36 Diabetic Retinopathy

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Keypoints

- In the Wisconsin study [1], proliferative diabetic retinopathy (PDR) occurred in 67% of persons with type 1 diabetes mellitus (T1DM) for 35 or more years. One would therefore expect that two-thirds of people with T1DM would need laser treatment for PDR during their lifetime.
- In the same study, the 4-year incidence of panretinal photocoagulation was 2.5 times higher than the rate of macular laser.
- In patients with type 2 diabetes mellitus (T2DM), the rate of PDR is not as high but it is estimated that 1 in 3 patients with T2DM will develop sight-threatening diabetic retinopathy requiring laser during their lifetime.
- The prevalence of blindness is influenced by duration of diabetes, blood glucose and blood pressure control, and by the presence or absence of screening and preventive laser treatment.
- Achieving a high compliance as achieved in Iceland [2] can lower the risk of blindness to very low levels.

Introduction – a historical perspective

In 1877, Mackenzie and Nettleship [3], in one of the first pathologic reports on diabetic retinopathy (DR), observed capillary aneurysms. In 1900, the average life expectancy for men was 48.5 years and for women was 52.4 years and this rose over the next century to 76.0 years for men and 80.6 years for women. In 1921, Banting and Best discovered insulin in the laboratory of Dr. J. MacLeod. In 1923, Banting and MacLeod were awarded the Nobel Prize for Medicine. In 1943, Ballantyne and Loewenstein [4] examining flat unstained retinas, noted many capillary aneurysms and they first coined the phrase "diabetic retinopathy." In 1953, Ashton [5] described changes in the arterioles in DR, studied in retinas removed postmortem. Examples of the Indian ink preparations published in his article [5] written in 1953 are shown in Figure 36.1.

The normal eye

The eye is an approximate globe with the innermost surface of the eye, the retina, containing specialized photoreceptor cells (Figure 36.2).

The central foveal region is thinner and is devoid of retinal blood supply; essential supply is provided through diffusion from the capillaries of the innermost vascular layer of underlying choroid through contact with the retinal pigment epithelium. The majority of the retina is provided with oxygen by means of the retinal vascular circulation (Figure 36.3).

The blood vessels in the retina exhibit tight junctions between adjacent cells maintaining the blood–retinal barrier. The normal structure of retinal vessels is shown in Figure 36.4.

The cells of the choroidal circulation have small gaps (fenestrations) between the cells in the walls of smaller choroidal vessels allowing transport of essential nutrients and other small molecules and hence support the nutrition and oxygenation of the foveal region through the retinal pigment epithelium.

Risk factors for diabetic retinopathy

Major international epidemiologic trials have established that the development of DR is related to the following modifiable and non-modifiable risk factors.

Modifiable risk factors

Blood glucose

Evidence for the link between poor glucose control and greater progression of DR was provided by numerous early studies.

The study that confirmed that intensive blood glucose control reduces the risk of new onset DR and slows the progression of existing DR for patients with type 1 diabetes mellitus (T1DM) was the Diabetes Control and Complications Trial (DCCT) [6]. In the DCCT [7], early worsening of DR was reported at the 6- and/or 12-month visit in 13.1% of patients assigned to intensive

Textbook of Diabetes, 4th edition. Edited by R. Holt, C. Cockram, A. Flyvbjerg and B. Goldstein.

