

The Natural History of Diabetic Retinopathy

GUY H. CHAN

Department of Ophthalmology, Medical College of Virginia, Richmond

Since the discovery of insulin and its use in the management of diabetes, the occurrence of diabetic retinopathy appears to have increased (Vogelius, 1949). In 1923, the incidence was 14.6% and in 1953, it had risen to 46% (Portsmann and Wiese, 1954). The progressive increase has been attributed to the longer survival of diabetic patients, in whom retinopathy usually develops after having had diabetes for 15 to 25 years (Ashton, 1958).

Although diabetic retinopathy is a common cause of blindness (Bradley, 1965), the etiology of the associated retinopathy is still unknown. From reports in the literature (Scott, 1951; Ehlers, 1953; Cogan, 1961; Lawrence, 1951; Mooney, 1963; Dobree, 1964) and recent clinical observations made on diabetic patients at the Medical College of Virginia, two types of diabetic retinopathy can be distinguished. They differ noticeably in two clinical aspects; the rate of visual deterioration, and the ophthalmoscopic findings during the early stages of the retinopathy (table 1).

TYPE I DIABETIC RETINOPATHY

This is the commoner variety. It is characterized by a slowly progressive course of visual deterioration and ophthalmoscopic changes. Caird reported in 1963 that approximately 14.5% of patients with this type of retinal pathology become blind within five years after the onset of first signs of retinopathy. The diagnosis of this disorder is based

on the detection of micro-aneurysms, round hemorrhages, and waxy exudates which are characteristically found in the posterior polar region of the eye (fig. 1).

Microaneurysms

The earliest abnormality to be noted is usually microaneurysms which are situated predominantly in the macular area, and in most cases are adjacent to the venous end of the capillaries. These aneurysms appear as small red dots, 20 to 30 μ in diameter, and are highly suggestive of diabetes (Ashton, 1958). They are visible in 55% of patients with diabetic retinopathy (Scott, 1951). Histologically, a microaneurysm is an aneurysmal dilatation of the capillary wall. The etiology is still unknown, although many theories have been proposed. Wise (1956) suggested that microaneurysms are an abortive form of neovascularization. Ashton (1958) demonstrated histologically that aneurysms develop from capillary loops. The opposing walls of the loops become fused and exudates form a cap on the aneurysm. Cogan (1961) found that in the diabetic retina the mural cells, which are normally present in the capillary wall, show degenerative changes, and the microaneurysms appear to begin at the sites of these cells. However, Bloodworth (1962) suggested that the initial lesion is the degeneration of neurons and glial cells, followed by aneurysmal dilatation of the capillary wall. Wolter (1962) noticed a significant increase of intervascular mesodermal

strands connecting the retinal capillaries, and suggested that microaneurysms may be due to traction of these strands developing within the process of pathological neovascularization.

Round Hemorrhages

Microaneurysms are located in the inner nuclear layer of the retina and hemorrhages commonly occur at the site of these aneurysms (Ashton, 1958). Ophthalmoscopically, the retinal microaneurysms in diabetes may be visible for many months in contrast to hemorrhages, which disappear within weeks. Round hemorrhages are intra-retinal bleeding spots located deep in the outer plexiform layer. The blood is confined by the retinal fibers,

which are arranged in the antero-posterior axis of the eye, and hence the hemorrhagic areas appear round. Hemorrhages of this type are seen in 85% of patients with diabetic retinopathy (Scott, 1951).

Waxy Exudates

The white or yellowish patches are exudates, consisting of lipoid and PAS-positive material, thought to be mucopolysaccharide. These substances seep through the walls of the blood vessels and eventually accumulate in the outer plexiform layer of the retina (Ashton, 1958). These well-defined waxy exudates form a characteristic ophthalmoscopic picture and are found in 76% of patients with diabetic retinopathy (Scott, 1951). Many small

exudates tend to coalesce to form larger plaques. In advanced cases, this formation of larger plaques can result in a circular pattern surrounding the macula which may be referred to as *circinate retinopathy*.

Vitreous Hemorrhages and Retinitis Proliferans

During progression of the retinal lesion, hemorrhages into the pre-retinal space and the vitreous can occur, and this may be followed by retinitis proliferans, which is a product of the proliferation of fibrous tissue in varying amounts associated with new fine vessels (Hanum, 1938). This advanced retinopathy marks the final stage of useful vision.

TYPE II DIABETIC RETINOPATHY

This proliferative type of retinopathy is characterized by a rapid progression of visual loss and ophthalmoscopic changes. Recently, much has been written on this type of retinopathy, with special reference to the visual prognosis, the evolution of the retinal lesions and the fundoscopic changes following hypophysectomy (Beetham, 1963; Dobree, 1964; Root, 1959).

