape factor and lenticular growth are all evidence for multifactorial theories of presbyopia. However, their suggestion proves neither their existence nor their role in the development of presbyopia. Glasser and Campbell (1998a) provide some of the first substantial experimental evidence which can be used to test the various theories of presbyopia. We conclude that the basis of presbyopia is predominantly lenticular, but that the results do not support a predominant role of the geometric theory. In his support of multifactorial theories Weale (1998) states "it has been stated that decapsulated lenses have a higher power than capsulated ones (Weale, 1962)". What Weale (1962) is 'stating' is the work of Fincham (1937) who photographed the lens profiles of a *single* monkey lens and a *single* sheep lens before and after the removal of the capsule. Our own experiments on 19 pairs of human lenses (Glasser & Campbell, 1996; Glasser & Campbell, 1998b) demonstrate that changes in lens power with decapsulation are restricted to young human lenses. Human lenses over the age of 50 years do not undergo the systematic changes in focal length with decapsulation that young human lenses do. The observed balancing of the elasticity of the lens matrix and capsule as alluded to by Weale in younger lenses, does not lead to a multifactorial theory in older, presbyopic lenses, in which the power no longer changes with decapsulation. Together with our previous work (Glasser & Campbell, 1998a) this indicates that the age change in deformability of the lens is a factor in presbyopia.

Weale (1998) contends that "Pierscionek and Weale (1995) showed that 8–10% of the age-related loss of accommodation can be attributed to lenticular growth". What is *shown* is, by their own admission "very approximate" and the result of numerous "assumptions" and "estimates" (Pierscionek and Weale, 1995), and is an amount small enough that Pierscionek and Weale (1995) state "the equatorial growth of the lens is unlikely to play more than a subsidiary role in the progression of presbyopia particularly after the age of 20". Our discussion (Glasser & Campbell, 1998a) does not preclude such additional contributions to presbyopia but emphasizes "the evidence for predominantly lens-based theories of presbyopia" based on our experimental findings. We conclude, on the basis of our experimental results, that "age changes in zonular insertion angle are an unlikely cause of presbyopia", but suggest further experiments to determine if this might be "a partial factor in older lenses". Our initial results do not however, show the patterns expected if lens thickness and shape were a factor in presbyopia. We also suggest that additional experiments are necessary to define the change in accommodation per unit release of zonular tension as a function of age.

We are surprised by Weale's (1998) choice of citations for studies that have "suggested" age-related changes in the ciliary muscle and involvement of the iris root in the development of presbyopia and his failure to cite the other, more recent, and arguably more significant, studies *demonstrating* extralenticular changes with a time course matching the progression of presbyopia which were cited and discussed in detail by Glasser and Campbell (1998a). In spite of these morphological changes, the changes in the lens alone can completely account for the progressive decline and ultimate loss of accommodation in humans. We discussed in detail the potential chicken and egg relationships of the lens and extralenticular changes (Glasser and Campbell, 1998a).

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With regard to lenticular sclerosis (i.e. a hardening; as in arterial sclerosis, a hardening of the arteries) Weale (1998) paradoxically states that "no one has produced any evidence in favor of its occurrence", yet concedes that "some hardening occurs". Our experiments (Glasser & Campbell, 1998a) demonstrate that the human lens gradually loses the ability to undergo changes in focal length in response to mechanical stretching with increasing age. Further experiments (Glasser & Campbell, 1996; Glasser & Campbell, 1998b) show that the human lens is increasingly resistant to compressive forces showing an exponentially increasing hardness over the human life-span. Together with previous data (Fisher, 1971, 1973; Pau & Kranz, 1991) this is indeed evidence of lenticular sclerosis. The fact that these age changes in the human lens occur at all is the basis for our arguments for a predominantly lenticular basis of presbyopia. The constancy of water content of the lens with age has been debated (Siebinga, Vrenson, de Mul and Greve (1991) suggest an increase with age; Lahm, Lee and Bettelheim (1987), suggest a decrease in the lens nucleus), and recent measurements (Clarke, Campbell & Piers, 1998) show an increase in refractive index at the center of the lens as a function of age, consistent with a loss of water from the center and an increase in hardness.