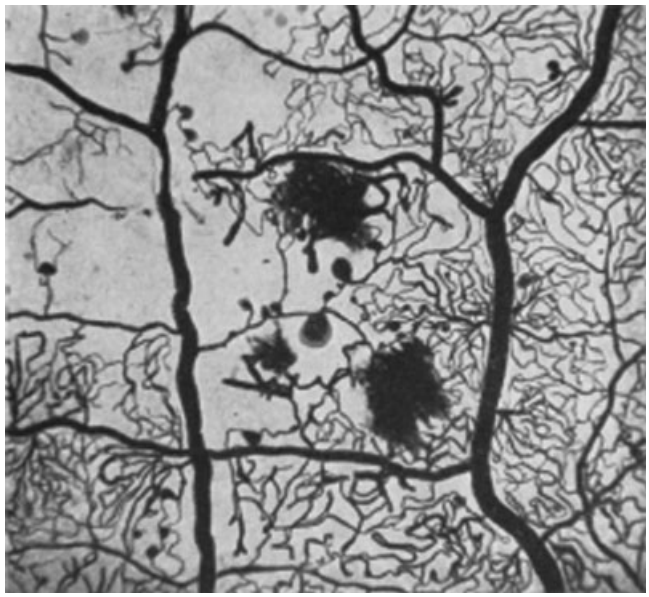
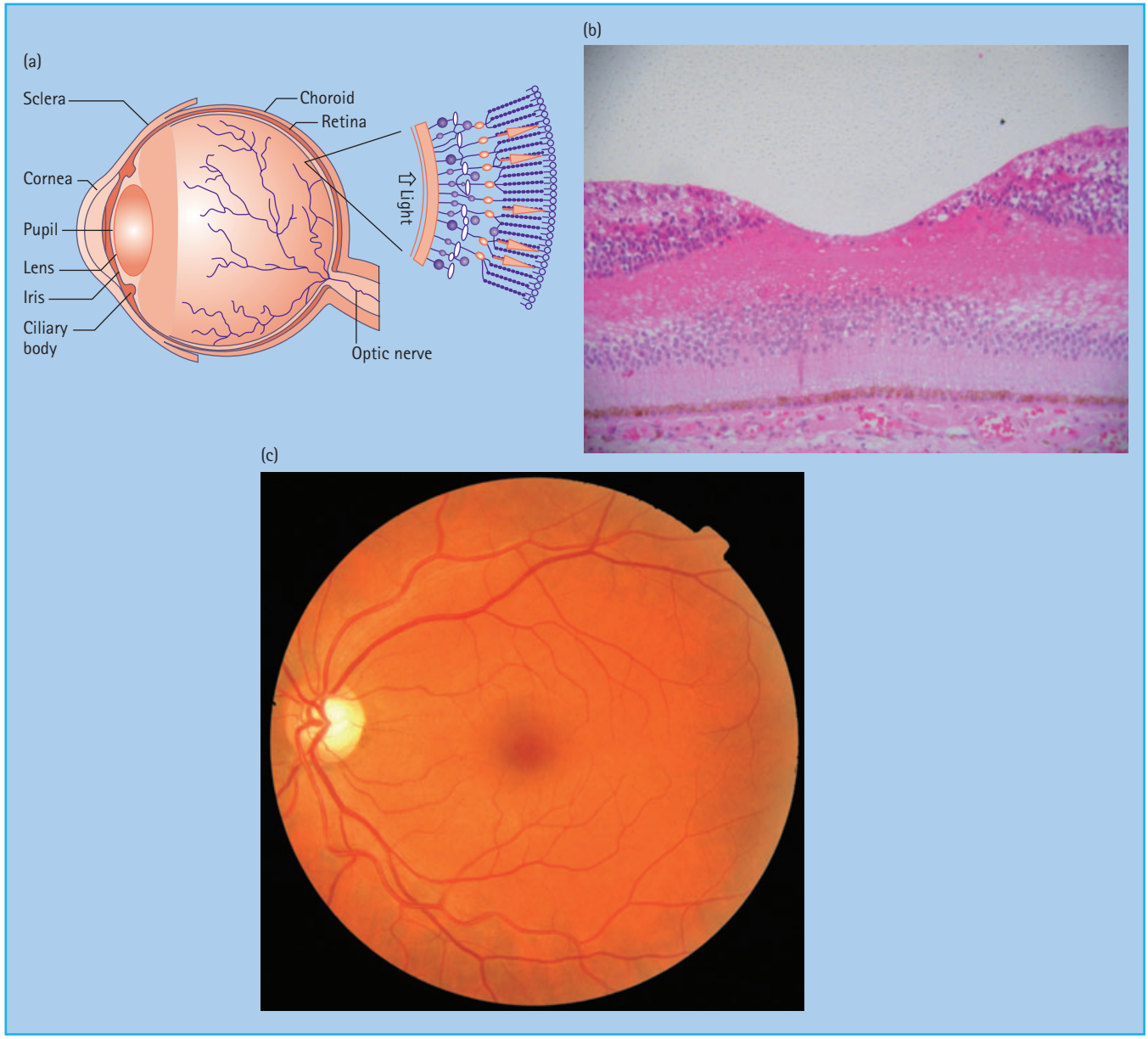


Figure 36.1 Diabetic retinopathy showing an artery on the left and vein on the right. Hemorrhages and microaneurysms are present; in the center of the picture they are seen on an arteriole. The arteriolar side of the circulation is extensively atrophied. Injected Indian ink. Periodic acid–Schiff stain ×44. Reproduced from Ashton N. Arteriolar involvement in diabetic retinopathy. *Br J Ophthalmol* 1953; **37**:282–292.