The incidence of proliferative diabetic retinopathy was recently found to be as high as 30% in diabetics with visible retinal changes. About 50% of this group of patients had fairly good vision and 30% had visual acuity of less than 20/200 in the better eye. The progression of this retinopathy from onset to "legal" blindness took an average of three years (Beetham, 1963).

Venous Engorgement, Vascular Proliferation, and Connective Tissue Condensation

In the early stages, the ophthalmoscopic signs are venous engorgement, vascular proliferation and connective tissue condensation. The



Fig. 1—Diabetic retinopathy, Type I, early stage. Photograph of macular area of fundus of 54-year-old diabetic, showing microaneurysms near the venous end of capillaries (arrow 1). Larger lesions with ill-defined borders are "round" hemorrhages (arrow 2). The well-demarcated white lesion is a waxy exudate (arrow 3).

most important diagnostic features are the neovascularization and connective tissue condensation which are found initially around the optic disc. Smaller collections of new vessels are also seen in the superficial retinal capillary plexus and the vitreous (fig 2). Vision and the retinal details may be blurred by larger proliferative lesions which project into the vitreous. The proliferative vessels sometimes assume a veil-like structure and wave in the vitreous at slight movement of the eye.

Vitreous Hemorrhages, Retinitis Proliferans, and Other Complications

Bleeding from fragile vessels gives rise to subhyaloid and vitreous hemorrhages which are liable to occur during exertion as in bending, stooping, or severe vomiting (Dobree, 1964). When absorption of blood takes place, the vision improves, only to be followed by repeated episodes of sudden blindness caused by recurrent vitreous hemorrhages. Eventually, severe retinitis proliferans develops (fig. 3). The latter, as with Type I, is the final stage, and the already blind eye may be further complicated by occlusions of the retinal vessels, retinal detachment, and secondary glaucoma.

COMMENTS

Despite the differences observed clinically, the proliferative retinopathy may be a variant of the more common, slowly progressive type (Cogan, 1961). The complex ophthalmoscopic picture of the former can be superimposed on a background of Type I diabetic retinopathy which may be of any degree of severity (Dobree, 1964).

It is significant to note that in spite of the relatively malignant course in visual deterioration with the proliferative retinopathy, spontaneous regression occurs in 10 to 15% of patients, some of whom

	Type I	Type II	
Age of onset	(5th or 6th Older decade)	(Before 4th Younger decade)	
Visual deterioration	Relatively slow	Relatively rapid	
Fundus Early	Microaneurysms, round hemorrhages, waxy exudates	Vitreous* hemorrhages	Venous engorgement, vascular proliferation, connective tissue condensation
Late	Fibrosis (retinitis proliferans), retinal detachment		

* Vitreous hemorrhages may occur in either type at any time during progression of retinal lesion.



Fig. 2—Diabetic retinopathy, Type II, early stage. Optic disc and adjacent retina of 42-year-old diabetic, showing growth of fine, tortuous brush-like vessels tending into the vitreous (arrow 1). White strands surrounding new vessels connective tissue condensations (arrow 2).

enjoy improvement of vision for as long as 10 years (Beetham, 1963; Dobree, 1964; Bradley, 1965).

It is of interest that, with maximal medical management fewer than 30% of patients with Type II retinopathy showed overall stabilization of retinal pathology and visual improvement, whereas following pituitary surgery, 50% or more had a favorable response (Bradley, 1965).

SUMMARY

Diabetic retinopathy is a common and increasing cause of blindness. The higher incidence of retinopathy is related to the longer survival of the diabetic patient.

The etiology of diabetic retinopathy remains unknown. However, two varieties appear to exist:

Type I retinopathy, characterized by a slowly progressive course

and ophthalmoscopic findings of microaneurysms, round hemorrhages, and waxy exudates; and Type II retinopathy, associated with a more rapid loss of vision, in which the main findings are venous engorgement, vascular proliferation, connective tissue condensation, and recurrent vitreous hemorrhages. Both types may result in retinitis proliferans and blindness. In the proliferative (Type II) diabetic retinopathy, regression of the vascular element, but not the fibrous tissue, may occur spontaneously or after hypophysectomy.

REFERENCES

ASHTON, N. Diabetic microangiopathy. *Advan. Ophthalmol.* 8: 1-84, 1958.
 BALLANTYNE, A. J., AND A. LOWENSTEIN. The pathology of diabetic retinopathy. *Trans. Ophthalmol. Soc. U. K.* 63: 95-115, 1944.

