Editorial

Intravitreal Injections: A Historic Background

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J Ophthalmic Vis Res 2018; 13 (2): 91–92

Although most of the discoveries are the result of hard laboratory work, the history of Medicine is filled with a number of accidents that have led to the discovery of a new concept or technology. The story of discovery of penicillin by Alexander Fleming (*https://www.nobelprize.org/nobel_prizes/medicine/laureates/1945/fleming-bio.html*) and light coagulation by Professor Meyer- Schwickerath (www.ascrs.org/honorees/gerd-meyer-schwickerath-md) are shining examples of both accidental observation and hard work. My involvement in the development of intravitreal injection of medication was a consequence of prior laboratory investigations and serendipity.

In 1970, when I came to the US as a retina fellow at University of California, Los Angeles (UCLA), I had in mind a project to evaluate the blood ocular barrier (with and without laser coagulation) using horseradish peroxidase as a tracer material. The study demonstrated that the tight junctions (zonulae occludentes) between the retinal pigment epithelium (RPE) and retinal vessel endothelial cells prevented the tracer material injected in the vitreous cavity from diffusing either toward the choroid or retinal circulation, and similarly the same tight junctions prevented the tracer material injected in the circulation from entering the vitreous/retina freely from the choroidal/retinal vessels.[1-4] Laser application damaged the RPE barrier and subsequently modified the structure of choriocapilaris and reduced its fenestrations.

These findings have clinical implications for systemic administration of medications for treatment of retinal diseases, and the effect of laser application on fluid leakage and transport across the choroid/retina borders in conditions such as central serous retinopathy (CSR) and diabetic retinopathy.[1-4]

This work was concluded before I accepted a position at University of Illinois in Chicago (UIC), as the chief of vitreoretinal surgery in June 1971. Because at that time, I did not have an assistant or a fellow, Dr. Morton Goldberg the chairman of the department, sent me a medical student to assist me in the lab for evaluation of an oscillatory vitrectomy system (The Vitrophage), I had developed for vitrectomy, in eyes of rabbits prior to its approval for use in humans.

I remember doing vitrectomy or lentectomy on a number of animals, which were kept for postoperative observation in the vivarium.

The day following rabbit surgery, I asked my student about the condition of the operated eyes. When he returned from checking the animals, I noticed that he was quite disturbed while reporting that all eyes were infected. I recalled from my experiments on the blood ocular barrier that it was useless treating the animals with systemic medication (hanging a bottle of antibiotic on their cages) because no medication could pass through the RPE, or the retinal vessel cell barrier, furthermore the antibiotic injected into the eye would be toxic. I concluded that, unfortunately, we would have to sacrifice the animals.

This event started my investigations on the toxicity of intraocularly injected antibiotics to find non-toxic doses that could be safely injected into the eye for treatment of endophthalmitis.[5,6] Since similar type of infections could occur again (in the future surgical procedures involving the vitreous or the lens), I started investigating the use of non-toxic doses of intraocular antibiotics for prophylaxis against endophthalmitis. However, in the first investigation, we overestimated the non-toxic dose of intravitreal gentamicin because there was leakage following the intravitreal injection due to scleral perforation. Due to a rise in intraocular pressure, some amount of fluid/antibiotic had escaped into the subconjunctival space after injection.

In subsequent works with my students and coworkers, including studies on methicillin with M. J. Daily,[7] dexamethasone with R. Graham,[8] clindamycin with J. Paque,[9] amphotericin B. with A. Axelrod,[10] prophylactic antibiotic therapy in cataract surgery with Paque/Meisels,[11] antineoplastic agents with Barrada/Fiscella,[12] antivirals with Jose Pulido,[13] slow release delivery liposomes with P. Fishman,[14] microspheres with M. Conway,[15] Avastin with R. Manzano,[16] and some other studies,[17,18] we performed

an initial anterior chamber tap to reduce IOP prior to the injection or pressed on the scleral injection site, with a cotton-tipped applicator after the injection, or reduced the volume of the injected medication. These maneuvers prevented the escape of fluid from the eye and the miscalculation of non-toxic doses. Toxicity could also occur by injecting medication close to the retina. We also found that non-toxic doses for the retina were not toxic for the corneal endothelial cells when injected in the anterior chamber.

I thank all my co-workers and Dr. M. Goldberg for their invaluable collaboration, support and encouragement in these historical investigations that ultimately led to the development and acceptance of one of the most commonly used prophylactic and therapeutic surgical procedures in ophthalmology.

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Website: www.jovr.org

DOI: 10.4103/jovr.jovr_54_18

How to cite this article: Peyman GA. Intravitreal injections: A historic background. J Ophthalmic Vis Res 2018;13:91-2.