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## Reflections

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And first he will see the shadows best, next the reflections of men and other objects in the water, and then the objects themselves; then he will gaze upon the light of the moon and the stars and the span-gled heaven; and he will see the sky and the stars by night better than the sun or the light of the sun by day.

Allegory of the Cave, by Socrates  
Plato's Republic, Book VII

This issue features a report on the histopathologic findings in 20 cases of vitreo-maculopathies of different types. On the basis of these findings, conclusions are drawn about the pathogenesis of these conditions, relating both to the role of glial cells in the formation of premacular membranes and to the appearance of hyperconvolution of the internal limiting lamina (ILL) of the retina. Attractive as these conclusions may seem, they are extrapolations based upon observations of histopathology which must be placed into the proper perspective.

Epistemologists have long cautioned us to realize the difference between what is seen and what is reality. Socrates spoke of our sensory experiences as mere shadows on the wall in the cave of our misconceived world. We remain chained in the cave due to our inability to recognize

the limitations and deficiencies of our perceptions, and the true nature of things thus eludes us. In addition to the limitations of our senses, even when enhanced by instrumentation, our view of the world is just a model, which is susceptible to conditions of context, preconception, and extrapolation. In observational science, failure to recognize this often results in over-interpretation of experimental or clinical findings and can lead to overly broad or far-reaching conclusions.

It is common for histopathologists to seek a cell type, structural abnormality, or anomalous tissue that can be alleged to be pathogenic. Observing such anomalies leads to hypotheses about pathogenesis that are tested in experimental models and subsequently in clinical studies, all intended to ultimately produce therapy to treat or even prevent disease. In the quest for this objective, pathologists traditionally begin by characterizing the nature of a cell or structural abnormality. Modern histologic and immunohistochemical techniques have enabled the identification of a variety of markers of gene expression that reflect a cell's activity and may indicate how the cell contributes or adapts to disease. Definitive proof that a given cell or structural abnormality is pathogenic requires either the creation of the disease with that cell or structural abnormality in an experimental

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model, in line with the landmark principles espoused in Virchow's cellular pathology theory [11], or its eradication by somehow altering the cell or abnormal structure. If it can be shown that eliminating the cell or abnormal structure cures, or better yet prevents, the disease, then the evidence for causation is highly plausible. It must be emphasized, however, that the mere presence of a cell or any observed structural abnormality may play no role at all in pathogenesis, but could simply represent the consequence of untoward effects by the true underlying pathophysiology; not, therefore, a cause, but an effect. These fundamental principles are a prerequisite for the acceptance of any claims that a certain cell or structural abnormality is responsible for a disease state. Without such corroborating evidence, a hypothesis remains just that.

Another important fundamental consideration is that regardless of the nature of an inciting event, the body possesses only a finite set of ways by which it responds. Often, the response is a non-specific inflammatory reaction involving resident cells as well as inflammatory cells derived from the systemic circulation. In an effort to preserve plasticity, nature has retained in most cells the ability to alter their structure and function based upon their milieu, their inherent needs, and their "purpose" at any given point in time. This is true of circulating cells that enter the tissue, as well as those that are already present, known as resident macrophages or tissue histiocytes. In the eye, hyalocytes are important resident macrophages located at the vitreo-retinal interface [9]. Since any given cell can look and work differently in different locations and circumstances, it would be incorrect to assume that the presence of a particular cell during a disease process constitutes evidence of its role in causing that disease. The risk that the appearance of a cell can lead to incorrect identification of its type, its origin, and its role in disease is partic-

ularly problematic in ophthalmology, owing to the reliance upon the putative power of observation. For more than a century, the seminal contributions and inventions of Purkinje, Helmholtz, and Gullstrand have enabled ophthalmologists to peer inside the human eye and observe its structure. When abnormalities are seen, a diagnosis is established. The lack of abnormal findings, such as lens opacities, retinal hemorrhages, or macular drusen, to name but a few, typically results in the proclamation that there is no disease. In point of fact, however, this is not a tenable position, since disease begins on a molecular level, a state we currently cannot identify in the eye because of a lack of *in vivo* techniques that can provide such molecular diagnostic acumen [1]. Only advanced stages of physiopathology result in the histopathology we currently recognize as disease by ophthalmoscopic criteria. Thus, in ophthalmology, the distinction between an observation, which is actually only a clinical finding on physical examination, and a diagnosis is quite blurred. Such an approach in ophthalmic pathology can lead to incorrect conclusions concerning the role of certain cells and structural abnormalities in the pathophysiology of disease, simply on the basis of the observation that they are present.

