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# Foveal Damage in Habitual Poppers Users

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**Objective:** To describe foveal damage in habitual use of poppers, a popular recreational drug.

**Methods:** Retrospective observational case series. Six patients with bilateral vision loss after chronic popper inhalation were seen in 4 university-based ophthalmology departments. Symptoms, medical history, ophthalmic examination, and functional and morphological tests are described.

**Results:** All patients experienced progressive bilateral vision loss, with central photopsia in 2 cases. Initial visual acuities ranged from 20/50 to 20/25. In all patients, a bilateral yellow foveal spot was present that, by optical coherence tomography, was associated with disruption of the outer segments of foveal cones. Functional and anatomical damage was restricted to the fovea. The poppers involved were identified as isopropyl nitrite in 3 cases. Four patients showed anatomical and/or functional improvement over several months after discontinuing popper inhalation.

**Conclusions:** Repeated inhalation of poppers may be associated with prolonged bilateral vision loss due to the disruption of foveal cone outer segments. Retinal damage may progressively improve following drug discontinuation.

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POPPERS ARE EXOGENOUS volatile nitric oxide (NO) donors.[1,2] A recent survey in France estimated that approximately 5% to 6% of teenagers have used poppers at least once,[3] especially in the gay male community. Many brands of poppers are legally sold in Western countries. Despite anecdotal reports of ocular toxicity,[4,5] poppers were considered harmless unless misused such as by ingestion. Recently, we described 4 patients who experienced acute and prolonged vision loss following poppers inhalation.[6] Symptoms were associated with optical coherence tomographic (OCT) evidence of damage to foveal cone outer segments. Here, we describe cases of chronic users of poppers who experienced similar visual disturbances and retinal damage.

## METHODS

During a 3-year period, 6 habitual users of poppers who presented with bilateral visual loss were identified from the medical records of 4 university-based ophthalmology centers. This study followed the tenets of the Declaration of Helsinki and the French regulations regarding clinical research.

## REPORT OF CASES

### CASE 1

A 42-year-old man with a history of human immunodeficiency virus (HIV) seropositivity and depression experienced painless, progressive vision loss in both eyes with photopsia over the course of several months. He was treated with antiretroviral tritherapy and paroxetine. He had also been a regular user of poppers (2 times per month) and cannabis for the last 10 years. He recently switched poppers brands from those containing amyl nitrite to those containing propyl nitrite (Jungle Juice; Perpol Limited, Whitegate, England). He first came to our department in July 2010. His initial visual acuity (VA) was 20/30 in both eyes. Anterior segments and intraocular pressure (IOP) were normal. Fundus examination showed a bilateral yellow central foveal spot. An OCT scan showed disruption of foveal cone outer segments, with slight foveal detachment bilaterally (**Figure 1**A). Adaptive optics fundus imaging (RTX camera; Imagine Eyes, Orsay, France) showed that the cone mosaic was normal outside of the fovea (Figure 1B). Isopropyl nitrite was identified by gas chromatography–mass spectrometry in the pop-



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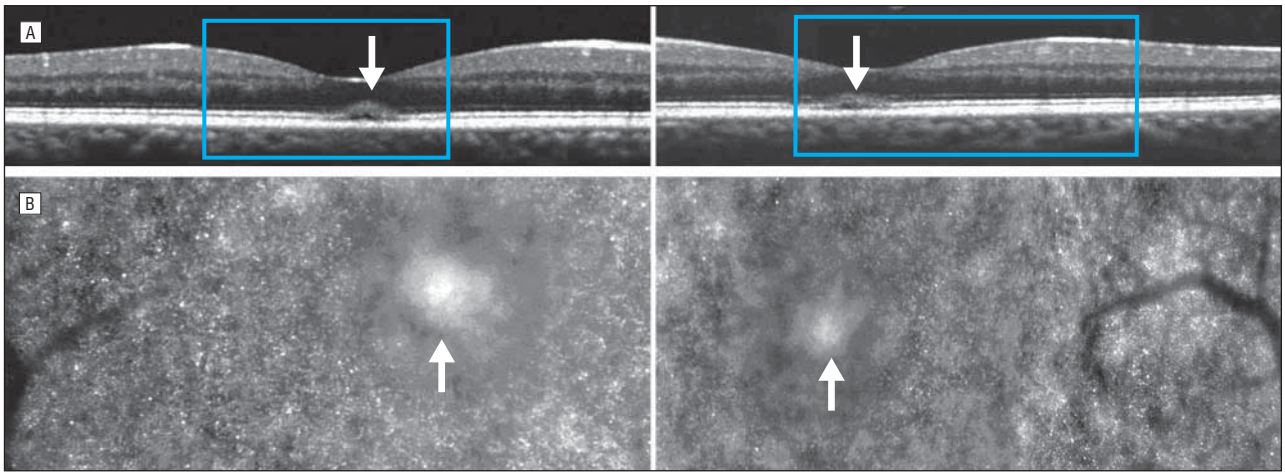



