BAD BLUE, GOOD BLUE, EYES AND VISION

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__ **THE COLOUR BLUE INSPIRES THE ARTS,** blue vibrates through literature, but we really should be referring to blues: from Aragon's *Blue sun of dreams*, and Balzac's *Life as blue as a pure sky*, there is only a breath, a ray to tip us towards Gorki's *Blue fires of anger* or Bobin's *The blue of disasters seen through the window*. "Bad Blue v. Good Blue", there's the challenge and the focus of this latest issue of *Points de Vue*, which seeks to answer the new questions that have arisen from recent scientific discoveries and clinical observations linking the blue-violet fraction of the visible spectrum – 380 to 500nm – to the eye and vision:

- Is high energy blue harmful to ocular tissue?
- What more do we know today about the physiological roles of blue light?
- What would be the benefits for human health of suppressing some of the blue and what would be the risks of suppressing too much of it?
- Are we exposed more today to harmful blue, and if so, why?

Significant progress has been made since the mid-nineties in terms of physiopathological knowledge about the consequences of exposing the eye to various types of blue light.

Previously, and since the advent of lasers in the seventies, the scientific community and public authorities controlling radio- and photo-protection performed experiments on animals in order to establish the thermal and photochemical danger thresholds of light, mainly involving UV rays and the anterior segment of the eye. This research also involved "high energy visible light", the blue-violet light renamed "blue light" for simplification, which is the light that potentially presents a danger of photochemical lesions in the retina. We know in fact that, except during childhood, ocular tissue filters out almost all UV rays and that it is indeed this "blue light" which is today incriminated in certain ocular pathologies.

In the nineties, progress made in cellular and molecular photobiology enabled exploration into which bands of visible light were the most harmful for the retina, which toxicity mechanisms were activated, distinguishing acute toxicity from chronic toxicity. This work was stimulated by the increased use of new intra-ocular implants that filter out blue, and also by the need to assess the risks to the retina of exploratory or eye surgery instruments.
Acute toxicity is the consequence of exposure to high intensity light over a short period, and results in thermal destruction of the retina's cells and cell death by necrosis.
Chronic toxicity is more insidious because photochemical mechanisms of oxidant stress lead to the accumulation of photo-sensitising components and oxidising reactive species (singulet oxygen, hydrogen peroxide, etc.) which, year after year, increase the danger to exposed cells from blue light and contribute to certain chronic ocular pathologies, such as AMD – Age-Related Macular Degeneration – or pigmentary retinopathies.

FIG. 1 | The topography and age relationship of lipofuscin concentration in the retinal pigment epithelium. - Wing G.L., Blanchard G.C., Weiter J.J.. IOVS (1978) 17(7) 601-7.

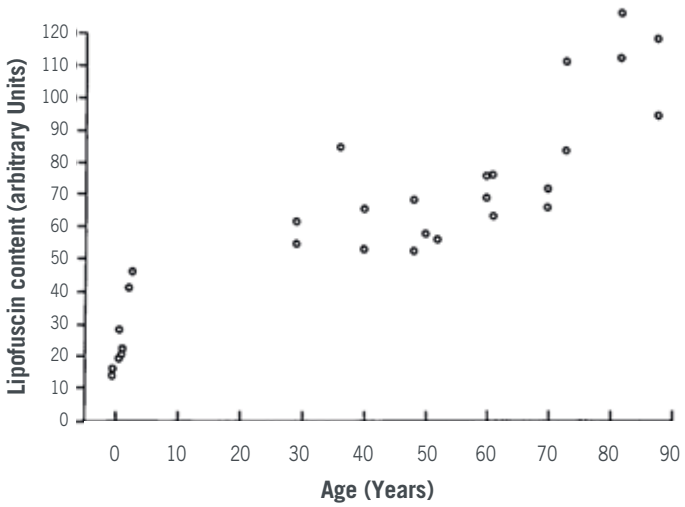
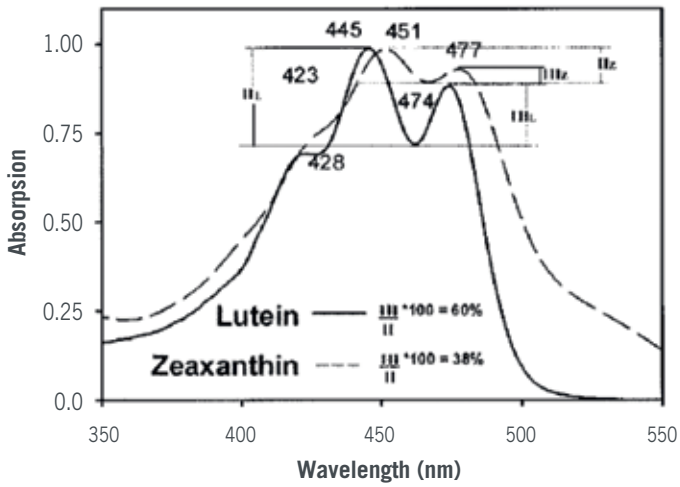