2. Experimental arrangements

The stretching apparatus was designed to allow stretching of the human lens while measuring optical changes using a scanning laser apparatus. This is an experiment that, despite the apparent existence of an appropriate apparatus (Pierscionek, 1993; Pierscionek & Weale, 1995) as indicated by Weale (1998), has not been previously performed. Our apparatus was NOT, as asserted by Weale (1998), especially "designed to *obscure* the profile of the anterior surface", but was designed to facilitate using the scanning laser apparatus while allowing uniform stretching of the tissues. We set out to measure the changes in the optical properties of the lens with age and stretching which Pierscionek (1993), Pierscionek and Weale (1995) failed to measure. Furthermore, not all accommodative changes are mediated by the anterior lens surface. There is substantial evidence that the posterior lens surface is neither stationary nor unchanging during accommodation (Storey & Rabie, 1983; Lepper & Trier, 1987; Drexler, Baumgartner, Findl, Hitzenberger & Fercher, 1997; Findl, Drexler, Schmetterer & Fercher, 1997; Beers & van der Heijde, 1997) and that the central posterior radius of curvature is reduced on accommodation (Brown, 1973). We made no claims that the lens was "buoyed up" in aqueous solution. As discussed in the paper, our salt solution may or may not mimic the action of the aqueous/vitreous, perhaps dependent on age and vitreal liquification. We also describe that we did carefully limit the extent of relaxation of the stretching to limit any complete relaxation of the zonular fibers and thus limit lens sagging. Further, as discussed (Glasser & Campbell, 1998a), we demonstrated that sagging did not occur as no systematic change in focal length of the older lenses was seen with stretching or relaxation of the zonule, thus demonstrating that the older lenses were not systematically affected by sagging. Despite this, however, it is clear that lens sagging does actually occur during accommodation in young rhesus monkeys (Glasser & Kaufman, unpublished observations; Glasser & Kaufman, 1998), thus representing a natural part of the accommodative process in monkeys.

The scarcity, the value and utility of the use of human lenses in research, in our opinion, justifies some of the compromises necessary in order to undertake the kind of study we have done. Care was taken to ensure that the lenses were in the best possible condition. Lenses were transported at 4°C in sealed bottles in eye-bank coolers specifically designed for the transportation of procured eyes.

The time taken for the dissection and attachment of the ciliary body to the stretching apparatus was between 45 and 60 min. The eye was thus maintained in room temperature saline for up to an hour prior to the scanning laser measurements being started. This is sufficient time for the lenses to reach room temperature and prevent the occurrence of reversible cold cataract (Weale, 1983). No evidence of cold cataract was ever visible in any of the lenses. The authors are familiar with the phenomenon of cold cataract (Munger, Campbell, Kröger & Burns, 1992; Ansari, Dhadwal, Campbell & Dellavecchia, 1992). The improvement in optical quality in one or two of the lenses after being in solution (Glasser and Campbell, 1998a) was due to an improvement in optical clarity of the anterior lens surface within the pupil which had been exposed to air after prior removal of the cornea.

While the postmortem time of tissue usage was as long as 120 h in one case, Weale (1998) is *incorrect* in stating that "after more than eight hours post mortem, lysis of the ciliary system will have set in (Fisher, 1977; Pierscionek, 1993), and render stretching experiments questionable". Dramatic changes in lens power occurred with stretching in the younger lenses at substantially longer than 8 h post mortem as indicated in Fig. 1, demonstrating the effectiveness of the mechanical stretching. Our statement that the zonule remained intact is a simple statement that the stretching was not of an extent sufficient to cause zonules to be broken. Excluding post-mortem lenses over 60 h does not alter the significance or form of the relationship shown in Fig. 5a of Glasser and Campbell (1998a) (Fig. 1).

Weale contends that "the largest dioptric changes occur within a few hours after death (Weale, 1983)". However two previous studies by Weale contradict this statement and Weale's (1983) data and suggest that only small post mortem optical changes occur. Weale (1985) states "[n]ow that it seems fairly clear that both the image-forming faculty of the lens and its spectral transmissivity in the visible part of the spectrum (in short, its optical properties) can be maintained in their normal state for a very long time…" and Weale (1988) states that "…no significant change in either the image-forming properties of the lens (Weale, 1983) or its transmisivity (Weale, 1995) could be detected". In light of these statements and the Weerheim and Sivak (1992) study quoted in our paper, one would be led to believe that we are *completely* justified in using the human lenses as we have (Glasser & Campbell, 1998a).

