Hypertensive Retinopathy

Introduction

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Since Liebreich [1], in 1859, first described 'albuminuric retinitis' in malignant arterial hypertension, hypertensive fundus changes have been regarded as an important part of the syndrome of malignant arterial hypertension. These changes have been given different names. Volhard and Fahr [2], in 1914, called them 'angiospastic retinopathy', a term also advocated later on by Wagener and Keith [3]. Fishberg and Oppenheimer [4], in 1930, called it 'hypertensive neuroretinopathy', which was later abbreviated to 'hypertensive retinopathy'. Wagener et al. [5], in 1947, suggested that different terminologies should be used for various types of hypertensive retinopathy, and these included retinopathy of: acute hypertension/chronic hypertension/terminal malignant hypertension. Finally, 'hypertensive retinopathy' came to be regarded as a universal term for all the fundus changes seen in any type of arterial hypertension. However, our studies [6–11] revealed that from the pathogenetic point of view, the various fundus lesions in malignant arterial hypertension consist of three distinct categories: (1) hypertensive retinopathy, (2) hypertensive choroidopathy, and (3) hypertensive optic neuropathy. Thus, optic disk edema, which was regarded as a very im-

portant sign of hypertensive retinopathy, in fact represents hypertensive optic neuropathy and is not a part of hypertensive retinopathy [10]. Similarly, the various retinal pigment epithelial lesions (e.g., the so-called Elschnig's spots), serous retinal detachment and some instances of macular edema represent manifestations of hypertensive choroidopathy [11].

A colossal amount of literature has accumulated on hypertensive retinopathy since its first description in 1859 [1]. In 1871, Allbutt [12] gave an admirable description of it and reviewed the already impressive collection of literature on the ophthalmoscopic and histopathologic findings of almost all the lesions seen in this condition. It is beyond the scope of this introduction to present even a bird's-eye view of the literature. Suffice it to say that, in spite of innumerable publications, hypertensive retinopathy is still the focus of many controversies. Our ability to produce experimentally malignant hypertension and hypertensive retinopathy in primates [8], the advent of fluorescein fundus angiography and its application in hypertensive retinopathy [13–19], and other modern investigative techniques have helped greatly to improve our understanding of this condition. In the papers published in this issue

of *Ophthalmologica*, we describe and discuss, in the light of our studies, many of the lesions of hypertensive retinopathy seen in malignant arterial hypertension *(but not in benign arterial hypertension)* and their pathogenesis, as well as some of the major controversies [20–24].

The retinal lesions which constitute hypertensive retinopathy, for descriptive purposes, can be divided into the following vascular and extravascular retinal lesions, although in some of the latter the primary factor may be retinal vascular derangements:

A: Retinal vascular lesions
1. Focal intraretinal periarteriolar transudates [9]
2. Cotton-wool spots (inner retinal ischemic spots) [21]
3. Retinal arteriolar changes [20]
4. Retinal capillary changes [21]
5. Retinal venous changes [25]
6. Increased permeability of the retinal vascular bed

B. *Extra vascular retinal lesions*
1. Retinal and macular edema [22]
2. Retinal hemorrhages [25]
3. Retinal lipid deposits ('hard exudates') [23]
4. Retinal nerve fiber loss [21]

For a full understanding of the pathogeneses of the various retinal lesions in hypertensive retinopathy associated with malignant arterial hypertension, one has to bear in mind some of the basic anatomical and physiological properties of the retina and retinal vessels. The properties include the following:

Retinal Arterioles. In the retina the so-called 'retinal arteries' are in fact arterioles, because they possess the following anatomic properties, typically seen in arterioles: (1) the widest part of the lumen of the retinal arterioles is near the optic disk and there its diameter is about 100 μm [26], which is typically the diameter of an arteriole; (2) unlike arteries, they possess neither an internal elastic lamina nor a continuous muscular coat [26, 27].

