Blue light and age-related macular degeneration (AMD): avenues for research

This publication is informed by the following research conducted on behalf of Thomas Pocklington Trust:


Prolonged exposure to blue light may cause damage to the retina. This means there is a possibility that blue light exposure may have a role in the development and progression of age-related macular degeneration (AMD). There is a need for fundamental, clinical and applied research to help answer three basic questions:

- Does long-term blue light exposure lead to retinal damage, particularly AMD?
- Would blue light filtering be a good idea in intraocular lenses?
- What are the consequences of reducing blue light exposure for visual and circadian functions?
**Introduction**

Blue light is conventionally defined as radiant energy in the wavelength range 400 to 500 nm. Burman-Roy and Blackhall (2005) revealed that prolonged exposure to blue light may cause damage to the retina by stimulating chromophores to generate reactive oxygen species and hence exert oxidative stress on the cells of the retina. This damage can be repaired at low dosages, but as dosage increases the likelihood of permanent damage increases.

While this mechanism is plausible, the role of blue light exposure in the development and progression of AMD in humans cannot be confirmed because the available evidence is inconsistent. There is evidence from animal studies that blue light exposure can cause retinal damage, but whether such findings are transferable to humans is open to question. There is some epidemiological evidence that many years’ exposure to high light levels is associated with the development of AMD. However, such evidence is often derived from groups working outdoors in bright sunlight, and it is unclear how relevant such evidence is to people who work indoors. There is still much to learn about the impact of blue light exposure on AMD. That knowledge will be gained through fundamental, clinical and applied research.

- The fundamental research is focused on understanding the onset and progression of AMD as well as the absolute and spectral sensitivity and the limits of reciprocity.
- The clinical research would provide a direct test of the significance of blue light exposure to AMD by undertaking a randomised clinical trial of the relative effectiveness of blue light-filtering and clear intraocular lenses respectively.
- The applied research is focused on accurate measurement of blue light exposure that occurs in everyday life and the consequences of reducing such exposure for visual and circadian functions.
Background

In 2004 Thomas Pocklington Trust funded a literature review on the effects of blue light on the eye to be carried out by Moorfields Eye Hospital Research and Development Department. ‘Blue light’ was defined as radiant energy in the wavelength range 400 to 500 nm. The NHS Dialog service was used to identify relevant research published after 1969. The researchers identified 181 documents as potentially relevant, but closer inspection reduced this to 55. These documents were all examined in detail to identify and analyse evidence for and against the hypothesis that exposure to blue light is a contributing factor in the incidence of eye disease. The strength of the evidence was assessed using the Bradford Hill criteria of causation. There are nine such criteria, representing requirements that need to be met if an association between two variables is to be considered causal and not accidental. They are:

- Temporal relationship: for an association to be causal, exposure must always precede the outcome.
- Consistency: for an association to be causal, the association should have been found by multiple investigators using different methods in different populations in different places.
- Strength of association: for an association to be causal, the outcome should be frequently found following exposure and not frequently found without exposure.
- Dose-response relationship: for an association to be causal, higher levels of exposure should lead to a greater probability of the outcome.
- Specificity: if an association is limited to specific populations or sites and there is no other explanation for the disease, then an association can be made between outcome and exposure.
- Coherence: for an association to be causal, the data should not conflict with the generally known facts about the outcome in question.
- Biological plausibility: for an association to be causal, the proposed causation should fit existing knowledge.
- Reasoning by analogy: sometimes it is possible to argue for an association by analogy, e.g. if other forms of optical radiation can be shown to cause retinal damage.

1 Burman-Roy and Blackhall (2005)
• Experimental evidence: the strongest evidence in favour of an association is direct experimental evidence that the presence of the exposure leads to the outcome and its absence does not. For ethical reasons such evidence is not easily obtained for humans. Of these nine criteria, the research relevant to an association between blue light exposure and eye disease demonstrated temporal relationships, consistency, strength of association, dose-response relationships and biological plausibility, and there was some experimental evidence on humans at the population level. The other three criteria: specificity, coherence and reasoning by analogy, were not clearly met.

The proposed mechanism, derived from laboratory experiments using a variety of animal models, is that exposure to blue light stimulates chromophores to generate reactive oxygen species and hence exert oxidative stress on the cells of the retina. This results in retinal lesions and other signs of retinal dysfunction. This damage can be repaired at low dosages, but as dosage increases the likelihood of permanent damage increases. Blue light is expected to be most potent because a short-wavelength photon of light carries more energy than a photon of longer wavelength light.

