Medical Hypotheses (2004) **62**, 808–816

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A two-compartment model of the human retina

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Received 13 March 2003; accepted 2 November 2003

Summary *Purpose:* In this article we question a basic concept in retinal pathology, which views the retina as composed primarily of neural elements, in a single compartment.

Methods: We suggest an alternative approach, centering on the epithelial-glial elements of the retina, dividing the retina into two distinct compartments. The framework of these two compartments is composed of two epithelial-like monostratified cell layers facing each other by their apical surfaces. This model is in agreement with the embryological development of the retina.

Results: Each compartment is composed of a monostratified cell layer in which neural elements are embedded and each is supplied by a different blood supply. The inner compartment, also referred to as the Muller cell compartment, extends between the inner and outer limiting membranes. The outer, or RPE, compartment extends between the outer limiting and Bruch's membranes. The border between the two compartments is formed by the outer limiting membrane (OLM). One simplified example utilizing the two-compartment concept is as follows: inner compartment edema (inner blood-retinal barrier breakdown) may manifest as cystoid edema, but not as serous retinal detachment, while outer compartment edema (outer blood-retinal barrier breakdown) may manifest as serous retinal detachment but not as cystoid edema, as long as the integrity of the OLM is maintained.

Conclusion: A two-compartment approach to the structure of the retina, centering on non-neural elements, may enhance our understanding of some retinal pathologies. Various retinal diseases, mainly of vascular origin, are limited to one of the two compartments.

Introduction

The retina is classically viewed as primarily composed of neural tissue with some epithelial and glial elements, forming a single compartment. In comprehending retinal anatomy and physiology, the epithelial-glial elements are considered of lesser importance, and often neglected, although interest in glial cells and recognition of their importance has been rising in recent years. In this article we present an alternative model, centering on neuroepithelial and glial elements, forming a two-compartment model of the human retina.

The current view

The retina is considered as a single compartment, composed of 10 layers, 7 of which are neural [1]

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0306-9877/$ - see front matter
doi:10.1016/j.mehy.2003.11.035

(Fig. 1). This description is based on light microscopy sections of the retina. Two vascular networks supply the retina, each separated from the retina by a blood-retinal barrier [2]. Based on experiments performed using horseradish peroxidase diffusion [3,4] no continuous barriers were described within the retina apart from the two blood-retinal barriers [5,6].

Based on this view one would expect that outer blood retinal barrier breakdown may lead also to macular edema, and alternatively, that inner blood-retinal barrier breakdown could lead to serous retinal detachment (Fig. 2). However, this does not seem to occur in retinal disease. For example, in central serous chorio-retinopathy, breakdown of the outer blood-retinal barrier results in serous detachment of the neurosensory retina, but edema within the inner retinal layers does not usually occur. Conversely, in diabetic retinopathy, breakdown of the inner blood-retina barrier may lead to macular edema but does not lead to serous retinal detachment. Discrepancies in understanding retinal pathologies using a single compartment model led us to question its validity. We would like to propose an alternative two-compartment model that may enhance interpretation of certain retinal conditions.

The two-compartment model

A gliacentric view, namely, placing primary importance on the neuroepithelial and glial components of the retina is the basis for our model. While the current dogma concentrates on the functional, vision related, elements of the retina (i.e. the neural cells), our model focuses on the supportive, neuroepithelial (RPE) and glial (Muller cell) components of the retina.

As viewed by this model, the basic framework of the retina is composed of two monostratified epithelial-like layers facing each other by their apical surfaces (Fig. 3). The outer layer is formed of RPE cells, while the inner layer is composed of Muller cells. Both layers have epithelial-like properties, common to all epithelial layers in the human body: a basal membrane on the basal surface, villi on the apical surface, and inter-cellular junction complexes on the lateral surfaces (tight and gap junctions) [7].