**Figure 1.** Case 1 at presentation (visual acuity, 20/30 OU). Optical coherence tomography (A) and adaptive optics fundus images (B) of both eyes show damage to the foveal cone outer segment bilaterally (arrows). The cone mosaic appears normal outside of the fovea.

pers vial. Interruption of poppers was recommended but the patient was unwilling to comply. Three months later, results of ophthalmological examination were unchanged.

## CASE 2

A 56-year-old man with a history of HIV seropositivity and depression experienced painless, progressive vision loss in both eyes over the course of several months. He was treated with antiretroviral tritherapy. He had also been a regular user of various brands of poppers (at least once per week) for more than 20 years and was a cocaine and chloral hydrate user. He recently switched poppers brands from those containing amyl nitrite to those containing propyl nitrite. He first came to our department in October 2008. He spontaneously attributed his loss of vision to poppers on chronological arguments. At that time, his VA was 20/40 OD, 20/50 OS. Anterior segments and IOP were normal. Fundus examination showed bilateral foveal yellow spots (**Figure 2**A). Autofluorescence fundus images revealed a perifoveal decrease in lutheal pigment absorption of the laser with pseudohyperautofluorescence (Figure 2B). Fluorescein angiography showed a bilateral window defect of the central fovea (Figure 2C). An OCT scan showed disruption of foveal cone outer segments, with a slight foveal detachment bilaterally (Figure 2D). Color vision, visual fields, and findings of full-field electroretinography (ERG) were normal. Multifocal ERG showed bilateral attenuation of central responses. Toxicological analysis of a vial of the brand most often taken by the patient revealed the presence of isopropyl nitrite, with no other detectable compound. The patient agreed to stop taking poppers. Subsequently, a progressive improvement in VA to 20/32 OD and 20/40 OS was observed during follow-up examinations over several months, as well as a partial regression of OCT changes.

## CASE 3

A 39-year-old man with seropositive results of testing for HIV who was treated with antiprotease (tenofovir) experienced painless, progressive visual loss in both eyes. He was a regular weekly popper user, with increasing doses over the last 3 to 4 months. The patient spontaneously attributed vision loss to consumption of poppers. He was first seen in our department in December 2007. At that time, his VA was 20/25 OD and 20/40 OS. Anterior segments and IOP were normal. Fundus examination revealed a bilateral foveal yellow spot. Fluorescein angiography showed bilateral window defect in the central fovea. An OCT scan showed bilateral disruption of foveal cone outer segments. Color vision, visual fields, and findings of full-field ERG were normal. A follow-up examination performed 1 month later showed an improvement in VA to 20/20 in both eyes but his OCT images were unchanged. The patient was then lost to follow-up.

## CASE 4

A 53-year-old man with a history of HIV seropositivity and syphilis experienced painless, progressive vision loss in both eyes over several months. He was treated with antiretroviral tritherapy. He had also been a regular user of poppers (at least once per week) for 3 to 4 years but denied using any other drugs. He first came to our department in December 2009. His VA was 20/32 OD, 20/50 OS. Anterior segments and IOP were normal. Fundus examination showed bilateral foveal yellow spots. Spectral-domain OCT showed disruption of foveal cone outer segments. Color vision, visual fields, and findings of full-field ERGs were normal. Multifocal ERG showed slight bilateral attenuation of central responses. Interruption of poppers was recommended. A follow-up examination performed 3 months later showed an improvement in VA to 20/32 in both eyes, with a slight improvement of OCT features.

