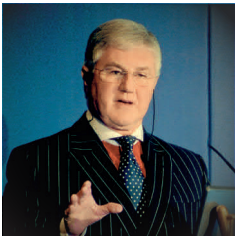


# THE BLUE LIGHT PARADOX: PROBLEM OR PANACEA

The penetration of optical radiation deep within the eye is a paradox as light is an essential component for vision but it may also be a biohazard. Short wavelength blue-violet light is potentially harmful whilst longer wavelength blue-turquoise is essential for healthy living. Prof. John Marshall explains in this article the pathogenic power of light but also its fundamental requirement to circadian rhythms. In the human eye evolutionary development both mechanisms have been integrated to facilitate separation of health and hazard.



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More recently in 2012 he received the Junius-Kuhnt Award and Medal for his work on AMD.

Professor Marshall has authored over four hundred research papers, 41 book chapters and 7 books.

## Light: vision and biohazard

The eye is the only organ in the body that has evolved to allow radiation to penetrate deep within it. In this process however the various ocular media, cornea, aqueous, lens and vitreous act as progressive wavelength selective filters such that ultraviolet B (280-315 nm)<sup>1</sup> radiation is absorbed almost exclusively in the cornea whilst ultraviolet A (315-400 nm)<sup>1</sup> may be attenuated by the cornea with almost all of the remaining radiation of this wavelength being absorbed in the lens<sup>2-4</sup> and only a very small amount passed to the retina (Fig 1). However optical radiation between 400 and 1400 nm made up of visible radiation or light (400-800 nm)<sup>1</sup> and infrared A (800-1400 nm)<sup>1</sup> not only passes through the various optical media to fall upon the retina but at the same time undergoes a concentration in irradiance of up to a hundred times between the cornea and the retina as a result of the refractive power of the cornea and to a lesser extent of the lens. It is this refractive property that concentrates the incident energy and converts for example the rays of the summer sun from the pleasantly warming sensation on the skin to a potential hazard to the eye if the sun is viewed directly. This penetration of optical radiation is the first paradox as radiation is a biohazard<sup>5-14</sup> but light is an essential component in the process we know as vision.

## Renewal processes of cells

In all biological systems cells under stress are normally replaced on a periodic basis in order to combat environmental attrition. For example the cells of the skin are replaced by a never-ending cycle whereby new cells progressively move towards the surface of the body and are then shed, usually within five days of creation. This

### KEYWORDS

blue-violet light, biohazard, ultraviolet, free radicals, retina, photoreceptor cells, light exposure, retinal pigment epithelium, lipofuscin, drusen, AMD, LEDs, foveal tritanopia, photoaging, circadian rhythm, SAD, seasonally adjusted disorder

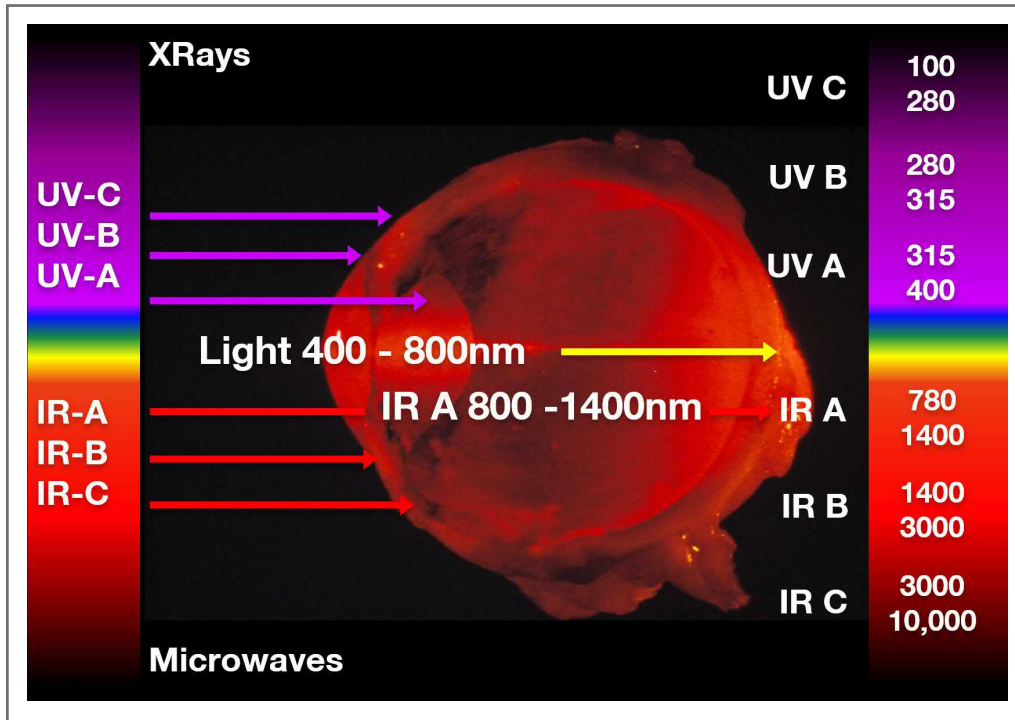


FIG. 1| Penetration of optical radiation within the human eye.