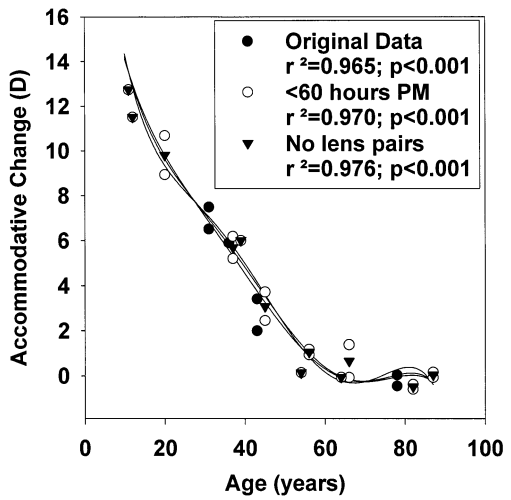

Fig. 1. Graph showing the relationship between the change in focal length with stretching as a function of age of human lenses (Glasser & Campbell, 1998). The filled circles show the original data replotted from Glasser and Campbell (1998a). This group comprises 27 human lenses. It includes all lenses used up to 120 h after death and lens pairs from the same donors. The open circles show a subset of the first data set comprised of the 20 human lenses that were used at less than 60 h post mortem. This subset also shows individual lens pairs from the same donors. The filled triangles show data from human lenses ($n = 13$) used at less than 60 h post mortem with each lens pair from the same donors ($n = 7$) averaged to represent a single data point. Three individual regression curves are shown, one for each data set. This figure shows that if we exclude lenses that were used at more than 60 h post mortem ($n = 7$ lenses) a 5th order polynomial fits the data ($n = 20$; polynomial regression; $p < 0.001$) with a level of significance no different from that shown in Fig. 5a of Glasser and Campbell (1998a). Further, if we then replot this same group of lenses used less than 60 h post mortem, but now also average lens pairs from the same donor (seven paired lenses), here too, a 5th order polynomial ($n = 13$; polynomial regression, $p < 0.001$) provides a relationship with a level of significance not different from our original. The regression coefficient increases in each case indicating that excluding lenses longest after death improves (but does not alter) the regression and that pairing lenses from the same donors further improves the regression (although again without altering the relationship). Necessarily, many of the data points are identical between the successive plots and therefore overlie each other.

3. Interpretation of results

Fig. 1 shows that Weale (1998), although perhaps correct in his criticism of our statistical methods, is *incorrect* in his speculation that the analysis he suggests will lead to a reduced level of significance. To the contrary, averaging lens pairs from the same donors results in an improved regression ($r^2 = 0.976$, $p < 0.001$) although without altering the relationship shown by Glasser and Campbell (1998a). Our results, thus provide an overriding demonstration that lenses older than 50 years of age cannot be made to undergo changes in focal length and that there is a significant relationship between how much the focal length can be changed and age. This fact cannot be disputed from our experiments.

After rechecking the analysis, we concur with Weale that the two regression lines in Fig. 4b are nonsignificant. We had stated that the slope of the pre-presbyopic lenses was not significantly different from zero. We are in error for not having specifically indicated a lack of significance for the presbyopic line segment and for having stating in the text that the slope of the presbyopic lenses is significantly different from zero.

The intercept of the linear regression shown in Fig. 4c (Glasser & Campbell, 1998a) is given and with a value of 4.5 it is only slightly greater than zero. Comparing the fit shown with a 1/1 line shows that the focal length of the youngest lenses is actually 7% *shorter* after the stretching tension is released, and also that the focal length of the oldest lenses is actually 2% *longer* after the stretching tension is released. The directions of these changes are inconsistent with the notion of irreversible changes having been induced and are sufficiently small that they are not likely to be of physiologically importance. No misleading conclusions were drawn and there is no systematic irreversible stretching of the lens, the capsule or the zonule

We justified the admittedly arbitrary division of the data at age 50 years in Fig. 4b on the basis that beyond this age it is generally accepted that no accommodation occurs. It was also important to show that the second line segment in Fig. 4b was not significantly different from that in Fig. 4a but that the stretched and unstretched younger lenses did differ. We have reconfirmed these two results. Since the intercepts and slopes of the two sets of data over age 50 (stretched and unstretched focal lengths as a function of age) are not significantly different ($p > 0.7$), we have pooled the data and tested the significance of the age variation of focal length. The focal length increases significantly over age 50 as a function of age:

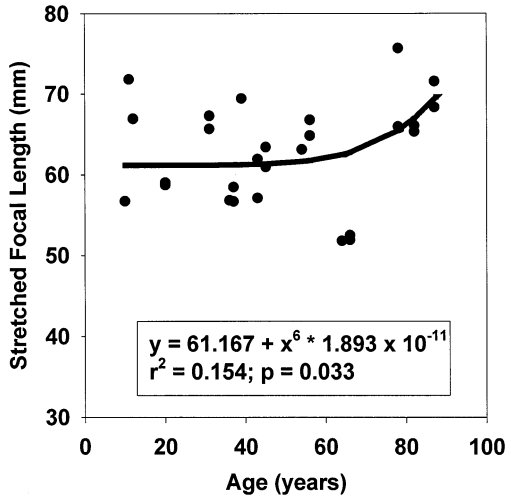

Fig. 2. Graph of the maximally stretched lens focal lengths as a function of age. The data are significantly fitted ($p = 0.0326$) with a regression line of an intercept plus a 6th order term to show that the focal length of the stretched lenses is not constant, but increases beyond age 60.