As for the experimental evidence on humans, four epidemiological studies have been performed at the clinical or population level. These were consistent with the cellular findings of the animal studies and suggested that exposure to sunlight, which is rich in blue light, is associated with the development of age-related macular degeneration (AMD) in the elderly and in pseudophakic and aphakic people.

Burman-Roy and Blackhall (2005) therefore supported the hypothesis that exposure to blue light is a contributing factor to the incidence of retinal eye disease. However, cumulative light exposure was not found to be associated with AMD in humans to a statistically significant extent, except in the elderly and in pseudophakic and aphakic people.

The objective of this paper is to consider what research is needed in order to answer the following questions:

• Does long-term blue light exposure lead to retinal damage, particularly AMD?
• Would blue light filtering be a good idea in intraocular lenses?
• What are the consequences of reducing blue light exposure for visual and circadian functions?
These questions are relevant to the work of Thomas Pocklington Trust. If long-term blue light exposure does lead to AMD, then the answers to the other two questions would allow guidance to be developed that would reduce the risk of retinal eye disease while preserving the benefits of blue light for visual and circadian function. Such research is also timely because of two current trends in lighting practice. One is the greater use of daylight in buildings. This trend is driven by the desire to reduce the consumption of electricity generated by burning fossil fuels. Daylight is rich in blue light so more exposure to daylight will increase exposure to blue light. The other trend is the enthusiasm for light emitting diodes (LEDs) as the electric light source of the future. Many white LEDs have a strong peak of radiation in the blue. If these two lighting trends are converted into common practice, many people will in future be exposed to higher levels of blue light for longer.

**Update**

Since the 2005 Burman-Roy and Blackhall report, there have been two particularly significant publications on blue light exposure and eye disease. One of these publications was based on the European Eye (EUREYE) Study. This was a large multi-national epidemiological study aimed at measuring the prevalence of AMD in Europe and exploring the relationship between sunlight exposure, antioxidant level and AMD. From a sample of people living in countries ranging from Estonia to Greece, data on sunlight exposure and antioxidant levels were available for 101 people with neovascular (wet) AMD, 43 with geographic atrophy (dry) AMD, 2,182 people with early AMD and 2,117 people with no signs of AMD. The lifetime exposure to sunlight and, by implication, blue light, was estimated from interviews and meteorological data. Antioxidant levels were measured from blood samples. The level of AMD was measured from fundus photographs. The EUREYE study did not find a direct association between sunlight exposure and wet AMD or early AMD. However, it did find a significant association between blue light exposure and wet AMD for people in the lowest quartile of

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3 The association between sunlight exposure and dry AMD was not investigated because of the small numbers of people with this condition.
antioxidant levels (Odds ratio = 1.4 for a one standard deviation increase in blue light exposure). This association grew stronger when some combinations of antioxidants were examined (Odds ratio = 3.7), so much so that blue light exposure could also be associated with early AMD. Fletcher et al (2008) conclude that, although it was not possible to establish causality between sunlight exposure and wet AMD, the general population should use ocular protection and follow dietary recommendations for key antioxidant nutrients.

The other important publication is a review of the impacts, both positive and negative, of blue light-filtering intraocular lenses (Cuthbertson et al, 2009). This is an important topic because intraocular lenses are most commonly fitted after lens removal due to a cataract forming in the lens. This usually occurs in the elderly, because they are most likely to have accumulated chromophores in the retina and such an accumulation makes the retina more liable to oxidative damage. Because the lens of the eye yellows with age, removing the lens will increase the amount of blue light reaching the retina, unless the replacement lens filters blue light. Cuthbertson et al review the evidence for a reduction in blue light exposure protecting the retina. They conclude that although studies using animals show retinal damage in response to blue light exposure, convincing epidemiological evidence of such damage for humans is sparse. The mechanisms underlying the pathogenesis of AMD are not well understood and probably involve many factors, including inflammatory and genetic factors as well as light exposure. Despite this uncertainty, Cuthbertson et al declare that it would be sensible to reduce blue light exposure for pseudophakic patients by using blue light-filtering intraocular lenses. This is especially the case where retinal damage may be accelerated due to an underlying pathology such as early AMD, or in the ageing eye where chromophores have accumulated.