process ensures that our skin is able to cope with the problems of both friction induced by touching things and of the effects of optical radiation. A similar process is found in the lining of the gut whereby renewal of cells overcomes the problem of focal trauma caused by the passage of food and the toxic chemical environment required for digestion. These renewal processes make the concept of ageing in biological entities an extremely difficult parameter to define as the cells of those parts of our body which are constantly dividing may be a few days or weeks old whilst those in other parts of the body which don't divide may have been created shortly after conception or some time during the developmental processes in the womb.

#### Toxic blend of oxygen and light

Here then is a second paradox in that the retina may be considered as part of the brain as it develops early from the neural tube and as the cells develop they ceased to have the capacity to renew themselves. The photoreceptor cells, rods and cones, have a significant problem in that they are not only exposed to optical radiation throughout life but they have to transduce it in order to initiate vision.<sup>15-16</sup> This process requires huge amounts of energy and as a consequence the cells have an extraordinary high oxygen demand being equipped with the highest concentration of mitochondria in any cells of the body. Thus this non-dividing cell system is simultaneously exposed to an environment with extremely high levels of both oxygen and radiation. This combination is known to be extremely toxic to biological systems because of the induced generation of superoxide and other free radicals.<sup>17-20</sup>

#### The beauty of inverted retina

The next paradox is generated by the need to provide metabolic sustenance to the rods and cones in order to sustain their huge metabolic demand. This has been solved in all vertebrates by the evolution of the so-called inverted retina. At first sight it would seem strange that the cells that do the transducing of light are on the side of the retina furthest away from the incoming radiation. This apparent anomaly becomes understandable when the requirements for a blood supply to the light-sensitive cells is examined. If the photoreceptors pointed towards the incoming light then they would either have to have a large blood supply between them and the incoming light, thereby limiting transmission and resolution, or a large blood supply between the photoreceptors and the next layer of neurones thereby limiting neuronal processing. The structure of the inverted retina avoids these issues by allowing the photoreceptor cells to derive their blood supply from the innermost aspects of the choroid via an acellular membrane, Bruch's membrane and the pigment epithelium.<sup>21</sup> This anatomical arrangement also enables the retinal pigment epithelium to act as an anti-halation screen absorbing much of the unused radiation that has passed through the photoreceptor cells and thereby prevents scatter and degradation of the retinal image.<sup>22</sup>

#### Auto-regenerative capacity of photoreceptors

The juxtapositioning of the photoreceptor cells and the retinal pigment epithelium also allows for a solution of the fourth paradox, that is how can non-dividing cells like the photoreceptors survive over a human lifetime in an environment of high oxygen and with the function of absorbing and transducer optical radiation. The solution is unique amongst neurones and that is throughout life



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the light-sensitive portions of the photoreceptor cells are constantly renewed. This is an exquisite process which differs between rods and cones. Animal studies in rods demonstrated that 3 to 5 of the light sensitive membrane structures or discs are being manufactured daily<sup>23-25</sup> on the innermost aspect of the light-sensitive outer segment and as new discs are added older discs are progressively displaced towards the retinal pigment epithelium.<sup>26-28</sup> Typically a rod outer segment contains about 1000 discs and thus in theory the whole system is replaced in approximately two weeks. When the older discs reach the surface of the retinal pigment epithelium they are phagocytosed in a process that seems to be initiated by the onset of light on first awakening in the morning.<sup>29-31</sup> Thus the spent products from our night-time photoreceptors, the rods, are phagocytosed first in the morning and then undergo “digestion” during the day by the action of lysosomes. By contrast it would appear that our daytime photoreceptor cells, the cones, are phagocytosed four hours or so into the sleep period and undergo degenerative processes during the night.