$$FL = 39.5 + 0.34*AGE \quad p < 0.009,\ r^2 = 0.27$$

where FL is the focal length in mm and AGE is the age in years.

We concur with Weale (1989) that discontinuities are a biological rarity, but the complete failure of a physiological function 2/3 of the way through the human life-span, such as occurs with presbyopia, may be just such a rarity. We did show the stretched lens focal length as a function of age as a continuous curve in Fig. 5b and we discuss this continuous relationship and the change in the slope at about age 60 in the text. In the same way that the loss of accommodation with age must be fitted with a continuous curve, so too must the change in focal length with age of the stretched lenses. Weale's nonsignificant linear fit cannot be justified. While a 6th order polynomial fit to the data in Fig. 4b) is not significant ($r^2 = 0.1903$; $p = 0.1106$), a constant term plus a single high order term, either an intercept plus a 5th order term ($p < 0.043$) or an intercept plus a 6th order term ($p < 0.033$), provides a significant fit to the complete range of data of stretched focal length as a function of age (Fig. 2). Adding the nested lower order terms back in does not improve the fit significantly. The intercept plus 6th order term alone is a better fit than any other nested lower order polynomial models using a test of the significance of the reduction in the sum of squares due to error. Although adding a 7th order term to this model does not provide a significant improvement in the fit, an intercept plus a 7th order term provides a more significant fit. This also justifies our original approximation of the data in Fig. 4a (Glasser & Campbell, 1998a) by two line segments (personal communication, statistics consultant, Erin Harvey). Fig. 2 shows a plot of this data fit with a constant and a 6th order term ($r^2 = 0.1544$) and demonstrates that the stretched lens focal lengths increase dramatically after age of 60, thus refuting Weale's claim of constancy of stretched lens focal length with age. Further, if Weale were correct in his supposition that focal length is independent of age for both stretched and unstretched lenses, an analysis analogous to Fig. 5b would indicate that there could be no change in accommodative amplitude with age.

Fits aside, no-one looking at our data in Figs. 4a, b and 5a of Glasser and Campbell (1998a) could believe Weale's assertion that "the focal length of stretched lenses, like that of unstretched ones (Weale, 1983, 1992) is, after infancy, independent of age". The unstretched focal lengths in Fig. 4a increase linearly with age ($r^2 = 0.8$, $p < 0.001$), doubling over the age range measured. Weale's incorrect conclusion is likely due to the fact that he studied *no* lenses between the ages of 9 months and 32 years (Weale, 1983) or that incorrect approximations and assumptions were made in his speculations which include no original data (Weale, 1992). The statistical interpretations used to support his conclusions (Weale, 1983) must also be questioned based on the criteria outlined by Weale (1998) himself as no indication of whether lens pairs from the same donor were used and no conditions of transport of the tissues between the hospital and laboratory were given. Young human lenses, when devoid of the outward directed zonular forces, will become accommodated. Glasser and Campbell (1996, 1998b) have measured the focal length of isolated human lenses and show, as expected, substantial change in focal length and surface curvatures over the age range omitted by Weale (1983).

Older lenses (> 55) show continued age related changes which are not significantly different between stretched and unstretched lenses. This demonstrates that these are presbyopic lenses beyond the age at which accommodation is lost. The lens paradox, frequently cited as a factor in presbyopia, claims a constancy of unaccommodated (or stretched as in the case of our experiments) lens focal length with increasing age and a changing gradient refractive index to compensate for increased lens curvatures. Clearly, if our data demonstrate a lack of constancy of focal length, this (1) demonstrates a progressive age related change in the lens that starts early in life; (2) disputes the lens paradox supposition for a constant lens focal length; (3) disputes that the gradient refractive index of the lens changes to maintain a constant lens focal length throughout life; and (4) disputes the proposed regulated compensation between lens curvatures and focal length. The lack of constancy of lens focal length over the entire life-span therefore provides evidence that presbyopia and the changing optics of the lens are the consequence of age changes (or aging of the lens) rather than preprogrammed, compensatory changes with age.