Cuthbertson et al also point out that reducing the amount of blue light reaching the retina, or stopping it altogether, can have an impact on visual function. Somewhat surprisingly, there is little evidence for a difference in colour vision between people with blue

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5 Ibid
6 Ibid
light-filtering lenses and those with clear intraocular lenses. Nor is there much evidence for a detrimental effect of blue light-filtering on photopic and mesopic contrast sensitivity. However, when it comes to scotopic sensitivity, there is a theoretical case that a reduction in blue light should have an adverse effect, because in scotopic vision only the rod photoreceptors are used, and these have a peak spectral sensitivity at 507 nm. This possibility is compounded by the fact that the number of rod photoreceptors declines with increasing age, even in healthy eyes. A combination of a smaller number of photoreceptors and reduced stimulation should produce slower adaptation for dark conditions and inferior visual function when adaptation is complete.

Another possible negative consequence of reducing blue light is a diminution in the light / dark signal used to synchronise the human circadian system. The photoreceptors used to signal to the master clock of the circadian system, the suprachiasmatic nucleus, are not the same as the photoreceptors used by the visual system, although the latter may be involved to some extent. The circadian photoreceptor has a peak sensitivity around 470 nm, i.e. in the blue light region of the visible spectrum. Therefore, reducing blue light exposure will also reduce the strength of the signal to the circadian system. A properly synchronised circadian system is characterised by a regular sleep / wake pattern, and there is evidence of improved sleep patterns in patients fitted with clear intraocular lenses after cataract removal. It is not known to what extent blue light-filtering intraocular lenses cause a deterioration in sleep patterns. If this did happen, it would be most likely to occur in people who spend most of their time indoors under low levels of electric lighting.
Conclusion

From the studies summarised above it is concluded that the role of blue light exposure in the development and progression of AMD remains a possibility rather than a certainty – a hypothesis rather than a fact. This is because the available evidence is inconsistent. There is certainly evidence from animal studies that blue light exposure can cause retinal damage, but whether such findings are transferable to humans is open to question, especially when nocturnal animals are exposed to light during the day. There is also some epidemiological evidence that exposure to high light levels for many years is associated with the development of AMD. This evidence is often derived from groups working outdoors in bright sunlight, however, and it is not clear how representative such exposures are to people who work indoors. There are also some epidemiological studies that have tried but failed to find an association between light exposure and the development or progression of AMD, and there may be more such studies that are unpublished, as there is a bias against publishing non-significant findings.

Even if epidemiology had been able to establish a clear link between blue light exposure and AMD, the risk associated with different levels of exposure would still be uncertain. This is because the exposures used in epidemiological studies are retrospective estimates. Such estimates are subject to large uncertainties because they are based on reported behaviour rather than measurement. Further, in most of the epidemiological studies, daylight has been used as a proxy for blue light. While daylight, or at least sunlight, is rich in short wavelengths, the intensity can vary enormously depending on the latitude, climate, season, time of day and state of the atmosphere.
Suggested Research

It is likely that AMD will be an active area of research for many years. This is because AMD is the most common cause of sight loss in developed countries, many of which have an ageing population. There are thus a great number of people with an interest in finding a solution to AMD. The research required to find out if light exposure makes a significant contribution to the development and progression of AMD can be divided into three areas: fundamental, clinical and applied.

Fundamental research

Fundamental research is research undertaken to determine fully all the factors that influence the onset and progression of AMD. Understanding the relevant factors could reveal a range of possible actions that might be taken to minimise retinal damage following exposure to light. Such actions may include pharmaceutical, dietary, behavioural and optical measures.

Among the many questions that need to be answered about the factors that influence the pathogenesis and development of AMD, three are significant for quantifying the effect of light exposure. They are:

- What is the spectral sensitivity of the mechanism that causes the damage? Only after this spectral sensitivity is established will it be possible to assess correctly the relative risk associated with exposure to light from different light sources, both natural and electric.
- What level of spectral irradiance is required to cause retinal damage in different groups? The answer to this question would make it possible to determine whether light exposure is a hazard to people only in areas of strong sunlight or if it occurs in all climates and even indoors.
- Under what conditions does the reciprocity between light intensity and duration of exposure break down? Using a measure of light exposure implies that the same level of retinal damage can be caused by exposure to high-intensity irradiance for a short time and by low-intensity irradiance for a long time. There is no doubt that the former can cause retinal damage but it is the latter situation that is of practical concern. Understanding if the results obtained using the former condition can be applied to the latter is important for making the best use of existing information and for accelerating research.
Research aimed at understanding the mechanism that causes retinal damage following light exposure will be a laboratory activity rather than a field study.