### Biomarkers of ageing

This process of daily shedding of spent material from the photoreceptor cells presents a huge biomass to the retinal pigment epithelium and not surprisingly the system becomes compromised as a function of age. In most retinae, by the late 20s, persistent partially degraded debris becomes present within the retinal pigment epithelium and is seen as **lipofuscin granules** which are autofluorescent and visible clinically.<sup>32-36</sup> As a result of further ageing processes debris begins to pass from the retinal pigment epithelium into the underlying Bruch’s membrane and may in some cases be seen in the six or seventh decade as focal excrescences termed **drusen**. Drusen are also visible clinically and are identified as high-risk factors for AMD<sup>37-41</sup> in the outer retina we see then an exquisite protection mechanism to preserve the functional lifetime of the rods and cones by constantly regenerating the light-sensitive components but one which ultimately leads to long-term problems for them by degrading the very transport mechanisms on which their survival is dependent. Regardless of the genetic make up of any given individual, photoreceptor cell function of

outer segment material will be degraded as a function of natural ageing processes and to some extent the rate-limiting steps of the degradation will be related to the rate of turnover of discs. Very simply the outer retina has evolved to sustain the lifetime of non-dividing highly specialised neurones, rods and cones, and to do so in a system that is irradiated by and absorbs optical radiation throughout life in a high oxygen environment. This system works extremely well over the period in which we should procreate but perhaps now with ever increasing life expectancy it is not surprising that the system shows significant signs of fatigue with increasing age.

### The pathogenic power of light

Throughout evolution man has been exposed to light cycles of roughly 12 hours of daylight and 12 hours of darkness with a further variance induced by the tilt of the Earth in summer and winter. **The sun is by far the brightest light source that we are exposed to and has by far the broadest emission spectrum with radiations from the ultraviolet through the shorter wavelengths of infrared.**<sup>42</sup> Fortunately our atmosphere shields us from the most damaging forms of optical radiation in that very little ultraviolet C (100-280nm) is able to reach ground level although the ever-increasing depletion of the ozone layer with “holes” over the Antarctic are of increasing concern.

Basic physics has long established the relationship between wavelength and energy. The shorter the wavelength the higher the energy of the component particles. In the electromagnetic spectrum this is easily remembered by the finding that ultraviolet radiation sits next to x-rays, which are highly energetic whilst infrared is adjacent to microwaves. **Simplistically from the ultraviolet through to the blue region of the spectrum individual photons have enough energy that by themselves they can induce photochemical changes in absorbing molecules.**<sup>10, 43, 44</sup> By contrast from the red region up through the infrared individual photons no longer have sufficient energy to act by themselves and damage mechanisms induced by radiation in these wavebands come about by multiple photons causing vibrational modes in absorbing tissues and damage resulting from



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thermal processes. **Thus in considering the potential hazards of any given light source, attention must be given to the spectral emissions and spectral radiances with blue rich sources being potentially much more damaging than those predominantly red or infrared.**<sup>42, 45</sup> This has interesting implications for man's artificial light environment.

#### The challenges of new indoor lighting

For thousands of years sources of light were dependent upon burning some components such as wood, oil candles or gas and thus were accompanied by heat. Attempts at increasing levels of illumination resulted in excessive heating and therefore the light environment after nightfall was limited. The extent upon which man was dependent upon solar radiation is seen in the prints of city life, such as those of London scenes by Gustaf Doré whereby scenes of night-time life are very dim and depressing. To some extent we are the first generation to have daylight levels of illumination at the flick of a switch.

High levels of artificial environmental lighting really came about with the advent of the fluorescent tube in the early 1940s. It took many years however for the biologically harmonious incandescent lamps which emitted very little blue and a spectrum predominantly in the red and infrared<sup>42</sup> to be progressively replaced by fluorescent lighting in commercial and industrial establishments and then more recently compact fluorescents and LEDs in the home. The drive by respective governments to introduce so-called low-energy lighting has resulted in the proliferation of numerous sources rich in blue and some also emitting a little UV. Concern has also been expressed about the emission spectra of devices such as smartphones and tablets which the media has erroneously identified as potential eye problems. While such systems do have a significant blue component in their screen emissions they are at such low levels that they do not in any way represent a biohazard.<sup>46</sup> **By contrast LEDs have much higher spectral emissions in the blue and at levels that may require attention over cumulative exposures during a human lifetime.**<sup>47-49</sup>