With respect to the age of intersection in Fig. 4b of Glasser and Campbell (1998a) being given to two decimal places, it was our intention to provide an accurate number that may be used in future calculations. That Weale (1989) chose to compute accuracy to four decimal places is obviously unreasonable.

No "numerical manipulations" were used to calculate the curves in Fig. 5b of Glasser and Campbell (1998a). This is simply a depiction of the equations from the continuous and *significant* curves shown in Fig. 4a (curve 2) and Fig. 5a (curve 1 converted to mm of change) (Glasser & Campbell, 1998a). The sum of these two curves produces a continuous curve similar to Fig. 2 in this paper. The fact that a continuous 5th or 6th order curve fitted to the data in Fig. 4b, as described above, produces a similar relationship to that shown in the upper curve in Fig. 5b shows that the plots are self-consistent. These curves are achieved through the well known relationships between power and focal length, which are by no means complex manipulations. The "unresolvable confusion" in the top two curves in Fig. 5b demonstrates precisely the point that there is *no* change in the focal length of the older lenses with stretching. This fact demands that the two curves are superimposed over this age range.

We concur with the statement from Weale (1998) that "care has to be exercised, in general, in the selection of data on presbyopia used to test hypothesies". Weale's work and his many review papers on presbyopia are well known to, and referenced, by us. The prevalence of review papers and the dearth of *new data* in the field of presbyopia provided us with the impetus to undertake these long overdue studies. We welcome, expect, and have already had (even between ourselves) considerable debate on the issues raised by our data. However, the data should drive the assertions, assumptions and theories.

While Weale (1998) may be critical of the frequently cited and classical work of Duane (1922), subsequent experiments using a variety of methodologies have found age dependent declines in accommodative amplitude that follow Duane's general trends (Hamasaki Org & Marg, 1956; Koretz, Kaufman, Neider & Goeckner, 1989). Duane's results were used since his data are provided in table form. Duane's substantial study population makes it clear that differences in accommodative amplitude occur between individuals of the same age, making the findings of Brückner, Blatschelet and Hugenschmidt (1989), of little significance. We acknowledge that the lens studies and subjective measurements of accommodation differ due to chromatic aberration, but by less than the range of subjective accommodative amplitude across individuals. No correction for depth of focus, blanket or otherwise, is applied to the data for change in lens power with age in Fig. 5a of Glasser and Campbell (1998a). In the discussion, we discuss the differences between lens power changes and accommodative amplitude. We suggest that Duane's curve can be "corrected" by subtracting 1.5–2 D of accommodation, representing depth of focus, based on a multitude of cited studies. Weale ignores the additional discussion of the difference between lens power changes and accommodative amplitude, which, we explain, would also cause the lens curve to be lowered. We discuss the impact of both these corrections (which move the two curves in the same direction) on the age at which accommodative amplitude reaches zero. We then discuss the good agreement between the age implied by our lens results and by the measurement of accommodative amplitude (Hamasaki et al., 1956; Koretz et al., 1989) We did not discuss the differing orrections needed as a function of age because the necessary age dependent values are not available. At no time do we attribute any correction to "the final dioptre of accommodation in Duane's study". The stretching of excised lenses may not give definitive answers, but photography of the living lens is also unlikely to. Photography does not give any data on the changes in the focal length of the crystalline lens or the refractive index changes with age and accommodation and it provides information on only a limited region of the posterior lens surface. We have discussed in depth the limitations of the stretching technique in conjunction with the insights it provides. It is unclear how the data can be "freed of inherent" limitations.

We thank Weale (1998) and an anonymous reviewer for the opportunity to clarify these points in our paper. We are, frankly, baffled by many of the points raised by Weale (1998) and his interpretations of our work. While it is clear that the intention was to raise some debate on the issues we have addressed, no evidence has been offered to refute our claims for a predominantly lens based theory of presbyopia or to demonstrate that the lens does not become less deformable with increasing age. We believe that we have demonstrated that the data are highly relevant to the contentious issue of presbyopia and we have discussed in depth their implications to many of the prevailing theories. Furthermore, the data support a predominantly lens based theory of presbyopia, and do not support some other theories. The data does not preclude other well documented extralenticular age changes in the eye which may (or may not) contribute to presbyopia. The absence of similar experimental results on presbyopia should be a wake-up call to researchers in the vision science and ophthalmic medical communities, especially in light of recent surgical approaches proposed for the reversal of presbyopia (Schachar, 1992). New and varied approaches and studies on presbyopia should be encouraged and welcomed.

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