## CASE 5

A 35-year-old man with a history of HIV seropositivity and syphilis experienced painless, progressive vision loss with photopsia in both eyes over several months. He was treated with antiretroviral tritherapy. He had also been


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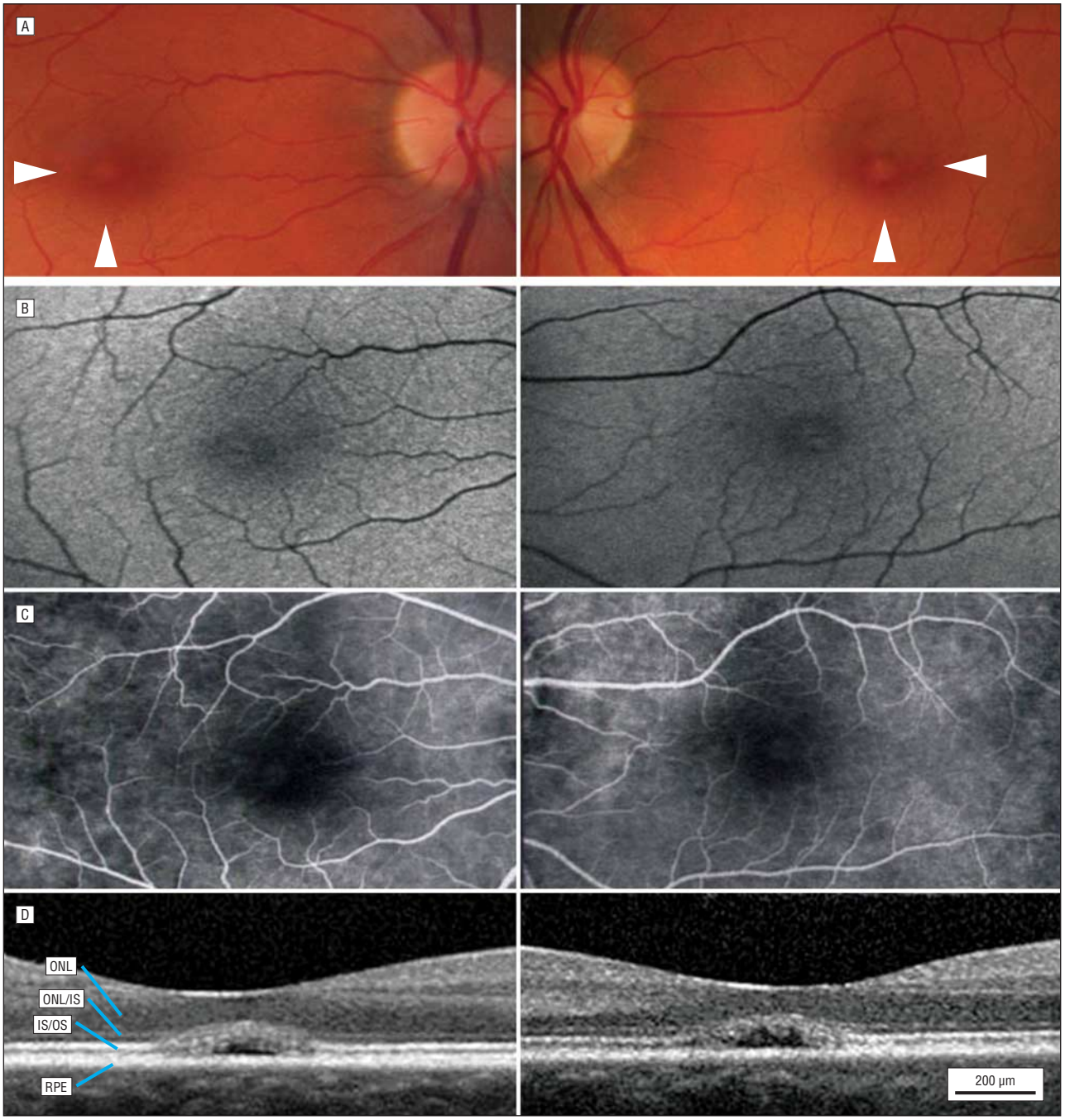