#### The dark side of blue-violet light

Interest in the potential damaging effects of light has extended over hundreds of years with claims that Galileo damaged his retina by viewing the sun through his telescope. This mythology is not sustained by detailed studies however many have damaged their vision by viewing the sun and systematic investigations began after the first explosion of the atomic bomb because of concerns about the associated flash. The real impetus however came in the early 60s subsequent to the development of the laser in 1960. Extensive military budgets were deployed to ensure that the potential for lasers to damage the retina were fully understood and ocular safety mechanisms were explored. Numerous studies at this time demonstrated that with short intense exposures lasers emitting blue light were a greater potential hazard than those in other regions of the optical spectrum.<sup>50-52</sup> The peak of the "bluelight hazard" in a normal eye with a natural lens present was shown to be around 440 nm<sup>6, 53</sup> although this peak moved into the ultraviolet in individuals that had undergone cataract surgery with the lens being removed. Recent research has confirmed the peak of blue light hazard at 435 nm, with an action spectrum from 415 to 455 nm<sup>10</sup>". The blue-violet light hazard is treated as a special case worldwide in all codes of practice designed to protect people against lasers. **Further work showed that with low-level irradiance but over very long periods, hours, days, months also resulted in retinal damage again highlighting that blue-violet light was more hazardous than other wavelengths.**<sup>19, 54, 55</sup> We now know that there are two mechanisms of light damage with slightly different absorption or action spectra but both peaking in the blue. For relatively low intensity and very long exposures we see what is described as type I damage which appears to result from absorption within the light-sensitive cells and short wavelength or blue cones seem to be the most sensitive.<sup>52, 56, 57</sup> By contrast for relatively high intensity shorter exposures we recognize type II damage whereby the primary damage seems to occur in the retinal pigment epithelium<sup>58</sup> and is thought to be associated with absorption by lipofuscin (Fig 2, 3).

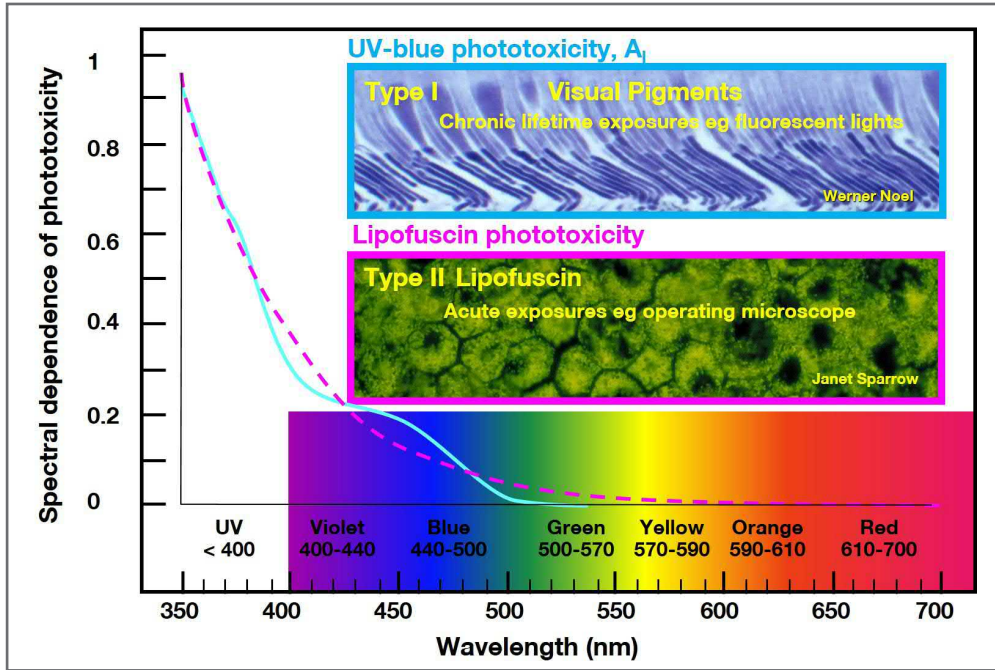


FIG. 2] Two mechanisms of light damage: type I (chronic), type II (acute).