Embryological development of the retina (infolding of the optic vesicle) seems to support this view of two layers of epithelial cells forming the basic structure of the retina [8—10] (Fig. 4). Initially, during early optic vesicle formation, the epithelial cells in the outer layer of the vesicle

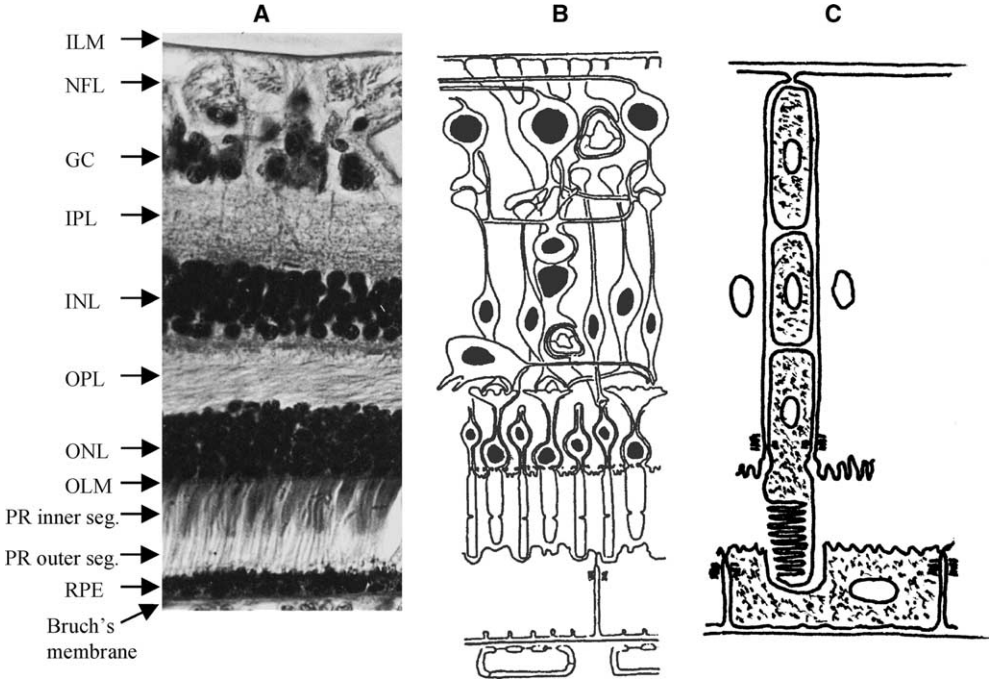

Figure 1 The classic view of the retina: (A) light microscopy image of the human retina, (B) schematic drawing emphasizing the neural cells and (C) simplified drawing of the three layers of neurons facing the RPE cell (ILM: internal limiting membrane; NFL: nerve fiber layer; GC: ganglion cell; IPL: inner plexiform layer; INL: inner nuclear layer; OPL: outer plexiform layer; ONL: outer nuclear layer; OLM: outer limiting membrane; PR: photoreceptors; RPE: retinal pigment epithelium; MC: Muller cell; CC: choroidal capillary; RC: retinal capillary; IPRS: inter-photoreceptor space; OBRB: outer blood-retinal barrier; IBRB: inner blood-retinal barrier; BM: Bruch's membrane).

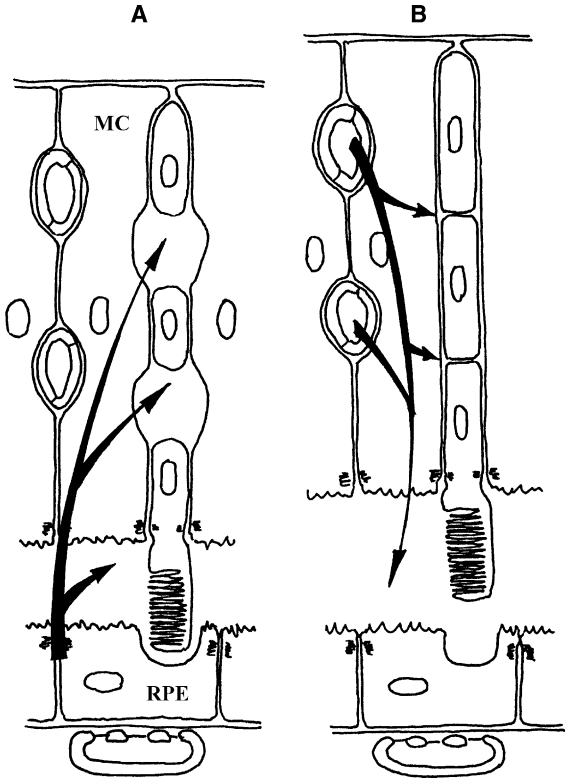

Figure 2 The current dogma: expected consequences of blood-retinal barrier breakdown. (A) Outer blood-retinal barrier breakdown, apart from serous detachment, should also lead to retinal edema. (B) Internal blood-retinal barrier breakdown, besides causing accumulation of fluid within the inner retina, is expected to lead to serous detachment.