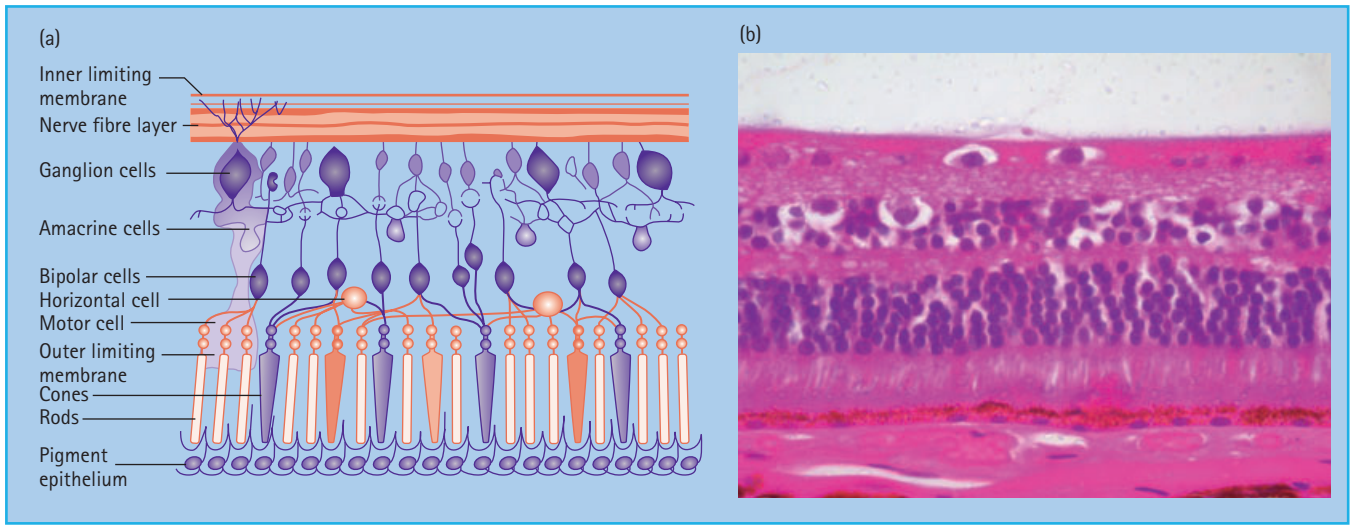


Figure 36.3 (a) This figure shows a retinal structure cross-section diagram. Reproduced from Scanlon PH, Wilkinson CP, Aldington SJ, Matthews DR. *A Practical Manual of Diabetic Retinopathy Management*. Published 2009 by Blackwell Publishing. (b) A histologic section showing the ganglion cell layer, the bipolar layer, the nuclei of the cones and rods, the pigment epithelium, Bruchs membrane and choroids vessels. Reproduced from Scanlon PH, Wilkinson CP, Aldington SJ, Matthews DR. *A Practical Manual of Diabetic Retinopathy Management*. Published 2009 by Blackwell Publishing.