BEETHAM, W. P. Visual prognosis of proliferating diabetic retinopathy. *Brit. J. Ophthalmol.* 47: 611-619, 1963.
 BLOODWORTH, J. M. B., JR. Diabetic microangiopathy. *Diabetes* 12: 99-114, 1963.
 BRADLEY, R. F., S. B. REES, AND C. A. FAGER. Pituitary ablation in the treatment of diabetic retinopathy. *Med. Clin. North Am.* 49: 1105-1124, 1965.
 CAIRD, F. I., AND C. J. GARRETT. Prognosis for vision in diabetic retinopathy. *Diabetes* 12: 389-397, 1963.
 COGAN, D. G., D. TOUSSAINT, AND T. KUWABARA. Retinal vascular patterns. IV. Diabetic retinopathy. *Arch. Ophthalmol.* 66: 366-378, 1961.
 DOBREE, J. H. Proliferative diabetic retinopathy: evolution of the retinal lesions. *Brit. J. Ophthalmol.* 48: 637-649, 1964.
 DOLLERY, C. T., AND N. W. OAKLEY. Reversal of retinal vascular changes in diabetes. *Diabetes* 14: 121-127, 1965.
 HANUM, S. Diabetic retinitis. *Acta Ophthalmol. Suppl.* 16: 11-174, 1938.
 HOUSSAY, B. A., AND A. BIASOTTI. Pankreasdiabetes und Hypophyse beim Hund. *Arch. ges. Physiol. (Pflügers)* 227: 664-684, 1931.
 LAWRENCE, R. D. Discussion on diabetic retinopathy. *Proc. Roy. Soc. Med.* 44: 742-743, 1951.
 MOONEY, A. J. Diabetic retinopathy—a challenge. *Brit. J. Ophthalmol.* 47: 513-520, 1963.
 POULSEN, J. E. The Houssay phenomenon in man: recovery from retinopathy in a case of diabetes with Simmond's disease. *Diabetes* 2: 7-12, 1953.
 ROOT, H. F., S. MIRSKY, AND J. DITZEL. Proliferative retinopathy in diabetes mellitus. *J. Am. Med. Assoc.* 169: 903-909, 1959.
 SCOTT, G. I. Discussion on diabetic retinopathy. *Proc. Roy. Soc. Med.* 44: 743-747, 1951.
 WISE, G. N. Retinal neovascularization. *Trans. Am. Ophthalmol. Soc.* 54: 729-826, 1956.
 WOLTER, J. R. The nature of capillary microaneurysms in diabetic retinopathy. *Diabetes* 11: 126-131, 1962.

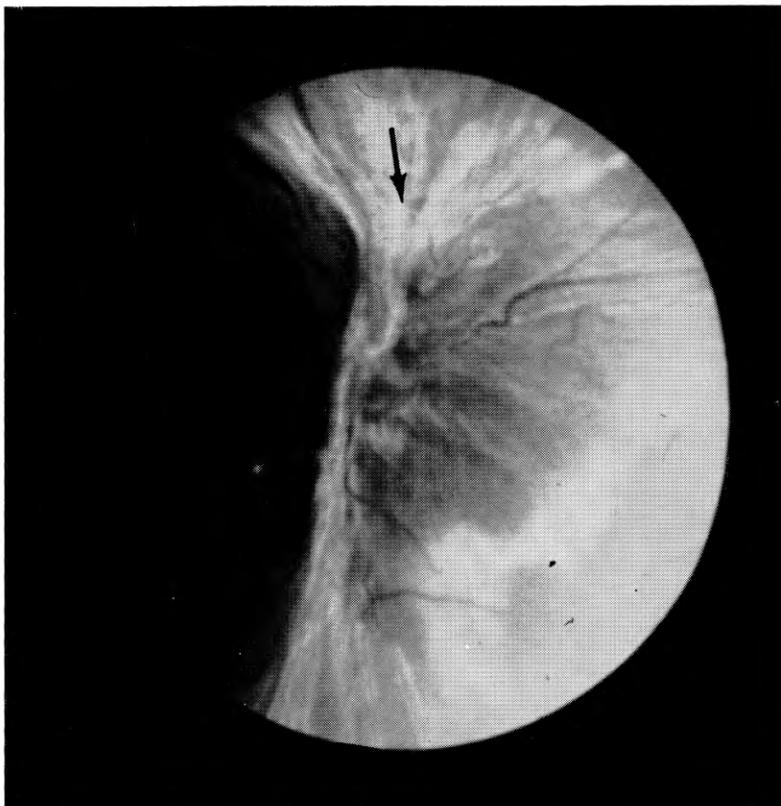


Fig. 3—Diabetic retinopathy, Types I and II, late stage. Retinitis proliferans (arrow), consisting of whitish bands of fibrous tissue and fine vessels.