**Figure 2.** Case 2. Color photographs (A), 488-nm autofluorescence (B), fluorescein angiography (C), and optical coherence tomographic images (D) at presentation (visual acuity, 20/40 OD, 20/50 OS). Note the bilateral yellow spot (arrowheads), the central window defect on the fluorescein angiogram, and the disorganization of foveal cone outer segments with subretinal fluid. ONL indicates outer nuclear layer; IS, inner segment; OS, outer segment; RPE, retinal pigment epithelium.

a regular user of poppers (3 to 4 times per week, most frequently the brand name Jungle Juice Platinum) and of cannabis for the last 3 years. He first came to our department in December 2009. His VA was 20/50 OD, 20/40 OS. Anterior segments and IOP were normal. Fundus examination showed bilateral foveal yellow spots. Spectral-domain OCT showed a slight foveal detachment bilaterally. Visual fields and findings of full-field ERG were normal. Multifocal ERG showed slightly attenuated central responses. Isopropyl nitrite was identified by gas in the poppers vial. Interruption of poppers was recommended. A follow-up examination performed 2 months later showed an improvement in VA to 20/25 OD, and 20/32 OS.

## CASE 6

A 45-year-old man came to our unit in December 2008. He had been experiencing painless, rapidly progressive vision loss in both eyes for 1 month. He had a history of depression and was treated with fluoxetine, chlordiazepoxide, sibutramine, and spironolactone. He had been


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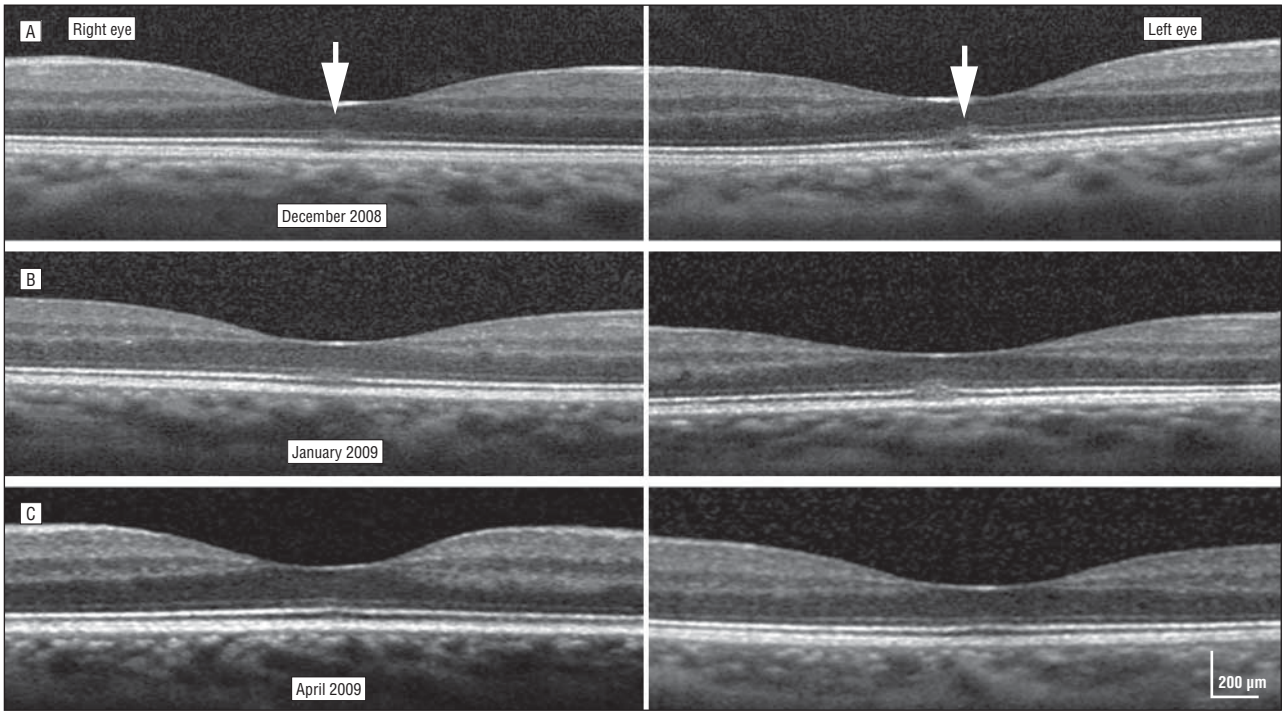