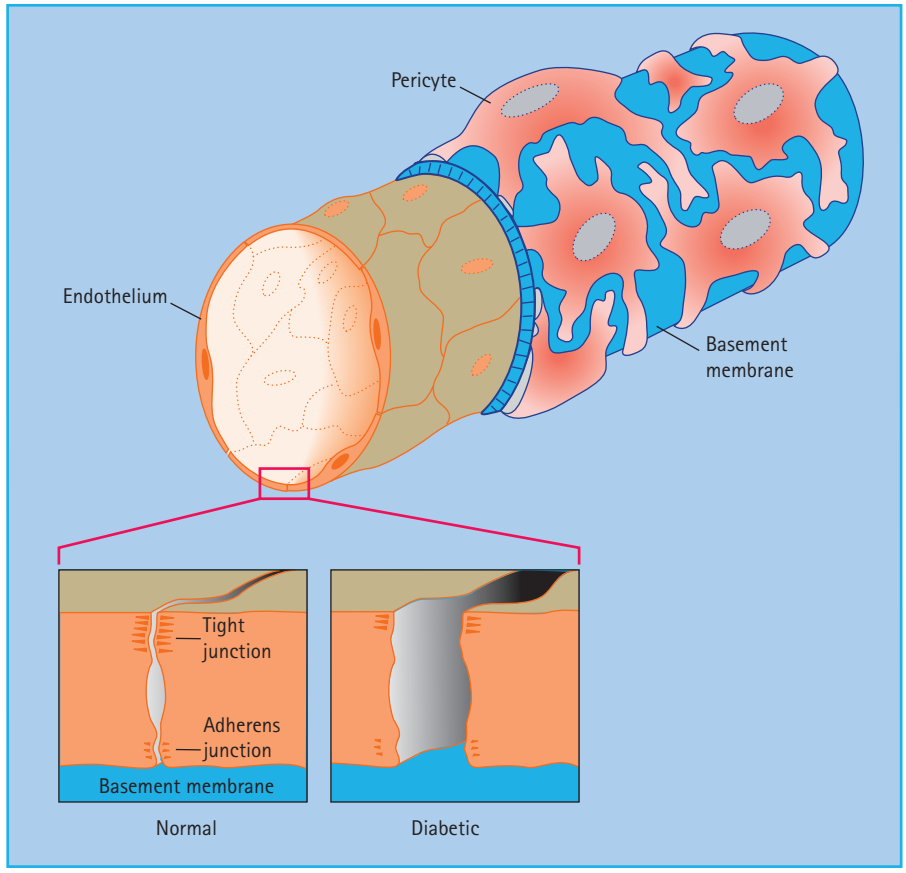


Figure 36.4 An inner layer of endothelial cells is enclosed by a tube of basement membrane, which in turn is surrounded by pericytes.

Figure 36.2 (a) Cross-section diagram of the eye and major structures. Reproduced from Scanlon PH, Wilkinson CP, Aldington SJ, Matthews DR. *A Practical Manual of Diabetic Retinopathy Management*. Published 2009 by Blackwell Publishing. (b) Normal human fovea. This shows the inner and outer nuclear cell layers at the edge of the fovea and the concentration of cones centrally. Reproduced from Scanlon PH, Wilkinson CP, Aldington SJ, Matthews DR. *A Practical Manual of Diabetic Retinopathy Management*. Published 2009 by Blackwell Publishing. (c) Color photograph of the left central retina, including the macula and disc. Reproduced from Scanlon PH, Wilkinson CP, Aldington SJ, Matthews DR. *A Practical Manual of Diabetic Retinopathy Management*. Published 2009 by Blackwell Publishing.

treatment; however, the long-term benefits of intensive insulin treatment greatly outweighed the risks of early worsening.

Similarly, for type 2 diabetes (T2DM) the UK Prospective Diabetes Study (UKPDS) [8] demonstrated that intensive blood glucose control reduces the risk of new onset DR and slows the progression of existing DR for patients with T2DM.

Blood pressure

Control of systemic hypertension has been shown to reduce the risk of new onset DR and slow the progression of existing DR [9,10].

Lipid levels

There is evidence that elevated serum lipids are associated with macular exudates and moderate visual loss; partial regression of hard exudates may be possible by reducing elevated lipid levels [11,12].

Smoking

There is some evidence that smoking may be a risk factor in the progression of DR in T1DM as described by Muhlhauser *et al.* [13] and Karamanos *et al.* [14]; however, in T2DM the evidence is controversial.

Non-modifiable risk factors

Duration

The major non-modifiable determinant of progression of DR is duration of diabetes [15,16].

Age

There is a rather complex link with age, with the Wisconsin Epidemiological Study [1,17,18] demonstrating that in those whose age of diagnosis was less than 30 years and who had diabetes of 10 years' duration or less, the severity of retinopathy was related to older age at examination, whereas when the age at diagnosis was 30 years or more, the severity of retinopathy was related to younger age at diagnosis. In the UKPDS [19], in those who already had retinopathy, progression was associated with older age.

Genetic predisposition

Early studies of identical twins with diabetes suggest familial clustering of DR. An association between severity of DR and human leukocyte antigens has been suggested in a number of studies [20,21], although this has not been uniformly accepted [22]. The majority of candidate genes studied exhibit weak or no association with retinopathy status, and where associations have been detected these results have not been replicated in multiple populations.

