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## REPLY BY AUTHOR

# *Re: Letter to the Editor - Proctor JG. Pentosan polysulfate and a pigmentary maculopathy: causation versus correlation?*

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PROCTOR JG. Re: Letter to the Editor - Proctor JG. Pentosan polysulfate and a pigmentary maculopathy: causation versus correlation? *Can J Urol* 2024;31(3):11869-11870.

Dear Editor,

I reviewed with interest the Letter to the Editor by Dr Foote et al.<sup>1</sup> In 2018, 22 years after pentosan polysulfate (PPS) was FDA approved, Pearce first described the pigmentary maculopathy (PM) in interstitial cystitis (IC) patients with chronic PPS exposure.<sup>2</sup> Jain noted that "it is unusual for a potential drug toxicity to manifest decades after initial FDA approval."<sup>3</sup> Pearce's study was a case series of patients self-reporting use of PPS that identified 38 patients, but only the 6 patients that had been previously evaluated by the authors for a PM were evaluated in the study. Soon afterward, the same institution (Emory Eye Center) was calling the PM a "pentosan polysulfate maculopathy."<sup>4</sup> In my article, I present a model postulating that the causative factor for the PM is the underlying immune inflammatory state associated with IC and not PPS use.<sup>5</sup> The pathophysiology of the PM has not been identified, and the role of immune inflammation in PM has not been evaluated. Therefore, I reviewed the pathophysiology and the role of immune inflammation in known maculopathies.

Most of the arguments that Dr. Foote et al discuss I have addressed in my article. Several studies have demonstrated that there is no temporality or PPS dose-response for the development of a PM. In 2020, Jain et al found that at 5 and 7 years, there was no significant risk of developing an atypical maculopathy (hereditary or secondary PM) in PPS-exposed patients compared to non-PPS cystitis (not IC) controls.<sup>3</sup> Ludwig reported on 227,325 patients diagnosed with IC for 5 years, and found

PPS users were less likely to develop a maculopathy at 2.37%, compared to 2.77% of IC patients not on PPS.<sup>6</sup>

Barnes et al (Emory) evaluated 1,394 patients with hereditary and other maculopathies as well as what the authors term "PPS maculopathy."<sup>4</sup> Fifteen patients were characterized with a "PPS maculopathy." Two expert graders, blinded to the clinical and medication history, evaluated the fundal imaging studies. Out of these 15 PM patients, 10 of 10 patients with PPS exposure were correctly classified with "PPS maculopathy," while 5 patients without PPS exposure were incorrectly classified with "PPS maculopathy." Expert senior retinal imaging specialists are misled by subtle findings, only to reclassify the diagnosis after further unmasked assessment. Jain stated, "the fundus findings in the condition [PM] are subtle and resemble other well-known maculopathies such as AMD and pattern dystrophy."<sup>3</sup>

There are many fundamental limitations with the studies describing the PM, which I reviewed in my article. These limitations include that there are no clear definitions of the control cohorts. Additionally, the studies on PM have an inherent selection bias. Jain also addressed this concern by stating "any study of this type has a risk of indication bias, where the reason for giving the drug is actually the cause of the association seen, and not the drug itself."<sup>3</sup>

Scholl and Klaver in *JAMA Ophthalmology* reported that based on current epidemiological evidence as well as retrospective studies and evaluation of all Bradford Hill criteria, a causal relationship cannot be established between PPS and a PM because of the variability in effect size, inconsistent diagnostic methodology, and the inability to prove temporality.<sup>7</sup>

Dr. Foote stated, "we have recently reported our findings in an animal model demonstrating that PPS exposure leads to deleterious impacts on visual function and retinal structure in mice."<sup>8</sup> In this 14-month study on mice, the average and maximal PPS doses were 1,358 and 2,000 mg/kg/day respectively. In a 70 kg human, this corresponds to a PPS dose of 95,060 and 140,000 mg a day. The FDA approved dose of PPS is 300 mg a day. This study used 129S2/SvPasCrl mice, which have phenotypic

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annotation related to premature death and urinary tract abnormalities, including abnormal renal morphology, hydronephrosis, bladder obstruction, and cystinuria.<sup>9</sup> The authors “observed RPE cell polymegathisms and geometric eccentricities in our drug-treated animals. This morphology is characteristic of aging and disease, both in mouse and human eyes.” Yet the mice used in the study have premature death. The authors also comment that “it is also possible that the toxic effects from the treatment were a result of decreased hemoglobin. PPS is a heparinoid, and a toxicology study showed that there were statistically significant decreases in erythrocytes and hematocrit in mice gavaged with 500 mg/kg PPS for 3 months.”<sup>10</sup> The authors note that PPS does not cross the blood-brain barrier due to its high molecular weight.<sup>11</sup> Therefore, this current data in mice does not corroborate a causal relationship between PPS and a PM.

Dr. Foote et al referenced an article from their group linking PPS use to a new onset colopathy that was diagnosed as inflammatory bowel disease (IBD) in many of their patients.<sup>12</sup> In this study, 13 patients with long-term PPS use with a PM and not currently taking PPS had a retrospective chart review of GI symptoms and 11 (84.6%) developed symptoms suggestive of IBD and/or irritable bowel syndrome (IBS). This article states “studies show that approximately 2% of patients with classic IC have IBD, compared to 0.07% prevalence in the general population.”<sup>13</sup> The reference for this statistic (13) states that “inflammatory bowel disease was not diagnosed in any of the patients with non-ulcer IC whereas 2.3% of the patients with classic IC had either ulcerative colitis or Crohn’s disease.”<sup>13</sup> Hunner-type (classic) IC is a small percentage (up to 5 to 10%) of patients with IC. IC patients have many known comorbidities. Studies in IC patients demonstrate up to 44% have symptoms suggestive of IBS and is significant when compared to controls (6%), and dyspepsia in 43%.<sup>14</sup> This article by Foote et al has not been published in a peer reviewed journal, and it is too early to ascribe any cause and effect between PPS and a colopathy.

I have vast experience in this area. IC patients not on PPS do not routinely get a full retinal screening exam. If IC non-PPS users do not get retinal screening, no PM will be found. A systemic IC phenotype that causes more symptom severity with a systemic immune inflammatory response could eventually lead to a PM.<sup>5</sup> In my experience, most IC patients with severe long-term symptoms have had at least a trial of PPS. Based on my research, several years ago I started recommending a baseline retinal screening exam on all my IC patients and appropriate follow up examinations. I have prescribed PPS since it was FDA approved, and I have many patients that choose

to continue with it as part of their IC treatment plan. I recommend dose reduction and even discontinuation of PPS in IC patients with symptom improvement.

In my article, I wanted to convey that the current data does not demonstrate that PPS is the cause of the PM. Therefore, instead of just convicting PPS as the causative factor, we must explore other potential causes of the PM. It is most likely that the underlying pathophysiology that is part of the IC phenotype is causing the PM and not the long-term PPS use. Prospective studies quantitating the immune system inflammatory response and evaluating the retina in IC patients without and with PPS exposure with similar age, symptom severity, and length of time of IC symptoms need to be performed to elucidate the etiology of the PM. I am delighted that we are discussing different possibilities as to the causation of the PM in IC patients. □

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