In recent years, the structure, function, and pathobiology of vitreous have been the subjects of much interest and study [3–7]. During aging, the gel vitreous liquefies, and in those individuals with weak adhesion at the vitreo-retinal interface there is separation of the posterior vitreous cortex from the ILL of the retina, known as posterior vitreous detachment (PVD). Vitreous liquefaction without vitreo-retinal dehiscence can cause anomalous PVD [8]. This unifying concept in vitreo-retinal diseases derives from the principle that a final common pathway is often at play during the late stages of seemingly disparate diseases. When there is extensive vitreous liquefaction without concurrent vitreo-retinal de-

hiscence, undue traction can occur at various locations in the fundus. In the periphery, traction induces retinal tears and detachments. In the macula there can be a split in the posterior vitreous cortex, known as vitreoschisis [2]. The outer wall of the schisis cavity can induce macular pucker or perhaps even macular holes [10]. Thus, cellophane maculopathy is probably not a true diagnostic entity, but a finding on physical examination that is most likely due to anomalous PVD, perhaps with vitreoschisis. It probably only differs from macular pucker in terms of degree of severity, with macular pucker representing a more advanced form of the disorder that features thickening of both the posterior vitreous cortex and the ILL as well as greater cellularity. Persistent attachment of the entire posterior vitreous cortex to the macula can cause alterations in the ILL and underlying retina. In vitreo-macular traction syndrome the predominant result is interstitial edema with retinal thickening. In this and other circumstances, traction by the unstable and liquefied vitreous upon the ILL, which is the basement membrane of Mueller cells, will be transmitted to the Mueller and other adjacent cells. The response of these cells to such an insult will likely include remodeling of the Mueller cells' basement membrane, the ILL, and probably even the stimulation of GFAP-positive glial cells that could migrate anteriorly from the retina. At the vitreo-retinal interface, these cells may appear as a new and distinct cellular entity, called laminocytes by the authors of the article in question. But, in fact, these findings may simply be the result of resident cells undergoing a predictable response to the injury induced by anomalous PVD with traction upon the retina. The authors propose that these laminocytes produce the collagen membrane and the hyperconvolution of the ILL. They also describe this cell as a glial cell, for which there is little argument. However, insofar as it is GFAP pos-

itive, produces intermediate filaments, and makes gap junctions, it would almost certainly be a specialized form of activated astrocyte. While the authors are to be commended for their modesty in not adopting the practice of the 19th century German pathologists who named cells after their discoverer, does an activated astrocyte need a new name? The hyperconvolution invoked as pathogenic by the authors of this article may similarly be an erroneous conclusion that results from assuming pathogenesis on the basis of an observation. This finding could very well be nothing more than the manifestation of basement membrane remodeling induced by insult to the

Mueller cell by anomalous PVD. Again, the question posed by Socrates arises: is this the true cause of the disease (Socrates' "object"), the intermediary mechanism of pathology (the "reflection"), or merely an artifact associated with the changes (the "shadow")?

Seeing the histopathologic changes described herein could prompt musings and considerations related to pathophysiology, but it would be prudent to not consider them as anything more. For the clinical diagnosis of a vitreo-maculopathy is only the starting point, where "first he will see the shadows best." As ophthalmologists we are comfortable with this level of knowledge, but we must ap-

preciate that we are only seeing shadows at this point. Detecting "laminiocytes" and "hyperconvolutions" is the next step in the advancement of our ability to see in the upper world where "next the reflections of men and other objects in the water" are seen. The authors of this article are to be congratulated for taking us to this next step in the evolution of our knowledge about these disorders. However, only when we shed the shackles that bound us in the cave of our ill-conceived view of the world will we see "the objects themselves," and only then will we appreciate the true nature of things. In this instance that is yet to be determined.

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