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The untenability of the sunlight hypothesis of cataractogenesis

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Abstract. The excess prevalence of cataract in thirld world countries led early this century to the hypothesis that sunlight causes cataract. The hypothesis, which ignored differences in diet, culture, poverty and prevalence of other diseases such as diarrhoea, received little support until about thirty years ago when biochemical studies were set up to explore the browning of lens proteins, which is a common feature of cataract on the Indian subcontinent. Initially these studies were encouraging in that exposure to sunlight caused some changes seen in cataractous lenses, but eventually the hypothesis was rejected because the first change in the laboratory was the destruction of tryptophan, but this was not found in brown cataract lenses. A brown nuclear cataract could not be produced artificially in the laboratory using sunlight or UV exposure. Exposure of laboratory animals has produced lens opacities, but in most experiments the doses required have also caused keratitis, conjunctivitis, iritis and inflammation. The cornea seems more sensitive than the lens, which is not surprising, as it gets the first chance to absorb damaging UV. The biochemical rejection of the hypothesis coincided with the re-start of the epidemiological studies. Most of these are simply latitude studies and are no more than a repeat of what was available sixty years ago. They do not help to find a cause. Two studies showed that cataract was less common at higher altitude in the Himalayas, but unfortunately led to opposing conclusions. On the basis of common knowledge that UV exposure was greater at higher altitute, the first altitude study led to the rejection of the sunlight hypothesis. The authors of the second study decided that UV-exposure was lower at high altitudes, notwithstanding important reflection from snow and rock. Only a few studies tried to assess individual exposure on basis of residence, etc., but these still ignore other factors. Some of these have been negative, some weakly positive. Most have assessed minor opacities rather than visually-impairing cataract. Three ocular conditions that are associated with sunlight exposure can be used to assess the exposure of the lens in individuals. None of these three conditions is associated with cataract. These results, together with the biochemical results and the altitude studies, provide powerful evidence against the sunlight hypothesis of cataract. There are plausible alternative hypotheses that deserve more attention.

Cataract is far more common in third world countries than in Western countries. At least sixty years ago this led to the hypothesis that sunlight causes cataract. The hypothesis was tested in 1937 and was not supported [1], but a quarter of a century later was resurrected for further study if not testing. The hypothesis comes in at least three forms.

The first claims that sunlight causes the excess of cataract in the third world. This ignores all other differences between third world countries and Western countries, such as poverty, nutrition, sanitation, diarrhoea, religion and culture. Repeated observations of the high prevalence in the third world do not test the hypothesis.

The second version of the hypothesis is that sunlight causes brown nuclear cataracts. It had been noted that exposure of lens proteins to sunlight caused

yellowing, increased fluorescence and crosslinking: all changes observed in human cataract [2, 3]. However, before these changes the sunlight destroys an essential amino acid, tryptophan, in the lens proteins. However no loss of tryptophan is found in human cataracts [4], even in the centre of the lens, the nucleus, where protein is not renewed [5]. No loss of tryptophan is seen in brown cataracts, even in those from India and Pakistan. Dilley and Pirie also pointed out that cortical and nuclear lens proteins are equally readily photoxidised in the laboratory but in human cataracts a brown nucleus is commonly seen surrounded by pale cortex [4].

The preservation of tryptophan in human cataracts indicates that the damaging UV never reached the central region of the lens (the lens nucleus) where there is no measurable protein turnover.

The third version of the hypothesis was that cataract is a major cause of cataract in the West. This version has been promoted largely by epidemiologists, who rapidly disowned the second version of the hypothesis because they never found any association between sunlight exposure and brown nuclear cataract.

Epidemiological studies have been conducted with altitude or latitude substituting for sunlight exposure. Two studies found less cataract at higher altitudes but came to opposite conclusions. In Northern India cataract was shown to be less common in the mountains and as it is well-known that UV intensities increase at higher altitude the conclusion was drawn that UV light is not a major cause of cataract [6]. In Nepal another group drew the opposite conclusion [7]. They took into account the loss of sunlight caused by living in the shadow of surrounding mountains. This ignored the high UV component of sunlight at high altitude that causes climbers and skiers to wear goggles, the reflection from snow and other reflective surfaces that provides most light impinging on the eye, and that the obstructed sunlight is at a low angle and consequently low in UV content.

