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The Histologic Basis of Ocular Disease

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Although the ophthalmologist (an ophthalmic pathologist disguised by a white jacket and a better bedside manner) uses some fancy magnifying equipment, in reality the ocular examination is nothing more than a macroscopic evaluation of tissue lesions using the same observational skills as you would use to evaluate a lung, liver, or kidney during exploratory surgery or postmortem. The clinical diagnosis of ocular disease is nothing more than a prediction of the microscopic changes that underlie the perceived gross lesions. This ability to envisage the histologic counterpart of the clinical lesion distinguishes the real student of ophthalmology from someone who can only diagnose what he/she has previously seen in real life, in books, or on slides at conferences. Unless the current lesion is almost an exact replica of what he/she has previously seen, the clinician who has learned ophthalmology "from the top down" has no chance of making a diagnosis. It is the purpose of this presentation to illustrate an entirely different approach to the understanding and diagnosis of ocular disease: the clinical appearance and functional significance of any ocular lesion is a reflection of the interaction of ocular anatomy with universal principles of general pathology. The trick is that the clinical appearance of such reactions, the immediate clinical significance, and the sequels are sometimes disguised by the peculiarities of ocular anatomy and physiology.

Corneal Ulceration

When you diagnose a corneal ulcer, you are not actually seeing the ulceration. Our eyes are simply not good enough to detect the loss of a few layers of stratified squamous epithelium. What you detect is actually the osmotic imbibition of the tear film fluid into the hydroscopic corneal stroma as an inevitable and rapid sequel to the loss of the hydrophobic epithelial barrier. The stromal accumulation of fluid changes the spacing of the stromal collagen fibers, resulting in a scattering of light and therefore the clinical impression of gray opacity. The use of fluorescein to "stain the ulcer" is not actually staining the ulcer, but rather adding green color to the absorbed edema fluid.

Corneal Scarring and Vascularization

I am sure you have all seen corneas that are diffusely opaque, scarred, vascularized, and even pigmented. The clinical literature does us a disservice by classifying such corneas with a bewildering plethora of names like chronic pigmentary keratitis, chronic stromal keratitis, chronic keratoconjunctivitis sicca, etc.. It is much more useful to recognize that all of these changes are the inevitable outcome of the marriage of general pathology with the anatomic constraints imposed by normal corneal anatomy.

Following shallow ulceration, the epithelium from the adjacent cornea will attempt to slide across the denuded corneal stroma to rapidly seal the defect and prevent the further absorption of fluid and potentially injurious leukocytes. This rapid sliding and eventual mitotic rebuilding is effective only if the superficial corneal stroma has remained relatively normal. If the original injury caused damage to the stroma, or if subsequent infection has allowed neutrophil enzymes to damage that stroma, the stroma itself will have to be rebuilt as a prerequisite for epithelial healing. The rebuilding uses exactly the same strategy as employed anywhere else in the body: the recruitment of new capillaries and fibrous tissue from the nearest available source. In the cornea, that means from peripheral sclera and bulbar conjunctiva. While you may think that the ingrowth of blood vessels and supporting fibrous stroma (i.e. granulation tissue) is some kind of

"disease", it is absolutely normal wound healing that provides the essential nutritional support for any successful epithelial rebuilding.

In situations like chronic keratoconjunctivitis sicca or entropion, the corneal epithelium may not actually be ulcerated, but it is nonetheless subjected to a chronic degenerative stress. The normal cornea is allowed to exist in its privileged avascular state only if all of the unique ocular physiologic adaptations are working properly: a qualitatively and quantitatively normal tear film that is properly distributed across the corneal surface, a cornea protected from desiccation and other irritation by properly positioned eyelids, and delivery of nutrients from the limbal blood vessels, from the tear film, and from the anterior chamber. Any significant imbalance in this precarious equilibrium represents a stimulus for the cornea to become tougher and more resilient. The resourceful cornea responds to such demand by recalling its embryologic heritage as skin, and it undergoes "cutaneous metaplasia". It becomes pigmented, keratinized, and vascularized so that it no longer requires the protection of the eyelids and tear film (Fig.1). While we interpret this as disease, from a biological perspective it is an entirely appropriate adaptation to a new set of environmental constraints.