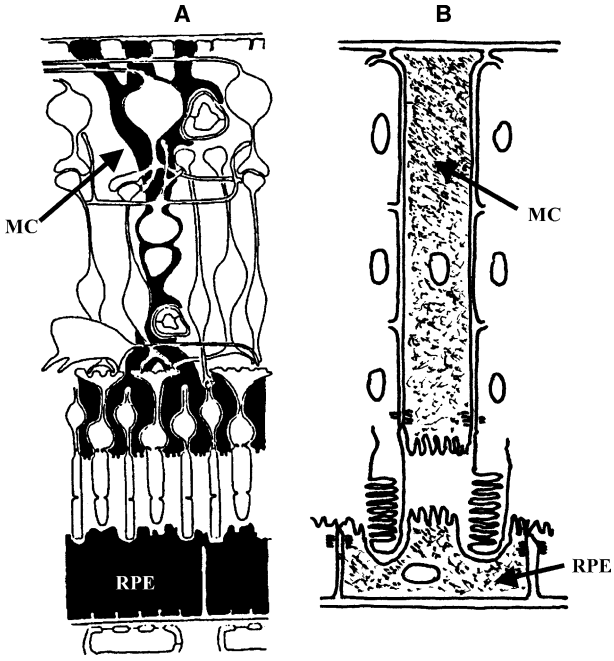

Figure 3 Gliacentric view of the human retina: (A) schematic drawing highlighting the epithelial and glial cells (drawn in black) and (B) a simplified drawing of the Muller cell facing the RPE cell (both have epithelial-like properties), with their apical villi surfaces towards each other.

(destined to become the RPE) face a monostratified layer of epithelial cells of the inner layer from which the Muller cells, among others, will later develop (Fig. 4). As maturation continues, (Fig. 4(B) and (C)) multiple layers of neuronal elements stratify within the scaffold of the epithelial cells. Like other epithelial tissues, these two layers (Muller cells on the one side and RPE cells on the other) are primarily avascular, contacting the mesodermal tissue (blood supply) via their basal surface. One may question this statement that the layer centered on the Muller cells is indeed avascular: how can one state this when it is obvious that retinal capillaries are "in" the retina and not on the internal limiting membrane (ILM)? We would like to put forth the argument that topologically the retinal capillaries are actually "outside" the retina.

In the retina, the two vascular networks are separated from the epithelial tissue by two blood-retinal barriers [2] (Fig. 5). The barrier of the outer compartment is formed by the basal and lateral cell membrane of the RPE cells, bound by tight junctions. The barrier of the inner compartment is formed by the cell membrane of the endothelial cells of retinal capillaries, bound by tight junctions.

In the rabbit, the retinal vessels lie on the basal surface of the Muller cells, as expected from epithelial tissues elsewhere, leading to the description of an "avascular retina" in these animals [11]. In humans, retinal capillaries invaginate into the neurosensory retina [12]. In fact, they are "sliding" between adjacent Muller cells (Fig. 6). Stated in other words, as all retinal vessels contain the blood-retinal barrier in their wall, and lie in between Muller cells, this invagination does not violate the inner compartment, which remains, topologically speaking, avascular. A simplistic, schematic explanation of how retinal vessels are located within the retina, but at the same time are not, is analogous to an incubator glove, whereby one can stick his hand into the incubator, via a rubber glove, but at the same time not violate the antiseptic barrier of the incubator.