Ethnicity

Emanuele *et al.* [23] reported a higher prevalence of DR scores >40 in Latin Americans (36%) and African-Americans (29%) than for whites of Northern European ancestry (22%). Simmons *et al.* [24] compared ethnic differences in the prevalence of DR in European, Maori and Pacific peoples with diabetes in Auckland, New Zealand. They demonstrated that moderate or more severe DR is more common in Polynesians than Europeans. In neither of these two studies could the differences be accounted for by an imbalance in traditional risk factors such as age, duration of diagnosed diabetes, HbA_{1c} and blood pressure.

Pathophysiologic events in diabetic retinopathy

Basement membrane thickening

An early histopathologic sign of DR is thickening of the basement membrane (Figure 36.5) [25].

Pericyte loss

Fallout of pericytes, which are sensitive to high glucose concentrations and undergo apoptosis [26], is an early and crucial event

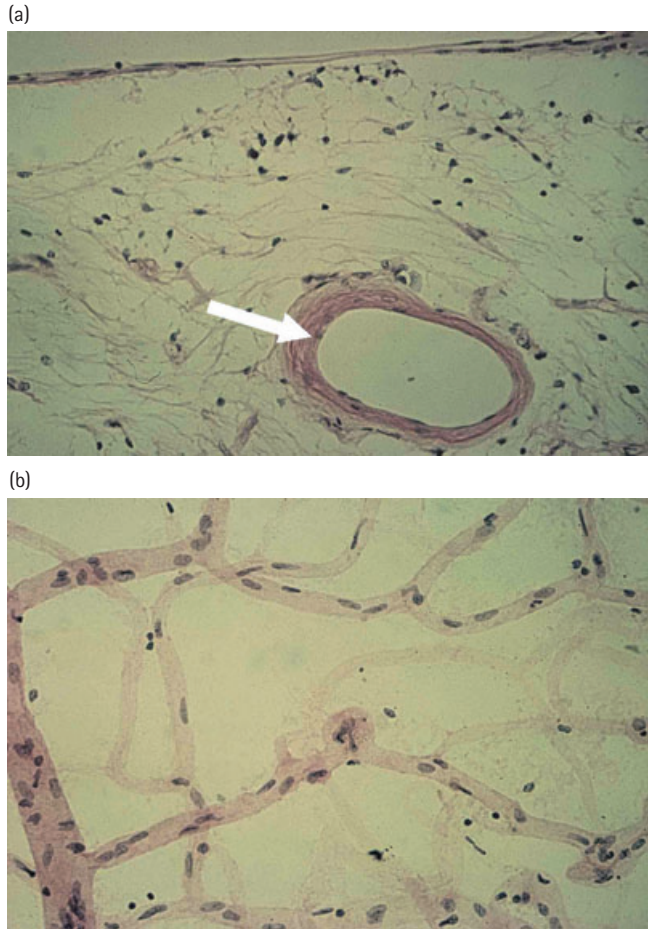


Figure 36.5 (a) Basement membrane thickening (arrow) in a retinal arteriole. Periodic acid–Schiff stain, original magnification ×250. (b) Pericyte loss, in a flat-mounted tryptic digest of retina. Pericytes (small, dark nuclei) normally occur in a 1:1 ratio with the endothelial cells (pale, elongated nuclei). Original magnification ×400.

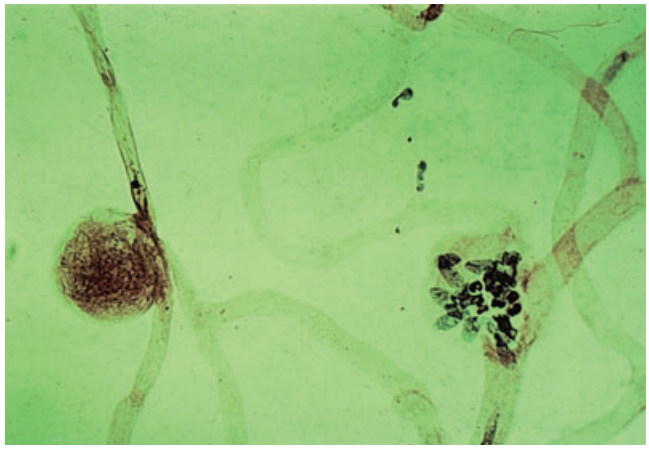


Figure 36.6 Tryptic digest of diabetic retina, showing two large microaneurysms in an area of acellular capillaries. One aneurysm (left) appears to be filled with clotted blood, while the second is hypercellular. Hematoxylin and eosin stain, original magnification ×400.

in DR (Figure 36.5b). Loss of retinal capillary endothelial cells follows soon after pericyte loss with the formation of acellular capillaries.