**Figure 3.** Case 6. A, Optical coherence tomographic scans at presentation are shown (visual acuity, 20/30 OU). Note the bilateral disruption of the optical reflectance of outer segments of central cones (arrows). During follow-up (B and C), there was progressive normalization in the images; the final visual acuity was 20/20 OU.

taking poppers on a weekly basis (brand name, Jungle Juice) over several months. His initial VA was 20/30 in both eyes. Anterior segments and IOP were normal. Fundus examination showed slight yellow central foveal spots. A presumptive diagnosis of optic neuritis led to prednisolone bolus therapy (1 mg/kg). Subsequently, visual evoked potentials were found to be normal, which led to prednisolone discontinuation. High-resolution OCT then revealed bilateral disruption of foveal cone outer segments (**Figure 3**A). Color vision, visual fields, and findings of full-field ERG were normal. Medical evaluation also revealed HIV seropositivity and tertiary syphilis, and the patient was subsequently appropriately treated. The patient agreed to stop taking poppers. Follow-up examinations showed progressive normalization of functional and morphological abnormalities (Figure 3, B and C).

## SUMMARY OF CASE REPORTS

We observed 6 cases of bilateral vision loss after chronic popper intake between December 2007 and July 2010. All patients were HIV-positive men. All were regular popper users and reported a reduction in vision during several weeks to months before seeking medical advice. Three patients took other psychoactive substances, such as cannabis and cocaine, simultaneously with poppers. Two patients described central photopsia in both eyes. On initial examination, VA ranged from 20/50 to 20/25. Fundus examinations revealed a yellow foveal spot in all cases. An OCT scan showed disruption in the reflectivity of the central photoreceptor outer segments in all cases, with a slight foveal detachment in 3 patients. In patients who underwent fluorescein angiography, a centrofoveal window defect was found but no evidence of fluid leakage. Color vision, visual fields including microperimetry, and findings of full-field ERG were normal or showed minimal abnormalities. Multifocal ERG showed reduced amplitudes for central responses in 3 patients. A complete or a partial regression of symptoms and fundus abnormalities was noted in the 4 patients who claimed to have discontinued popper intake. There were no pigmentary changes at any time. Isopropyl nitrite has been identified in the vials taken by 3 of them.

## COMMENT

Popper-related damage to foveal cone outer segments is a recently recognized entity.[6] We previously described 4 cases of acute toxicity in which vision loss occurred after a single exposure to poppers and persisted for several weeks. Other causes of yellow foveal spots were ruled out by context and OCT findings such as stage 1 macular hole, niacin maculopathy, or best-like dystrophy. All patients described here were HIV positive; however, this is probably coincidental because poppers are popular among the gay community and the cases described by us[6] were in HIV-negative subjects.

To our knowledge, during the past 10 years there have been only 2 case reports of vision loss following inhalation of poppers.[4,5] A similar case of vision loss has been reported by Pece et al,[4] in which a patient experienced acute, bilateral vision loss hours after inhaling isobutyl nitrite. Their patient had bilateral foveal spots


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but normal findings on time-domain OCTs and experienced a spontaneously favorable clinical course over several weeks. Normal findings on time-domain OCT scan does not, however, rule out the presence of minute foveal damage. Indeed, in our cases, careful, iterative scanning of the fovea by OCT was often necessary to highlight disruption of central outer segments, a procedure that is easier to perform with current high-speed, high-resolution spectral-domain OCTs. The finding of minute foveal damage may also be complicated by the fact that patients will tend to avoid fixation into this area. The case described by Fledelius[5] was of acute and severe bilateral optic neuropathy, but the relationship with poppers was disputable; viral optic neuritis was a more likely diagnosis.

These findings raised the question of the effect of repeated poppers intake. We report here that there is no evidence of extrafoveal extension of the lesions or of aggravation of visual loss, even after several years of poppers intake. Hence, poppers-related foveal toxicity is not cumulative, is restricted to the fovea even after prolonged exposure, and causes overall limited visual impairment in the long term. Improvement after interruption appears to be the rule, although our data are still incomplete regarding this point.