This concept may be supported by the fact that retinal vessels differentiate from a layer of mesodermal cells, which originate from the adventitia of the hyaloid artery, which is basically a vitreal structure [13]. Further support may come from the

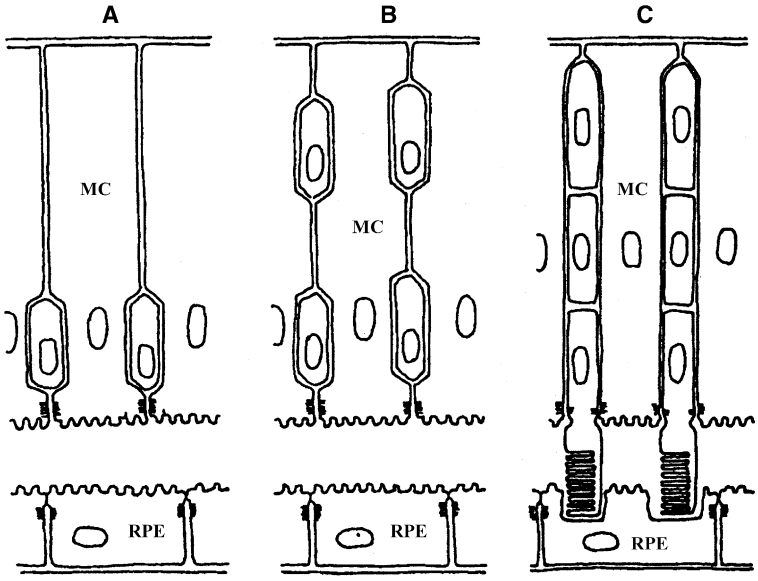

Figure 4 Schematic drawing of the development of the human retina. Notice that two monostratified epithelial-like layers are defining the structure of the retina. (A) Putative Muller cells form a continuous gap-junction sheet (already at the 8 mm embryo stage). The neural cells are embedded within the primitive Muller cell compartment. (B) The neural tissue proliferates to form two layers, still fully embedded within the Muller cell compartment. (C) Photoreceptors inner and outer segments grow out of the Muller cell compartment, into the RPE compartment, and the neural elements of the inner retina stratify to form three main layers.

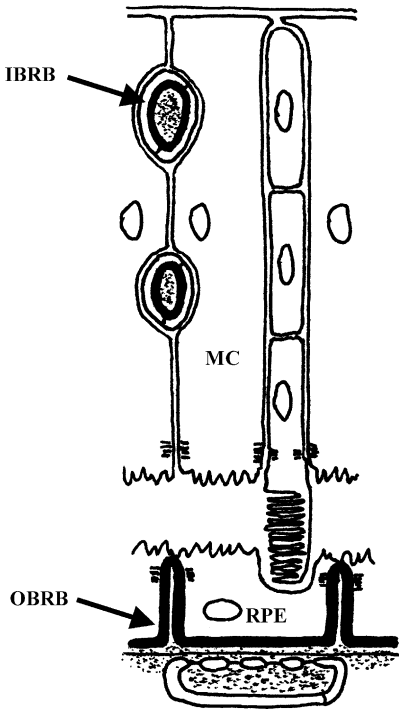

Figure 5 Schematic drawing of the blood-retinal barriers. The outer blood-retinal barrier is formed by the basal and lateral cell membrane of the RPE cells, bound by tight junctions. The inner blood-retinal barrier is formed by the inner cell membrane of the endothelial cells of retinal capillaries, bound by tight junctions.

observation that in proliferative retinopathies new vessels will tend to grow on the basal surface of the Muller cells (between retina and vitreous) rather than inside the retina.

In this two-compartment model two epithelial cell layers are forming separate homeostatic compartments. Neural elements are embedded in these two layers such that photoreceptor inner and outer segments alone reside within the outer compartment while the remaining neural elements (three sheets of neurons and their inter-connections) are embedded in the inner compartment. Each compartment has its own blood supply, such that blood vessels are in contact with glial (epithelial) elements, but never directly with neural cells [14,15].