FIG. 2 | Spectra of lutein and zeaxanthin, in ethanol, illustrate the characteristic differences in the absorption properties of the two carotenoids - Landrum JT, Bone RA. Lutein, Zeaxanthin and the Macular Pigment. Arch. Biochem. Biophys. 2001 (385) 28-40.



From a clinical point of view, the correlation between exposure to blue light and the prevalence of AMD is difficult to establish. Nevertheless several epidemiological studies, including the "Beaver Dam Eye Study" have concluded that cumulative exposure to the sun increases the risk of AMD, and that it is more due to visible light than to UV rays[1].

In terms of cells, the photoreceptors (cones and rods) and the retinal pigment epithelial cells (RPE), two groups closely linked to cells in the retina, have been identified as being the main cells involved both as contributors and victims to this oxidant stress and this chronic blue light phototoxicity, resulting in cell death by apoptosis (programmed cell death). The RPE is essential to photoreceptors because it supplies them with oxygen and nutrients and, in return, ensures phagocytosis of their external segments for each visual cycle, and the metabolic regeneration of the visual pigment (rhodopsin).

The dangers of blue light to photoreceptors have been demonstrated in animals. C. Remé and C. Grimm showed in 2000[2] in rats that blue light, unlike green, causes photoreversal of the whitening of photoreceptors; this rapid regeneration of the rhodopsin caused by high energy blue light leads to degeneration of the photoreceptors by apoptosis. Molecular mechanisms were explored further by M. Rozanowksa[3] who showed a combined role played by rhodopsin and the 11-cis-retinal and 11-trans-retinal retinoids ("ATR" all-trans-retinal) the accumulation of which contributes to the phototoxicity mechanism on photoreceptors.

The action spectrum of light phototoxicity on RPE cells was studied by J. Sparrow and M. Boulton[4] who demonstrated the central role of lipofuscin accumulation in the amplification of photo-oxidation mechanisms, resulting in cell death by apoptosis. Death of the RPE leads, in turn, to the loss of photoreceptors, because they are inter-dependant. The granules of lipofuscin form in large numbers when the phagocytosis of the oxidised segments of photoreceptors is incomplete, which leads to cascades of inflammation and oxidant stress. Made of lipids and proteins, these granules contain a particularly photosensitising molecule, bisretinoid "A2E", made from two ATR, which has an absorption peak in blue at around 440 nm, which explains the particular toxicity of blue light for the RPE, with a spectrum of action that does not follow the light energy level exactly. The collections of lipofuscin in the RPE increase with age, during childhood and then again after the age of 45 *(fig.1)*, as well as in pathological conditions such as AMD or pigmentary retinopathy. Moreover, with age, ocular diseases and bad diet, the natural mechanisms of retinal defence against oxidant stress are reduced: reduced "detoxifying" enzymatic activity (catalase, SOD, etc.), reduced fixing of the macular pigment in the centre of the retina, notably of lutein and zeaxanthin, which are absorbed from food, the maximum levels of absorption and protection of which are astonishingly close to the maximum toxic absorption of A2E.