Given the absence of a detectable contaminant in the poppers vials examined to date, it is likely that visual symptoms were directly linked to NO intake. However, the putative mechanisms linking poppers to retinal toxicity remain elusive. There is little knowledge regarding the pharmacological effects of inhaled alkyl nitrites on neural tissues.[7,8] At physiological doses, NO modulates photoreceptor metabolism and function,[9,10] in particular through activation of guanylate cyclase, a key enzyme of phototransduction.[11] The presence of photopsias in many patients suggests permanent activation of central cones rather than their inhibition, which would be expected if only guanylate cyclase activation was involved. Accordingly, an increased ERG after NO administration was described in rats,[12] and another study suggested that NO potentiates the light response of cones, while it decreases that of rods.[13] At higher doses, it has been shown that photoreceptors are among the most sensitive retinal neurons to the toxic effects of NO, both in vitro and in vivo.[14,15] Nitric oxide is also known to decrease the threshold of light toxicity.[16,17] Yet, these studies were performed in retinas that do not have a fovea; thus, their relevance to the clinical toxicity described here is questionable. Accordingly, the elective targeting of the fovea in our patients suggests light-induced damage, although patients denied having stared at bright lights. Moreover, in addition to their effect on neuronal metabolism, it has been reported that NO interacts with the macular pigment zeaxanthin,[18] which protects the fovea against light damage. In our patients, the presence of a central increase in autofluorescence and a central window defect and the absence of pigmentary changes even after months of exposure suggest a defect of macular pigment that may potentiate light toxicity. Measuring the concentration of macular pigment in these patients may thus be of interest to understand the physiopathology of the affection.

Vision loss following poppers intake could be considered to be a rare event, although in Web forums discussing poppers effects, photopsia is reported as a common adverse effect. Therefore, the reason for the apparent outbreak of popper toxicity that we describe remains to be determined. It may be due to the conjunction of an increased use of popper in the population as reported in France in recent surveys (http://www.ofdt.fr/BDD/publications/docs/eisxacp6.pdf), the availability of more powerful popper brands, and/or to improvements in retinal imaging technologies. Indeed, the results of an ophthalmological examination may be considered normal if the careful search for a yellow foveal spot and damage to foveal cone outer segments has not been carefully done. In this regard, the recent availability of spectral-domain OCT technology considerably facilitated such diagnosis because of the higher speed of acquisition and of the higher resolution. Also, many popper users with transient visual symptoms may not request medical advice or may not report popper consumption.

Several recommendations may be drawn from these findings. Consumers and ophthalmologists should be aware of the possible long-term retinal toxicity of isopropyl nitrite, and possibly of all brands of poppers. In cases of unexplained bilateral vision loss with central scotoma, especially in presence of photopsia and/or yellow foveal spots, toxicity related to poppers should be considered as a possible diagnosis. Specific questioning and a careful search for foveal damage by high-resolution OCT should be conducted to ascertain the diagnosis. There may be an improvement in symptoms following drug discontinuation. Finally, the determination of the molecular basis of the toxic effects of poppers may be of interest to further document the role of NO in retinal function and diseases and to identify protective mechanisms against such toxicity.

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One cannot gain skill and experience in cataract operations without doing less than the best. I will illustrate this by a case from my own experience. It occurred while I was undergoing my apprenticeship to Major Smith at Jullunder. It happened, at the time, that I was under the influence of quinine, and to add to my troubles I had as spectator a distinguished stranger.

When the lens was nearly three quarters delivered and I was on the point of hooking it out a bead of vitreous appeared beside it and threatened to burst. Instead of doing what I should have done, what I should do now, and perhaps what I would have done then had my nerves been steadier and my judgment unperturbed, instead of doing the right thing I did the wrong. I suddenly lifted mu [*sic*] hook to relieve all pressure from the eye, with the result that the lens, which was more than half delivered, dropped back into the eye with sufficient impetus to become buried in the vitreous.

**Source:** McKechnie WE. Cataract operations and the preparation of the surgeon. *Arch Ophthalmol*. 1911;40:27.


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