The blood supply to the inner compartment is derived from the central retinal artery. "Retinal neurons are nourished by Muller cells" [15], as all three neurons are embedded within the framework formed by the Muller cells. The blood supply to the outer compartment is derived from the choroidal vasculature, through the RPE. Where precisely does the "watershed" zone between the choroidal and retinal circulations pass? It roughly parallels the two-compartment division (Fig. 7). More precisely, it appears that the photoreceptor cell, which has components in both compartments, can survive severe ischemic insults of any

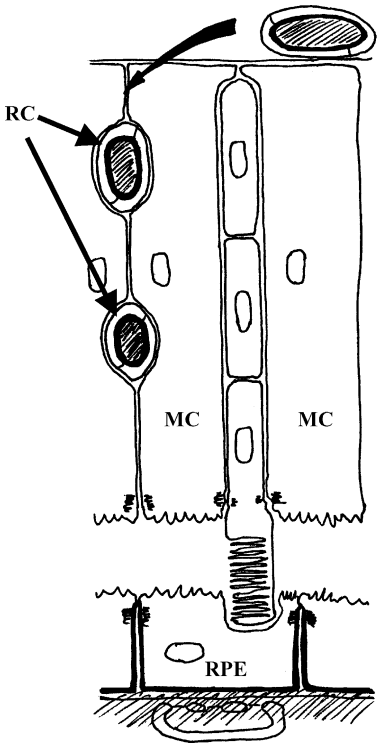

Figure 6 Schematic drawing of the "sliding" of the retinal vasculature from the basal aspect to the lateral aspect of the Muller cell. Note that the capillaries are accompanied by the internal blood-retinal barrier "inside" the retina. Thus, the relation of the capillaries to the neural elements has not changed. While the distance between the capillaries and neurons has decreased, they do not have direct contact with each other, but only across the Muller cell.

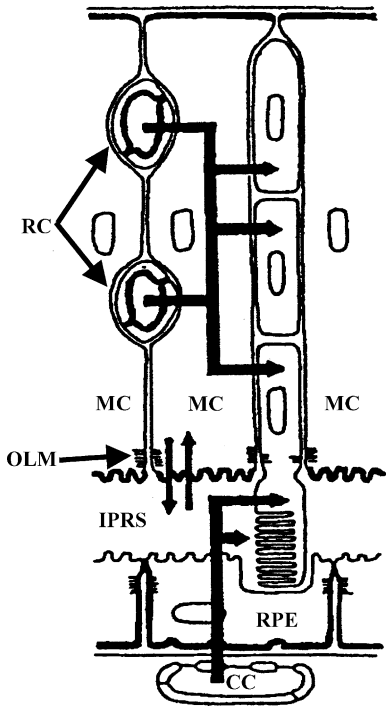

Figure 7 Relative distribution of the blood supply to the retina. The RPE cell feeds the photoreceptor cell inner and outer segments from the choroidal vasculature. The Muller cell feeds the three neuron layers from the retinal vasculature. In addition, Muller cells may also be able to uptake metabolites from the inter-photoreceptor space.

one of the two blood supplies, as long as the other blood supply is intact. Such is the case with central retinal artery occlusion on the one hand, and serous retinal detachment on the other, as both do not normally lead to death of the photoreceptor cell layer. It should be added that Muller cells might be able to uptake nutrients from the inter-photoreceptor space via their apical villi [14,15].

Outer compartment: light transduced into membrane potential

The outer compartment extends between the OLM and the RPE basement membrane. It is supplied by the chorio-capillary network [16], through the outer blood-retinal barrier, via the RPE cells. This barrier is formed by the RPE cell and the tight junction sheets between these cells. In this compartment the epithelial-like monostratified cell is the RPE, while the neural elements are the inner and outer segments of the photoreceptor cell. These segments actually lie in the space between the two monolayer sheets (the inter-photoreceptor space, which is the former ventricular space) but since they invaginate into, and are metabolically dependent on the RPE, they are considered as part of the outer compartment [17,18].

One of the main metabolic activities of this compartment is the control of the retinol cycle by the RPE [19,20]. Retinoid-binding protein was found in the inter-photoreceptor space up to the level of OLM, and not between Muller cells [19,20] (Fig. 8). In this compartment photic energy is transduced into neuronal electrical signals [21]. This requires vast oxygen and metabolite supply as well as mobilization of large quantities of heat. Therefore, the choroidal capillaries are short, wide, fenestrated and of high volume.