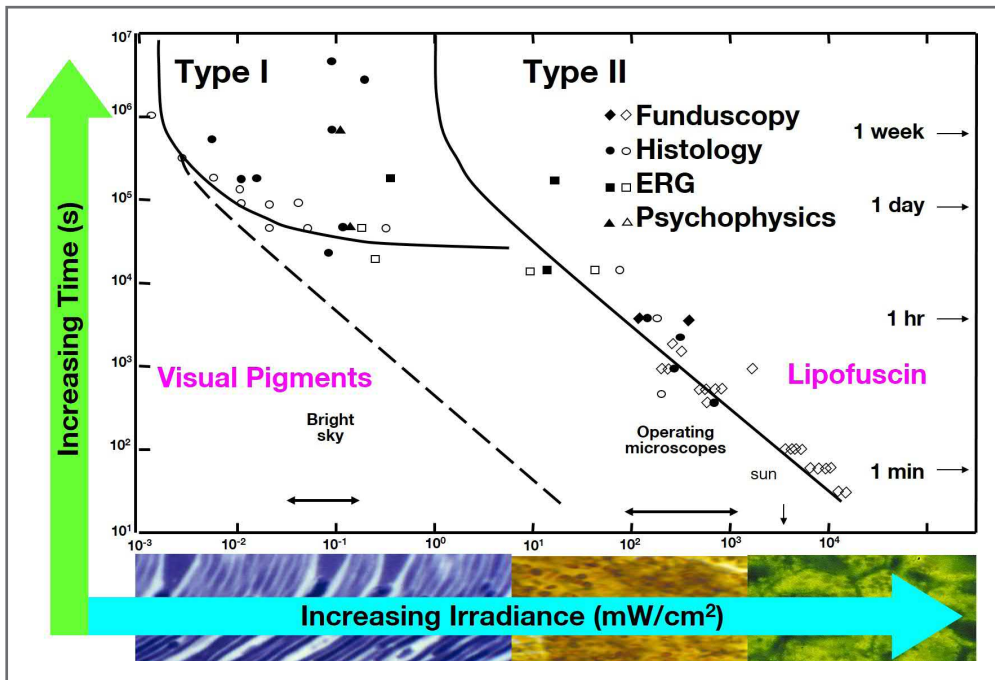


FIG. 3] Spectral dependence of phototoxicity with type I damage (chronic), type II damage (acute).

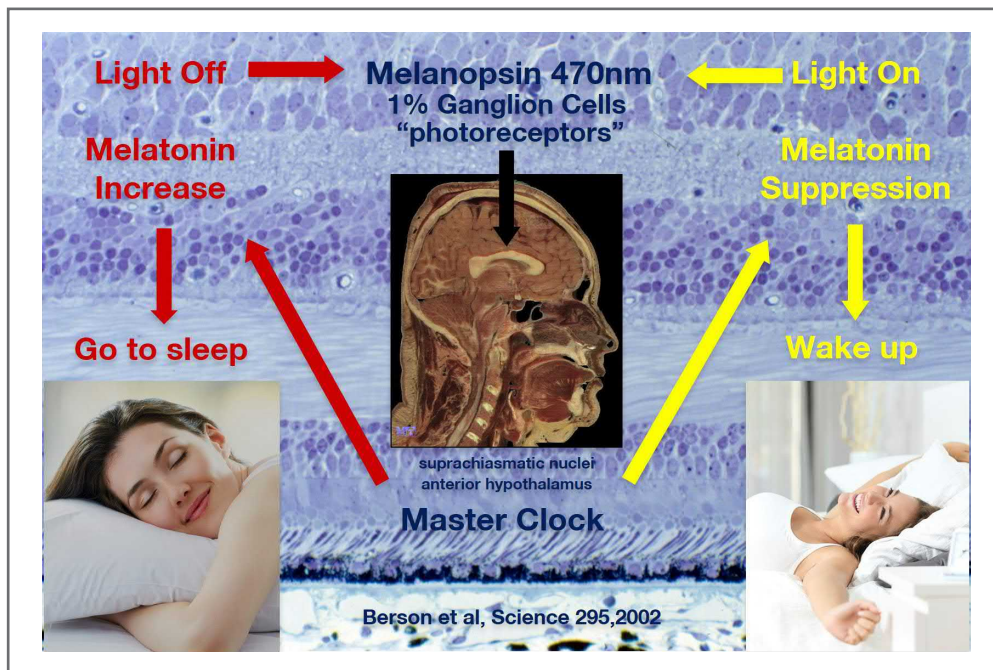


FIG. 4| Regulation of sleep-wake cycle by light.