Absent Autonomic Nerve Supply. It is generally agreed that the vessels in the retina have no adrenergic vasomotor nerve supply [28–30]. However, in a recent study [31], blood vessels lying on the inner surface of the retina in rabbits were claimed to have sympathetic innervation originating from the superior cervical ganglion, distributed in the arterioles from the optic disk to the periphery and also in a few veins; these nerve fibers were numerous near the optic disk and sparse on the peripheral vessels. In view of the overwhelming evidence against the existence of such innervation in man and primates, and also the possibility of species difference, further confirmation of these latest findings is required.

Presence of Autoregulation. The object of autoregulation in a tissue is to keep the blood flow relatively constant during changes in its perfusion pressure. A number of studies have shown the presence of autoregulation in the retina [32–37]. The exact mechanism responsible for the autoregulation is still obscure but it is considered to be a feature of arterioles, particularly the terminal arterioles. With the rise or fall of blood pressure (BP) beyond the normal levels, the arterioles constrict or dilate, respectively, to regulate the blood flow. However, autoregulation becomes ineffective when the BP rises or falls beyond certain limits. With chronic malignant hypertension, the autoregulation adjusts itself to higher than normal levels as a compensatory mechanism, so that the breakthrough of autoregulation may occur at comparatively higher BP levels than in normal persons [38, 39]; we discussed the importance of this at length elsewhere [10].

Presence of Blood-Retinal Barrier. This is well established and is produced by the tight junctions between the endothelial cells of the retinal vessels (due to the presence of extensive zonulae occludentes) [40, 41]. The tight

interendothelial cell junctions block movement of macromolecules from the lumen toward the interstitial space. With a severe rise of BP (i.e. above the level of autoregulation), the autoregulation breaks down, resulting in focal or generalized dilatation of arterioles [9]. Morphological studies of the dilated segments have revealed endothelial cell loss, discontinuity of the endothelial cell layer or interendothelial separation as the initial event. These changes result in the failure of the blood-retinal barrier and increased permeability. The subject of breakdown in the blood-retinal barrier in malignant arterial hypertension is discussed at length elsewhere [9]. Tight cell junctions between the retinal pigment epithelial cells also produce a blood-retinal barrier, preventing the leakage of fluid from the choroid into the retina; this barrier breaks down when the eye develops hypertensive choroidopathy [11]; the role of breakdown of the blood-retinal barrier in the retinal pigment epithelium in the production of the various retinal lesions is also discussed at length elsewhere [11, 22, 23]. The retinal tissue itself has no barrier in its stroma so that fluid may be able to diffuse from one part to the adjacent parts.

Blood Column of Retinal Vessels. As elsewhere in the blood vessels in the body, in the retinal blood vessels the blood flow is fastest in the axial part of the blood column, while it is almost stationary in the peripheral shell, which is in contact with the vessel wall. Also the cells in the blood concentrate in the axial stream, the peripheral part of the blood column being mainly plasma. Ophthalmoscopy or color photographs of the retinal vessels show only the width of the central column of red blood cells. On the other hand, fluorescein fundus angiography reveals the entire width of the blood column, including the peripheral column of plasma.

Relevance of Experimental Studies on Hypertensive Retinopathy in Primates to Man. Finally, the inevitable question arises about the relevance of our experimental studies on hypertensive retinopathy in renovascular malignant arterial hypertension in primates (reported by us in the various papers in this issue) to man. There are no apparent differences between the human and primate in this area of their systemic and ocular anatomy, physiology or other relevant factors, including those discussed above; it would therefore seem logical to conclude that the findings of our experimental studies in primates are equally valid for man. This is further suggested by the close similarities between the hypertensive fundus lesions which we have observed in patients with malignant arterial hypertension, and in our experimental animals. In the experimental studies we were able to do systematic, detailed studies which are not usually possible in man and thus our experimental studies provide information which we may be missing in man.

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