Breakdown of the outer blood-retinal barrier leads to serous retinal detachment [22,23] (Fig. 9). This compartment is extensible; hence, pathological fluids can accumulate in large amounts in the potential inter-photoreceptor space without damaging the compartment borders.

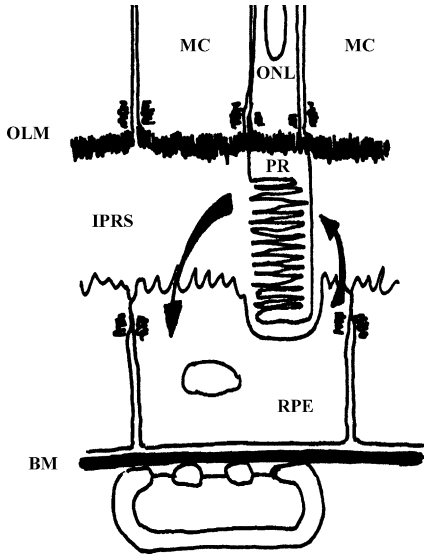

Figure 8 Schematic drawing of the outer compartment. Photoreceptor inner and outer segments lie in a homeostatic environment controlled by the RPE cell.

Inner compartment: transmission and processing of the visual signal

The inner compartment extends between the OLM and the Muller cell inner end-feet and their basal membrane, the ILM. It is largely supplied by the central retinal artery through the inner blood-retina barrier. This barrier is formed by endothelial cell inner membranes of the retinal capillaries and a tight junction sheet between these endothelial cells. In this compartment the monostratified cell is the Muller cell, and the neural elements are the three vertical neural levels of the retina (photoreceptor, bipolar and ganglion cells) and their inter-connections. Here action potentials are transmitted and processed and all three neuronal layers bathe in a similar homeostatic environment.

The main metabolic task of this compartment is related to the electrical and biochemical activity of the neural elements. This activity depends largely on oxygen supply. Therefore, retinal capillaries are long, narrow, and non-fenestrated. These qualities enable intimate and long-duration contact between erythrocytes and the capillary wall. Consequently, oxygen exchange is maximized. Since retinal endothelial cells never come in direct contact with neurons, but only with Muller cell processes [15], it is concluded that the Muller cell is entirely responsible for the homeostasis of this compartment (Fig. 10). Apart from mediating transfer between blood vessels and neuronal cells (and vice versa), the Muller cell also plays a pivotal role in maintaining and controlling extra-cellular

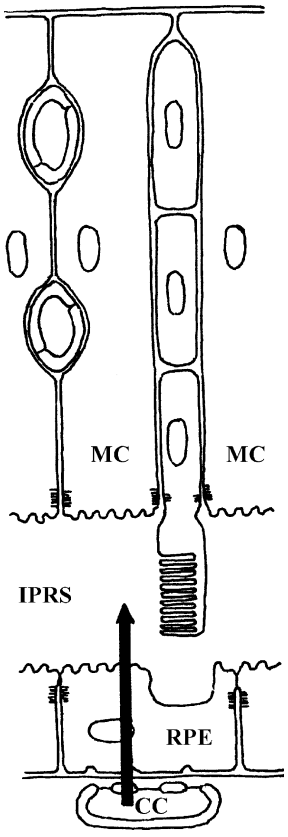

Figure 9 Breakdown of the outer blood-retinal barrier leads to serous retinal detachment.

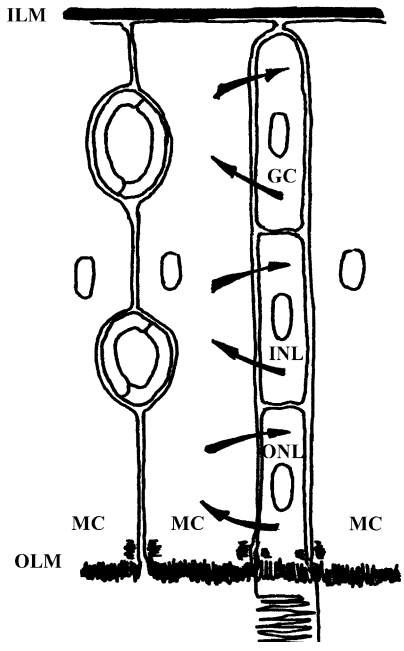

Figure 10 Schematic drawing of the inner compartment. The three layers of neurons lie in a homeostatic environment controlled by the Muller cell.