Latitude studies do little more than repeat what was known sixty years ago that cataract prevalence increases towards the equator. One of these may be the basis for widely-publicised estimates of the increased number of cataracts that will result from depletion of the ozone layer. This study, based on data from the major HANES survey, indicated that cataract was more common in sunnier parts of the U.S., but this means broadly that it is more common in the southern states than the northern states [8]. They point out particular differences between the sunniest site Tucson, Arizona, where only 15 people were examined, and Albany, New York but undoubtedly there have been many differences between the northern and southern populations over the time taken for cataracts to develop apart from their assumed exposure to UV.

A study in China claimed a relationship with latitude, again a surrogate for sunlight [9], but the result was not consistent with latitude and no account was taken of the ages of the different populations.

A few studies tried to assess exposure of individuals to the supposed risk factor usually by recording residential history. This was slightly more useful than latitude studies but still ignores any other factors associated with living further south. Even within the U.S. the South was traditionally poorer, drier, dustier than the North and more blacks lived there. Cataract has been associated with various aspects of poverty in many studies, is more common in blacks than in whites, and is associated with dehydration and diarrhoea.

Collman et al. [10] using residential history elicited over the telephone did not find sunlight or working outdoors to be a significant risk factors for cataract; nor were sunglasses associated with a protective effect. Residential history together with time working on boats, use of hats and spectacles was used to assess sunlight exposure in 838 American watermen [11]. A marginal association was found between estimated UV-B exposure and cortical lens opacity (not with visually-impairing cortical cataract). There was no relationship with nuclear lens opacity [11] and no relationship between any types of opacity and estimated UV-A or visible light exposure [12]. It is important to note that only 2% of the watermen had had cataracts extracted – that is had had visual impairment sufficient to warrant surgery – whereas 77% of them had pingueculae and 17% had pterygia both conditions caused at least partly by sunlight.

The same type of individual history was used in a case-control study in US [13]. For this 160 cataract surgery patients were compared to 160 controls. In the final model there was no association between cataract and sunlight exposure, use of spectacles and hats or frequent sunbathing; so there was no support for the sunlight hypothesis. Residential history was used in further studies in India and the U.S. In New Delhi a large case-control study found no risk associated with outdoor occupation, but claimed that lifelong residence in an area with an extra 50% of the sky occupied by cloud provided 20% protection against cataract [14]. It is difficult to understand what this represents in people interviewed in New Delhi. In Wisconsin, US, data on a variety of sunlight-related factors were analysed for their relationships with three types of lens opacity in the two sexes separately [15]. Such multiple analyses are likely to produce spurious associations. There was no association between any of the light exposure variables and any lens opacity in women. Similarly there was no association with nuclear sclerosis or posterior subcapsular cataract in men. The only positive association, which was of marginal significance, was between estimated UV-B exposure and cortical opacity in

men. The authors conclude that there must be more important risk factors for cortical cataract.

Three other ocular conditions are associated with sunlight: pingueculae, pterygia and climatic droplet keratopathy. If cataract is caused by sunlight it should be found in the same populations, indeed in the same individuals, as these three conditions. Perkins found no association between pinguecula and cataract in individuals [16]. He considered that the development of a pinguecula in the conjunctiva, close to the cornea but not covering it, served as an index of sunlight exposure over a lifetime. Pinguecula, but not cataract, was more common in outdoor workers. The lack of relationship between pinguecula and cataract was confirmed by Taylor [11] who also reported no association between pterygium and cataract. This lack of association was reported previously [17, 18]. Equally conclusively there is no association between cataract and climatic droplet keratopathy [17, 19–21].

Whereas the latitude, altitude and residential studies were inconclusive, the lack of association between cataract and these three conditions is powerful evidence against any sunlight hypothesis.

The biochemical evidence that the UV-sensitive amino acid tryptophan is not destroyed in cataract is also powerful evidence against the sunlight hypothesis.

Finally it has to be recognised that when one hypothesis fails there is a need to provide an alternative. I thought that the sunlight hypothesis had failed twenty years ago. In its place I suggested that severe diarrhoea could be a major factor to account for the excess cataract in the third world [22]. Subsequently some support was provided by laboratory studies but, more importantly, it was tested in studies of cataract patients, first in Raipur in India [23], and later in Orissa [24]. Life-threatening diarrhoea was identified as a powerful risk factor for cataract. In the meantime severe diarrhoea was identified as a risk factor for cataract in two case-control studies in England [25, 26]. While the diarrhoeal hypothesis appears convincing there are other aspects of poor living conditions notably poor nutrition that have been proposed as contributions to cataractogenesis.