It is of interest that within the eye there are two naturally occurring systems which attenuate transmission of blue light. In the natural lens progressive yellowing occurs with age which serves to limit the passage of light towards the neural retina. At the centre of our vision, the macula there is a second pigment, the luteal pigment which is also yellow with an absorption peak at about 445 nm.<sup>59,60</sup> Further at the centre of this region, the fovea, responsible for our highest acuity vision there are no short wavelength, or blue responding, photoreceptors, giving rise to the often forgotten phenomenon present in all of us, foveal tritanopia.<sup>61</sup> These findings on the potentially damaging effects of ultraviolet and blue radiation led to the companies that manufacture intraocular lenses fitted subsequent to cataract surgery first introducing ultraviolet blocking systems in all intraocular lenses. This occurred without any significant clinical trials and in today's parlance in the absence of "evidence-based medicine". Nevertheless few if any cataract surgeons would now place an intraocular lens into a human eye that did not have UV filtration. It is of interest that over the past 15 years many companies have introduced intraocular lenses with blue attenuating filters. These lenses have an attenuation factor similar to that of a natural lens in its late 30s or early 40s. This has been a little more controversial because it arrived in the era of "evidence-based medicine" but even in the absence of extensive long-term clinical trials it is still a system used by many informed surgeons.

### The beneficial blue-turquoise light

The apparent unimportance of blue light for vision has recently been challenged in the greater forum of blue light for overall health. In a series of studies it has been demonstrated that blue light in the region of 470 nm (blue-turquoise light) is a fundamental requirement to initiate aspects of circadian rhythm.<sup>62-64</sup> These studies have further demonstrated that a small percentage of retinal ganglion cells contain a pigment, melanopsin, whose absorption of blue light triggers a mechanism via the brain which regulates melatonin levels in the blood. When the retina is exposed to light with a blue component the absorption within melanopsin initiates a process whereby melatonin production is suppressed and the individual exposed "wakes up". By contrast switching off absorption at night up regulates melatonin production and the individual goes to sleep (Fig 4). This process underlies the condition known as seasonally adjusted disorder (SAD) therefore it is obvious that longer wavelength blue-turquoise light around 470 nm is essential for well-being. Thus we have an apparent paradox whereby short wavelength blue-violet light at 441 nm is potentially harmful whilst longer wavelength blue-turquoise at 470 nm is essential for healthy living. It is of interest that the ganglion cells responsible for absorbing 470 nm are anatomically arranged such that they occur prior to the components of the retina that absorb the harmful 441nm as light is transmitted from the cornea to the retina. Thus in our evolutionary development both mechanisms have been integrated to facilitate separation of health and hazard.

### Conclusion

Modern sources of artificial light have revolutionised our light environment with the potential to flood our individual places of work or homes at levels of illumination far beyond that experienced by our ancestors. Almost daylight levels of illumination can now be achieved at any time of the day or night by flicking a switch and governmental trends towards the use of low-energy lighting has seen the development of many blue rich sources, in particular LEDs. This takes modern man out of the evolutionary boundaries determined by solar radiation into a new era. It will be interesting to monitor the effects of our new environmental boundaries on the health of the outer retina further complicated by our increased life expectancy and the increasing prevalence of AMD. We have learnt from the dermatologists that light contributes to photoaging with UV and short wavelength visible playing a role. **Given the increase in irradiance for any given exposure between the eye and the skin it seems sensible to limit our exposure to short wavelength radiation whenever possible.** Most individuals use UV and light protection in high light environments by wearing so-called sunglasses. Depending upon the absorption spectra these can be very useful ocular protectors, if they attenuate ultraviolet and short wavelength blue-violet but they can also be less than useful if they transmit these wavelengths yet by reducing overall brightness cause the pupil to open and individuals to stay in the sun for longer. The recent introduction of UVA blocking systems and attenuation of short wavelength blue-violet for everyday wear clear lenses seems a sensible development in the face of our ever-changing light environment. •



### KEY TAKEAWAYS

- The penetration of optical radiation deep within the eye is a paradox as light is an essential component for vision but it is also a biohazard.
- The inverted retina is designed to avoid scatter and degradation of the retinal image and to ensure an efficient neuronal processing.
- The light-sensitive portions of the photoreceptor cells are constantly renewed to survive, over a human lifetime, in an extremely toxic environment due to oxygen and light radiation.
- With ageing, the accumulation of lipofuscin in Bruch's membrane may form drusen identified as high-risk factors for AMD.
- LEDs have high spectral emissions in the blue and at levels that may require attention over cumulative exposures during a human lifetime.
- Retinal phototoxicity has been demonstrated by several studies for high energy wavelengths, blue-violet light, ranging up to 455 nm.
- Blue-turquoise light, ranging from 465 to 495 nm, is a fundamental requirement for circadian rhythm and thus essential to maintain good health and well-being.
- UV and blue-violet light are both responsible for skin and ocular photoageing, therefore it is of great importance to limit our exposure to these radiations whenever possible.

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