potassium levels surrounding the neurons. Muller cells possess specialized cell organelles for this purpose: orthogonal arrays of particles, the inward rectifying K^+ channels, that help in actively siphoning K^+ out of this compartment and into the vitreous [14]. These specialized potassium channels, located on the lateral and basal surfaces of the Muller cell, can be found from the OLM and inwards [15], and it follows that the part of the retina dependent metabolically on the Muller cells starts at this level.

Breakdown of the inner blood-retinal barrier leads to retinal edema accumulating within the compartment down to the level of the OLM [24—27] (Fig. 11). In many pathological conditions edema and hemorrhages can be clearly seen to extend up to the boarder of the OLM, but rarely is this border disrupted. The inner compartment is not extensible; therefore, even relatively small amounts of fluid may compromise the compartment borders as well as the neural elements. When pathological fluids accumulate, two possibilities exist: in chronic conditions the accumulated fluid results in degeneration and ultimately replaces neural elements. In acute conditions the compartment borders may disrupt, as in the case of severe retinal hemorrhage progressing into hemorrhagic retinal detachment (Fig. 12) or breakthrough hemorrhage into the vitreous. Table 1. summarizes the important features of each compartment.

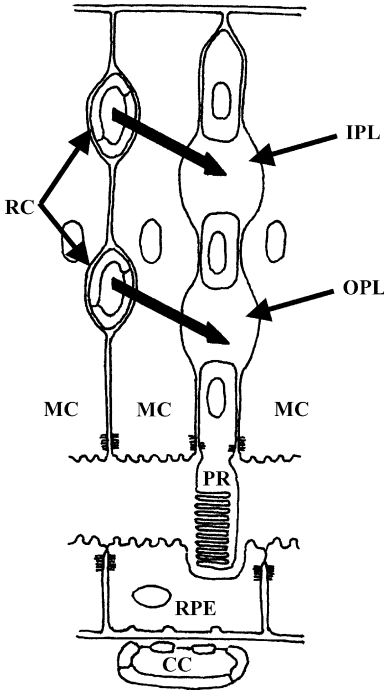

Figure 11 Breakdown of the inner blood-retinal barrier leads to retinal edema.

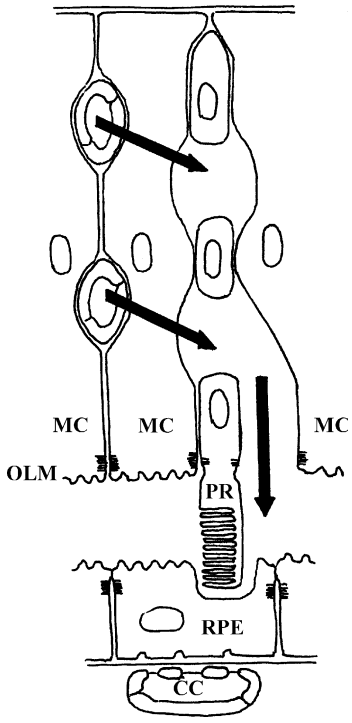

Figure 12 If, on top of breakdown of the inner blood-retinal barrier, the OLM also disrupts, a qualitative difference appears. The two-compartment division of the retina is violated, forming a single compartment.

Discussion

In this manuscript we present a new concept by which the retina is viewed as a two-compartment structure. Each compartment is based on a single-cell layer of supportive cells that form the framework of the compartment (RPE in one and Muller cell in the other), and each includes its unique blood supply, its blood-retinal barrier and embedded neural elements. The RPE and Muller cell are facing each other via their apical surfaces and each has a basement membrane outlining their basal surface (the ILM of the Muller cells and the inner aspect of Bruch's membrane of the RPE cells). In fact, these two compartments, when neural elements are disregarded, are almost a mirror image of each other.