Increased capillary permeability

Endothelial cells form a continuous sheet with each cell being fused to neighbors by tight junctions that maintain the inner blood–retinal barrier, which may break down in DR leading to leakage of plasma proteins. Focal leakage is also observed around microaneurysms but this is likely to be caused by local endothelial cell damage caused by inflammatory mediators released from adherent leukocytes [27].

Microaneurysms

The microaneurysm is the hallmark of retinal microvascular disease in patients with diabetes (Figure 36.6). It has been suggested that microaneurysms may be asymmetric dilatations of the capillary wall where it is weakened or damaged, following the loss of the supporting pericytes (Figure 36.5b) and localized increases in hydrostatic pressure [28]. Early stage microaneurysms may be extensively infiltrated with large numbers of monocyte and polymorphonuclear cells (Figure 36.6) [28].

Smooth muscle death

Progressive death of vascular smooth muscle cells in the retinal arteries and arterioles has been established in the diabetic human retina [29].

Capillary weakening

Increasing closure of capillaries may be linked with the occurrence of intraretinal microvascular abnormalities (IRMA). These structures contain large numbers of endothelial-like cells and occur in association with acellular capillaries close to the arterial side of the circulation [29].

Retinal blood flow

Most clinical hemodynamic studies in diabetes conclude that increased blood flow and impaired autoregulation are features of DR [30]. Persistent dilatation of retinal arterioles is a well-known phenomenon in diabetes [31]. As DR progresses, increasingly large and widespread areas of retinal ischemia develop, caused by capillary occlusion and intravascular coagulation, which is considered to be enhanced by increased platelet stickiness in some studies [32], but not others [33].

The consultation

A carefully taken history and high quality clinical examination is a vital component of the care of any patient with DR.

Practical assessment

- History, which includes past ocular, diabetes, medical, family, drug and psychosocial history.
- Eye examination, which includes assessment of visual acuity and, where appropriate, color vision, inspection of external structures, visual fields to confrontation, ocular movement, pupillary reactions to light and accommodation, red reflex with an ophthalmoscope and slit-lamp biomicroscopy of the anterior eye.
- Both pupils are dilated with 1% tropicamide and in many patients 2.5% phenylephrine as well.
- Direct ophthalmoscopy has a limited two-dimensional field of view and has been shown to have a limited sensitivity and specificity for the detection of sight-threatening DR but is useful for ad hoc detection of DR.
- Slit-lamp biomicroscopy of the retina is the most common method employed by ophthalmologists to diagnose and monitor retinal disease using condensing lenses or fundus contact lenses (contact lens biomicroscopy).
- Binocular indirect ophthalmoscopy is useful for evaluating the posterior segment and retinal periphery. A larger area can be viewed than with slit-lamp biomicroscopy but this view is less magnified.

Multidisciplinary management

It is very important for an ophthalmologist to be aware of the control of risk factors in the individual patient and to have good communication with the diabetic physician or general practitioner who is looking after this aspect of the patient's management.

Investigative techniques to assess diabetic retinopathy

Retinal photography

Digital color retinal photography is increasingly being used as a record of retinal lesions.

Fundus fluorescein angiography

This is a diagnostic procedure, when sodium fluorescein injection is given rapidly into the arm and the fluorescence of the dye in