The clinical interpretation of the patterns of corneal vascularization is something we have all learned by rote. Superficial wandering bright red vascularization is a reflection of superficial corneal disease (usually with recent ulceration), whereas the observation of purple straight blood vessels extending into the deeper cornea from the limbus is an indication of uveitis. When you think about it, this is the inevitable outcome of the interaction between the events of wound healing and preexistent corneal anatomy. The vascular proliferation associated with granulation tissue is inherently branching and random. When you have superficial corneal injury, there is destruction of the preexistent stroma and so the ingrowing granulation tissue has no constraints upon its natural inclination to branch and wander. In uveitis, the intraocular angiogenic growth factors produced as part of any ongoing inflammation percolate outwardly through the trabecular meshwork and "accidentally" contact the limbal blood vessels. These blood vessels respond by budding and migration, but they migrate into an adjacent corneal stroma that still retains its normal dense laminar configuration. The vessels are thus not allowed to wander, and their bright red color is muted by the overlying stroma and by the edema that always surrounds new blood vessels (Fig. 2).

The Clinical Disguises of Uveitis

Bringing simplicity to the innumerable clinical manifestations of intraocular inflammatory disease might seem like a hopeless task, but again all of these variations are simply the predictable outcomes of the interaction between the standard events of inflammation and preexistent ocular anatomy. Let us simply review the basic events of inflammation and see how they are manifested within the globe:

Serous effusion: the very earliest events of inflammation are related to hyperemia and effusion of fluid from blood vessels responding to locally-generated inflammatory mediators. In most tissues such serous effusion is of little consequence, but the unforgiving anatomy of the eye presents some special problems. Serous effusion from the choroid, for example, creates instantly blinding retinal detachment that might ultimately result in irreversible retinal damage because the retina is separated from its nutritional choroidal support. Alternatively, the leakage of protein into the aqueous humor changes its optical properties and results in aqueous flare, and the abnormal chemical composition of the aqueous is a potential cause for cataract because the lens depends entirely upon the delivery of quantitatively and qualitatively normal aqueous humor for its nutritional health.

Fibrin: in some instances, the leakage of small molecular weight proteins from reactive vessels is followed by the leakage of larger proteins like fibrinogen, resulting in the extravascular accumulation of fibrin. The potential for adhesion between adjacent inflamed, sticky surfaces is little more than an inconvenience in most tissues, but within the globe the adhesion of iris to lens creates posterior synechia with the potential for pupillary block, iris bombe, and secondary glaucoma (Fig. 3). Similarly, the accumulation and subsequent contraction of fibrin within the vitreous creates the risk of traction retinal detachment.

Accumulation of leukocytes: the stimuli and mechanics of leucocytic accumulation are no different within the globe than in other tissues. They may accumulate and settle by gravity within the anterior chamber as they attempt to exit the globe via the trabecular meshwork (hypopyon), or form adherent clusters that stick to the corneal endothelium (keratic precipitates). Because the globe is a closed sphere, inflammatory mediators and various cytokines associated with leucocytic recruitment or subsequent events of wound healing are distributed throughout the globe, so there is really no such thing as localized intraocular inflammation. Although clinically we distinguish, for example, anterior uveitis from choroiditis, from a histologic perspective all intraocular inflammation is diffuse (i.e. endophthalmitis).

Intraocular Wound Healing

The chemical mediation and mechanical events of wound healing are the same within the globe as in any other tissue. These events, while theoretically beneficial, often become problematic within the globe because of its unforgiving

anatomy and precarious physiology. A little bit of scarring that is beneficial or at least inconsequential in other tissues might create pupillary block glaucoma, occlusion of the filtration angle, traction retinal detachment, or other changes that have serious consequences for ocular health. A particularly common consequence of otherwise well-controlled ocular inflammation is the formation of preiridal fibrovascular membranes (Fig. 4). The blood vessels within the iris are in constant communication with the chemical constituents of the aqueous humor. Elevated levels of angiogenic cytokines occur with such diverse events as chronic endophthalmitis, retinal detachment, and growth of intraocular neoplasms. Those cytokines act, apparently by accident, upon the iris blood vessels and cause them to form a fibrovascular membrane on the anterior surface of the iris. That membrane achieves clinical significance if it occludes the pupil or trabecular meshwork, or if it causes persistent hyphema.

A similar proliferative response occurs following injury to lens epithelium, especially following perforating injury. The plaque of reparative epithelial proliferation under the lens capsule will cause cataract that may be clinically significant. If it escapes through the rent in the lens capsule, this proliferating epithelium undergoes fibroblastic metaplasia and can grow in a tumor-like fashion to cause pupillary block and secondary glaucoma. In cats, it undergoes malignant transformation to cause life-threatening primary ocular sarcoma.