While the neural elements of the retina have prime importance in retinal physiology, it is our opinion that the supportive framework is crucial for understanding the extent of many pathological conditions of the retina. Conditions such as edema, hemorrhage, and exudation, largely respect the two-compartment configuration of the retina. Pathological conditions that eventually break the OLM (the inter-compartmental border) extending into the other compartment, are qualitatively dif-

Table 1 Main features of the two retinal compartments

	Outer compartment	Inner compartment
1. Embryology	Outer layer of optic vesicle	Inner layer of optic vesicle
2. Blood supply	Choroidal vasculature	Central retinal artery
3. Outer limit	Inner part of Bruch's membrane	Outer limiting membrane
4. Inner limit	Outer limiting membrane	Internal limiting membrane
5. Barriers	Outer blood-retina barrier	Inner blood-retina barrier
6. Epithelial cell	RPE	Muller cell
7. Neural elements	Photoreceptor outer and inner segments	Three perikaryon neural layers and interconnections
8. Homeostasis	Retinol cycle	Spatial buffering of K^+
9. Function	Transformation of light into membrane potentials	Transmission of the visual signal
10. Barrier breakdown	Serous retinal detachment	Retinal edema
11. Possibility of fluid accumulation	Extensible (inter-photoreceptor space)	Inextensible

ferent once the integrity of this important border is disrupted.

A key element in our model is the unique function of the OLM, a semi-permeable barrier separating the two compartments. The OLM, a structure that is often overlooked, is formed by a continuous sheet of gap junctions connecting the external end-feet of Muller cells with the proximal part of the photoreceptor inner segment, as they emerge from the cell body. This continuous gap-junction sheet connects Muller cell to photoreceptor, and occasionally Muller cell to Muller cell and photoreceptor to photoreceptor. The OLM is not a barrier like the outer and inner blood-retinal barriers, since the blood-retinal barriers are composed of tight-junctions [2], while the OLM is composed of gap-junctions [5]. Horseradish peroxidase, for instance, will cross the OLM while it does not cross the blood-retinal barriers [3,4]. However, the OLM does possess partial barrier properties. For example, it was shown to be a barrier for retinoid-binding proteins [19]. This barrier property for larger molecules may explain the confinement of various retinal pathologies to a single compartment, on either side of the OLM. OLM gap-junctions possess "primarily mechanical function" [5]. This mechanical stability may be one of the factors underlying the isolation of many inner compartment retinal conditions (such as cystoid edema, retinal hemorrhages and exudates) that usually do not extend into the outer compartment.

Once we begin to apply the two-compartment concept, many examples of pathologies involving one compartment, such that the other compartment remains largely unaffected, can be identified.

Following are the four different combinations possible:

Outer compartment pathologies: these include central serous chorio-retinopathy, APMPPE, serpiginous choroidopathy and subretinal neovascularization, among others. These pathologies may have in common compromise of the outer blood-retinal barrier, often leading to a serous retinal detachment, while the neurosensory retina (the inner compartment) remains largely unaffected.

Inner compartment pathologies: for example: cystoid edema, retinal vein occlusion, non-proliferative diabetic retinopathy. These pathologies have in common accumulation of fluid within the neurosensory retina, usually up to the level of the OLM, while sparing the inter-photoreceptor space (the outer compartment).

Pathologies involving both compartments concomitantly: these are conditions involving both compartments simultaneously (such as some forms of vasculitis), while the integrity of the compartment borders is not disrupted.

Pathologies compromising the integrity of the OLM and thus extending from one compartment to the other: an example of a pathological process breaking from the outer to the inner compartment is the more advanced stage of exudative macular degeneration, while an example of a pathology breaking from the inner to the outer compartment is Coat's disease. These examples have in common disruption of the OLM (the inter-compartment border) leading to formation of one functional compartment. This has implications on the healing and long-term sequela of the pathological process.

In summary, the two-compartment model discussed in this manuscript splits the retina into two

distinct compartments, based on supportive, rather then neural, elements. This division may become useful in comprehending various types of retinal diseases, ranging from central serous chorio-retinopathy to microcystic edema, and from sub-retinal neovascularization to proliferative retinopathies.

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