Recently, a team of photobiologists from the Vision Institute in Paris (UPMC, Inserm, CNRS), Dr Serge Picaud and Dr Emilie Arnault, under the direction of Professor José-Alain Sahel, and in collaboration with Essilor, sought to narrow the spectrum of action of blue light phototoxicity on RPE cells, by putting the cells, for the first time, in chronic toxicity illumination physiological conditions, in stages of 10nm, taking account of the spectral ratios of the solar spectrum and of filtering by ocular media. They present their work here, for *Points de Vue*.

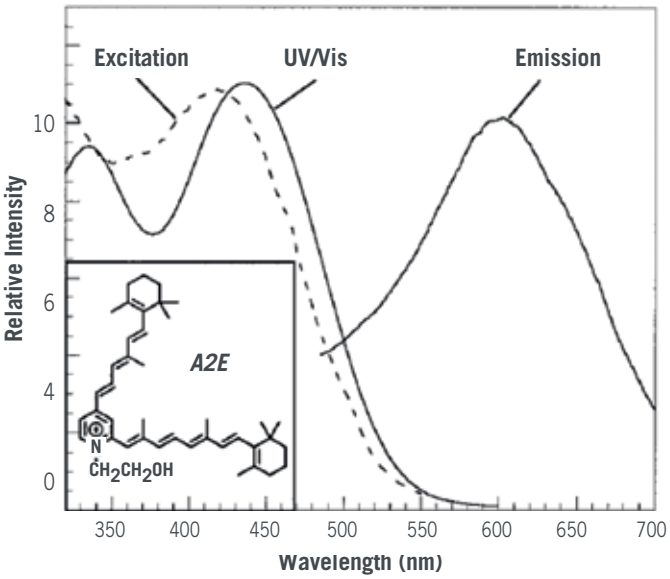


FIG. 3 | UV/Vis, excitation, and emission spectra of A2E in methanol. The absorbance spectrum had a major peak at 435 nm and lesser peak at 335 nm.

The excitation spectrum monitored at 600 nm emission, was similar in shape with a maximum at 418 nm. A 400 nm excitation wavelength generated a yellow emission centered around 602 nm. Inset, structure of A2E. Sparrow JR et al. IOVS 2000 (41) 1981-9

Thus, all the *in vitro* work done confirms the dangers of cumulative exposure to a certain blue light, *Bad Blue*.

But, in 2002, chronobiologists discovered a 3rd photoreceptor in the retina, which furthered the clinical knowledge of the eighties in terms of the extent and mechanisms of the eye's non-visual functions, modulated by a blue-turquoise band, *Good Blue*, centred at 480nm (ca. 465-495nm). This photoreceptor projects onto several non-visual areas of the brain, enabling resynchronisation of the so-called circadian physiological functions over the 24 hours of the Earth's rotation: sleep, vigilance, mood and body temperature are just a few examples of these functions, demonstrating the importance of not disturbing this *Good Blue*, if ever we were to seek to cut out all or some of the *Bad Blue*. Doctor Claude Gronfier (Inserm, Lyon) develops, in this issue of *Points de Vue*, the current level of knowledge of blue light and circadian rhythms.

Bad Blue, Good Blue, between "chagrin of Azure" (Louis Aragon, *Elsa's Eyes*) and "the magnificent radiation of a heavenly eye" (Victor Hugo, *The Rhine, Letters to a friend*), our eyes, our exposure to the new artificial lighting (see C. Martinsons in this issue), our vision of colours (see F. Viénot in this issue), our predisposition to eye diseases, or quite simply to glare (see B. Girard in this issue), our body, our rhythms, in short our whole physical and psychic life is influenced by light acting on our retinal and cortical sensors and, more specifically, by its proportions of *Good Blue* and *Bad Blue*. •

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