Chapter 4

ANIMAL MODELS OF DIABETIC RETINOPATHY

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Abstract: If they are diabetic long enough, most or all species available for laboratory research will develop lesions characteristic of the early stages of diabetic retinopathy, including nonperfused (and acellular) capillaries and apoptotic loss of capillary cells. Although none of these animal models reliably proceed to preretinal neovascularization, they nevertheless provide valuable insight into the role of specific biochemical pathways and cell types in the early stages of retinopathy. An increasing number of therapeutic approaches have been identified that significantly inhibit the development of capillary obliteration in the retina. The challenge now is to integrate the results of these studies to identify the sequence of events that ultimately results in the characteristic histopathology in diabetes. Why diabetic animal models have not been found to develop the neovascular stages of diabetic retinopathy remains an important question, and one likely reason for this “failure” is that much less vaso-obliteration develops in the retina of the diabetic animals during the short duration of their diabetes as compared to that of some diabetic patients who, over many years, develop extensive vaso-obliteration. Nevertheless, the models are still useful, because preventing progressive capillary obliteration from occurring in the retina is likely to be a more beneficial therapeutic goal than merely inhibiting neovascularization in an already damaged and ischemic retina.

1. INTRODUCTION

Diabetic retinopathy is a major complication of Type 1 and Type 2 diabetes mellitus, being observed in most patients after 15 years of diabetes, and increasing the risk of blindness 25-fold above normal.¹,² The natural history of clinically demonstrable retinopathy has been carefully documented, and
important stages have been identified: vascular occlusion, formation of capillary microaneurysms, excessive vascular permeability, proliferation of new vessels and fibrous tissue, and contraction of the fibrovascular proliferations.\(^3\) This chapter will focus on the histological lesions that develop in animal models, and their relation to the lesions that develop in diabetic patients. Physiological abnormalities such as retinal blood flow and permeability have been reviewed elsewhere.\(^4,5\)

The general picture that has emerged of the pathogenesis of vision loss in diabetic retinopathy focuses primarily on increased capillary permeability, which leads to retinal edema, and neovascularization. Retinal edema can result in appreciable visual impairment, presumably due to physical distortion of the retina. Neovascularization can prevent light from reaching the photoreceptors secondary to development of a fibrovascular membrane in front of the retina.

![Diagram](image)

**Figure 4-1.** Simplified scheme postulated for the pathogenesis of diabetic retinopathy.

The nonproliferative stage of the retinopathy includes capillary cell death and capillary obliteration, microaneurysms, pericyte loss, and increased permeability. Pericyte loss was once believed to be the initial and most important lesion of the retinopathy, but it has since been demonstrated that both retinal endothelial cells and pericytes die at approximately the same rate.