**Clinical research**

In the past, epidemiology has had limited success in finding a link between light exposure and the development or progression of AMD. Today, the widespread use of intraocular lenses following the removal of cataracts provides an opportunity for a direct test of the role of blue light exposure in the development and progression of AMD. Intraocular lenses are commercially available with and without blue light filters. A randomised clinical trial designed to determine the effectiveness of blue light-filtering intraocular lenses relative to clear intraocular lenses would be valuable. Such a trial should examine both changes in the state of the retina over time and the consequences of those changes for functional vision and quality of life.

**Applied research**

If it can be shown that exposure to blue light is a significant factor in the development or progression of AMD, then a number of applied research topics become worthwhile. Such research should explore the amount of blue light produced by different light sources, the actual light exposures experienced by people in their everyday lives and the consequences of various actions that might be taken to limit exposure to blue light. These consequences can take two forms: changes in the levels of exposure to light and changes in visual capabilities.

The light sources to which people are exposed can vary widely. For those working outdoors, the dominant light source will be daylight. For those working indoors, the dominant light source will be one of a wide range of electric light sources, some rich in blue light and some not. The relative amounts and the spectra of such exposures need to be quantified. This can be done by laboratory measurements of different light sources and by field measurements of people’s exposure over many days. Such measurements are currently being made of the exposure of the human circadian system to light. There is no reason why similar measurements should not be made for retinal damage once the necessary spectral sensitivity has been established.
A number of proposals have been made to reduce light exposure in practice ranging from the temporary, such as wearing a hat or sunglasses outdoors, to the permanent, such as implanting blue light-filtering intraocular lenses. How effective these various measures are in reducing the irradiance at the eye and retina needs to be quantified. Ideally, this would be done after the spectral sensitivity of the mechanism linking light exposure to retinal damage had been established, but until that is achieved it should be possible to measure the spectral irradiance at the eye allowing any spectral sensitivity curve to be applied at a later date.

Another area that deserves investigation is the visual consequences of some of the methods proposed to reduce light exposure. Not all the methods proposed need to be studied. It is always possible to remove a hat or sunglasses, but the same is not true of intraocular lenses. Theoretically, the most likely areas of concern are visual performance in very low light levels and the impact on the circadian system. Some work has already been done on this topic but has used standard ophthalmological tests. It would be interesting to explore the consequences of using blue light-filtering rather than clear intraocular lenses for carrying out tasks common in everyday life.

These applied research topics are likely to involve a mixture of laboratory and field research. Accurate measurement is easier in the laboratory but field research should be more representative of reality. Whichever method is used, accurate interpretation of the level of risk posed by the exposures measured will remain difficult. The relative risk posed by different light sources and after different remedial measures might be established by using an appropriate level of sunlight as a starting point but absolute risk will be impossible to determine without an understanding of the causes of AMD.
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How to obtain further information
For more detail on the research project discussed above, Burman-Roy, S and Blackhall K (2005) Systematic review of the effects of blue light on the eye, contact:
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Copies of this paper in large print, audiotape or CD, Braille and electronic format are available from Thomas Pocklington Trust
**Background on Pocklington**

Thomas Pocklington Trust is a leading provider of housing, care and support services for people with sight loss in the UK. Each year we also fund a programme of social and public health research and development projects.

Pocklington’s operations offer a range of sheltered and supported housing, residential care, respite care, day services, resource centres and volunteer-based community support services. We strive to improve continuously the quality standards in our operational centres to meet the changing needs and expectations of our current and future service users. We are proud to be an Investor in People and a Positive about Disability organisation.

Our research and development programme aims to identify practical ways to improve the lives of people with sight loss by improving social inclusion, independence and quality of life, and improving and developing service outcomes as well as focusing on public health issues.

*In this publication, the terms ‘visually impaired people’, ‘blind and partially sighted people’ and ‘people with sight loss’ all refer to people who are blind or who have partial sight.*