References

1. Wright RE. The possible influence of solar radiation on the production of cataract in certain districts of southern India: a preliminary investigation. Indian J Med Res 1937; 24: 917–20.
2. Pirie A. Fluorescence of N^1-formylkynurenine and of proteins exposed to sunlight. Biochem J 1972; 128: 1365–67.
3. Buckingham RH, Pirie A. The effect of light on lens proteins *in vitro*. Exp Eye Res 1972; 14: 297–99.
4. Dilley KJ, Pirie A. Changes to the proteins of the human lens nucleus in cataract. Exp Eye Res 1974; 19: 59–72.

5. Harding JJ. Cataract: biochemistry, epidemiology and pharmacology. London: Chapman and Hall, 1991.
6. Chatterjee A. Cataract in Punjab. Ciba Fdn Symp 1973; 19: 265–79.
7. Brilliant LB, Grasset NC, Pokhrel RP, Kolstad A, Lepkowski JM, Brilliant GE, Hawks WN, Pararajasegaram R. Associations among cataract prevalence, sunlight hours, and altitude in the Himalayas. Am J Epidemiol 1983; 118: 250–64.
8. Hiller R, Sperduto RD, Ederer F. Epidemiologic associations with cataract in the 1971–72 National Health and Nutrition Examination Survey. Am J Epidemiol 1983; 118: 239–49.
9. Mao WS, Hu TS. An epidemiologic survey of senile cataract in China. Chin Med J 1982; 95: 813–18.
10. Collman GW, Shore DL, Shy CM, Checkoway H, Luria AS. Sunlight and other risk factors for cataracts: an epidemiologic study. Am J Public Health 1988; 78: 1459–62.
11. Taylor HR, West SK, Rosenthal FS, Muñoz B, Newland HS, Abbey H, Emmett EA. Effect of ultraviolet radiation on cataract formation. New Engl J Med 1988; 319: 1429–33.
12. Taylor HR, West S, Muñoz B, Rosenthal FS, Bressler SB, Bressler NM. The long-term effect of visible light on the eye. Arch Ophthalmol 1992; 110: 99–104.
13. Dolezal JM, Perkins ES, Wallace RB. Sunlight, skin sensitivity, and senile cataract. Am J Epidemiol 1989; 129: 559–68.
14. Mohan M, Sperduto RD, Angra SK, Milton RC, Mathur RL, Underwood BA, Jaffery N, Pandya CB, Chhabra VK, Vajpayee RB, Kalra VK, Sharma YR, and the Indian-U.S Case-Control Study Group. India-U.S case-control study of age-related cataracts. Arch Ophthalmol 1989; 107: 670–76.
15. Cruickshanks KJ, Klein BE, Klein R. Ultraviolet light exposure and lens opacities: The Beaver Dam Eye Study. Am J Public Health 1992; 82: 1658–62.
16. Perkins ES. The association between pinguecula, sunlight and cataract. Ophthalmic Res 1985; 17: 325–30.
17. Franken S, Mehta KR. A survey to determine the ophthalmic morbidity in the population living in the dry belt of Southern Panjab and Haryana. Christian Medical College, Ludhiana, Punjab, 1968.
18. Peckar CO. The aetiology and histopathogenesis of pterygium. A review of the literature and a hypothesis. Documenta Ophthal 1972; 31: 141–57.
19. Freedman A. Climatic droplet keratopathy. 1. Clinical aspects. Arch Ophthalmol 1973; 89: 193–97.
20. Rodger FC. Clinical findings, course, and progress of Bietti's corneal degradation in the Dahlak Islands. Br J Ophthalmol 1973; 57: 657–64.
21. Johnson GJ, Minassian D, Franken S. (1989) Alterations of the anterior lens capsule associated with climatic droplet keratopathy. Br J Ophthalmol 1989; 73: 229–34.
22. Harding JJ, Rixon KC. Carbamylation of lens proteins: a posssible factor in cataractogenesis in some countries. Exp Eye Res 1980; 31: 567–71.
23. Minassian DC, Mehra V, Jones BR. Dehydrational crises from severe diarrhoea or heatstroke and risk of cataract. Lancet 1984; (i): 751–53.
24. Minassian DC, Mehra V, Verrey JD. Dehydrational crises: a major risk factor in blinding cataract. Br J Ophthalmol 1989; 73: 100–105.
25. van Heyningen R, Harding JJ. A case-control study of cataract in Oxfordshire: some risk factors. Br J Ophthalmol 1988; 72: 804–808.
26. Harding JJ, Harding RS, Egerton M. Risk factors for cataract in Oxfordshire: diabetes, peripheral neuropathy, myopia, glaucoma and diarrhoea. Acta Ophthalmol 1989; 67: 510–17.

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