Retinal Pathology Made Easy

The interpretation of retinal lesions is probably the best example of how an understanding of ocular histology allows you to replace memorization with understanding. Just think of the ocular fundus as consisting of a series of tissue layers, some of which are transparent, some absorptive, some pigmented, and some reflective. In your own mind, simply replace these histologic layers with familiar household items like wax paper (the slightly opaque retina), aluminum foil (the reflective tapetum), black cardboard (the pigmented choroid) and white cardboard (the sclera). By layering them in the proper order, you have reconstructed the ocular fundus. You can then predict the histologic nature of various fundus lesions by imagining what kind of manipulation of your "kindergarten fundus" you would have to perform in order to recreate the real life lesion. Do you scrape away someone wax from your "retina" to increase the reflectivity of your tapetum (this is the basis for the hyper-reflectivity of PRA)? Do you punch a hole in your aluminum foil to allow the black choroid to show through (thus re-creating a healed scar of a previous chorioretinitis)? Do you put a blob of shaving cream on top of the retina so that the reflection from the aluminum foil becomes muted (thus re-creating a preretinal exudate associated, for example, with cryptococcosis)? Or do you put creases in the wax paper retina to recreate the wandering tracts of gray opacity typical of retinal dysplasia? The possibilities are endless, but the key is that they suddenly become **understandable**!

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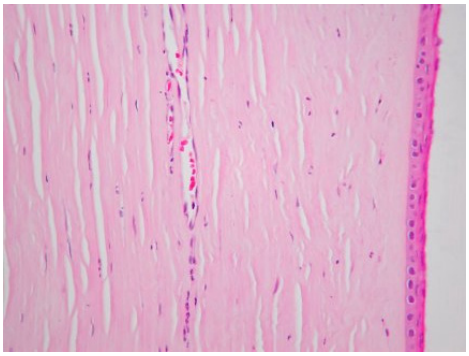

Fig. 1. Cornea from a dog with chronic keratoconjunctivitis sicca. There is adaptive cutaneous metaplasia characterized by epidermal hyperplasia, early formation of rete ridges, epithelial and stromal pigmentation, stromal vascularization, and fibrosis.

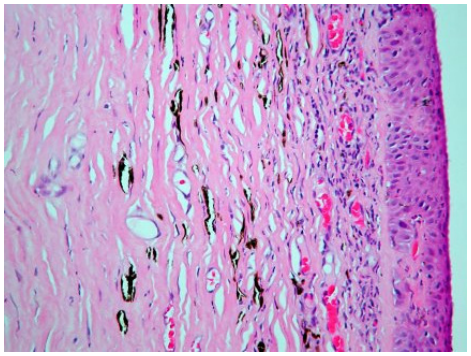

Fig. 2. Midstromal straight vascularization in an otherwise normal cornea, an indicator of chronic uveitis.

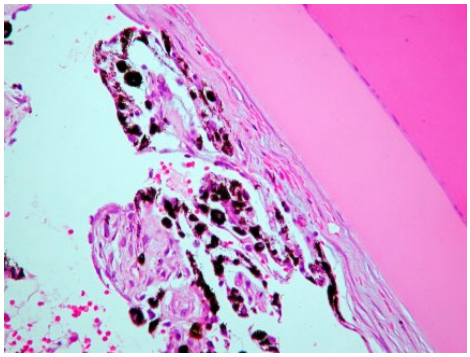

Fig. 3. Fibrous adhesion of the pupillary margin to the anterior lens capsule, creating posterior synechia. If this adhesion is extensive, it creates the possibility of pupillary block and secondary glaucoma.

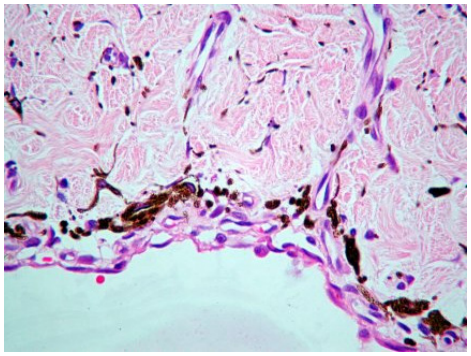

Fig. 4. This preiridal fibrovascular membrane, with budding of iris blood vessels and fibroblasts onto the anterior surface of the iris, is perfectly normal wound healing that is anatomically "out of place". It creates the potential for unwanted hyphema, pupillary occlusion, or obstruction of the filtration angles.

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