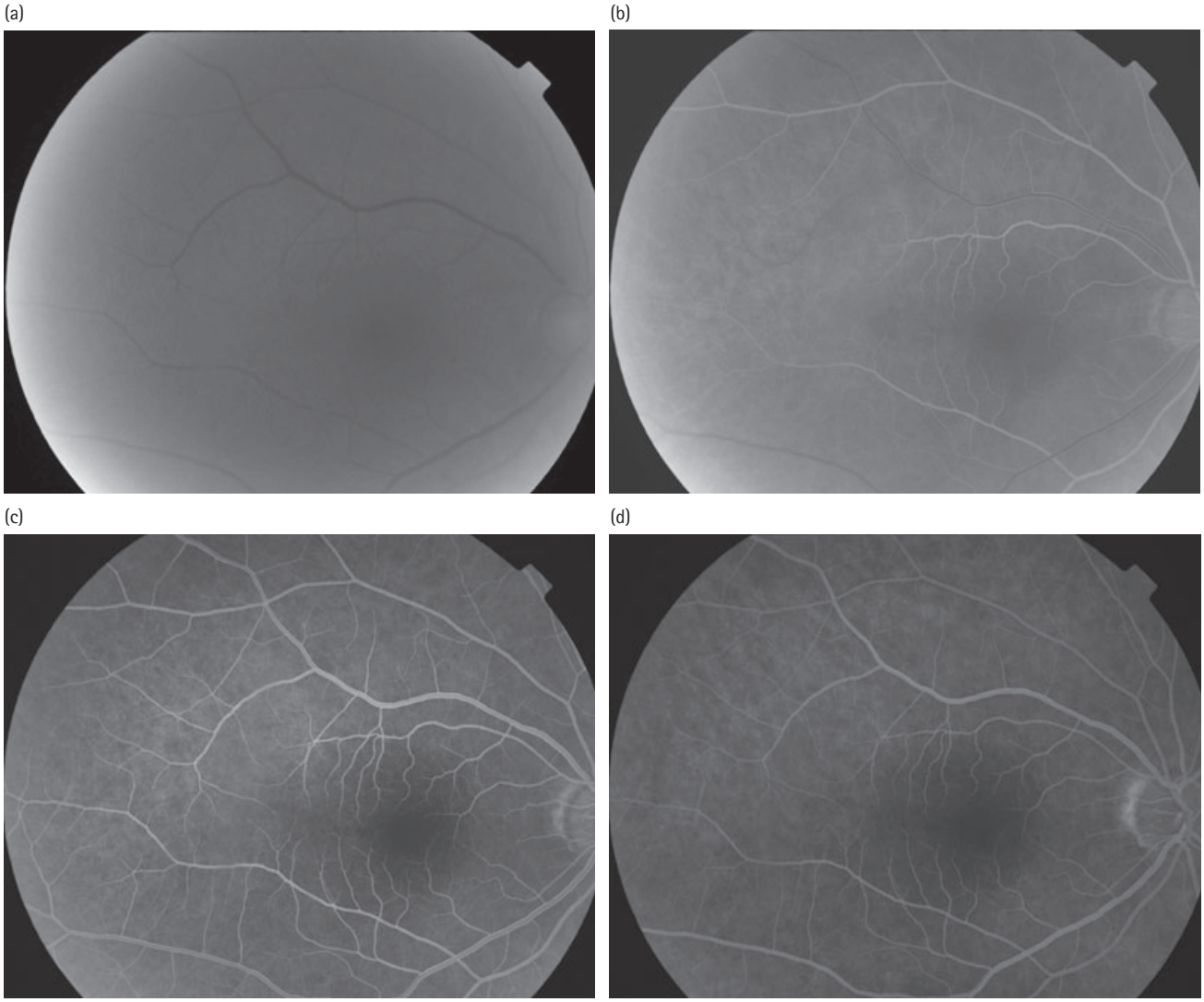


Figure 36.7 Fundus fluorescein angiography. (a) Choroidal flush. (b) Retinal arterial stage with very early signs of fluorescein in veins. (c) Arteriovenous phase. (d) Venous phase.

blue light enables photographs to be taken as it appears in the retina (Figure 36.7). The fluorescein dye causes a few side effects such as nausea, vomiting, occasional syncope, skin rashes and itching. More serious side effects of bronchospasm, anaphylactic shock and cardiac arrest are extremely rare.

Optical coherence tomography

Optical coherence tomography (OCT) is an imaging technique that interprets reflected optical waves using interferometry. OCT images can be presented as either cross-sectional images or as topographic maps (Figure 36.8).

Ultrasound B scan examination

Ultrasound B scan examination uses high frequency ultrasound to examine the density and extent of a vitreous hemorrhage and the presence or absence of a retinal detachment where the retinal view is obscured.

Perimetry

Perimetry is the systematic measurement of differential light sensitivity in the visual field by the detection of the presence of test targets on a defined background in order to map and quantify the visual field, normally testing each eye independently but binocularly for driving field assessment.

Screening for diabetic retinopathy

The definition of screening that was adapted by the World Health Organization (WHO) [34] in 1968 was "the presumptive identification of unrecognized disease or defect by the application of tests, examinations or other procedures which can be applied rapidly. Screening tests sort out apparently well persons who probably have a disease from those who probably do not. A screening test is not intended to be diagnostic. Persons with posi-

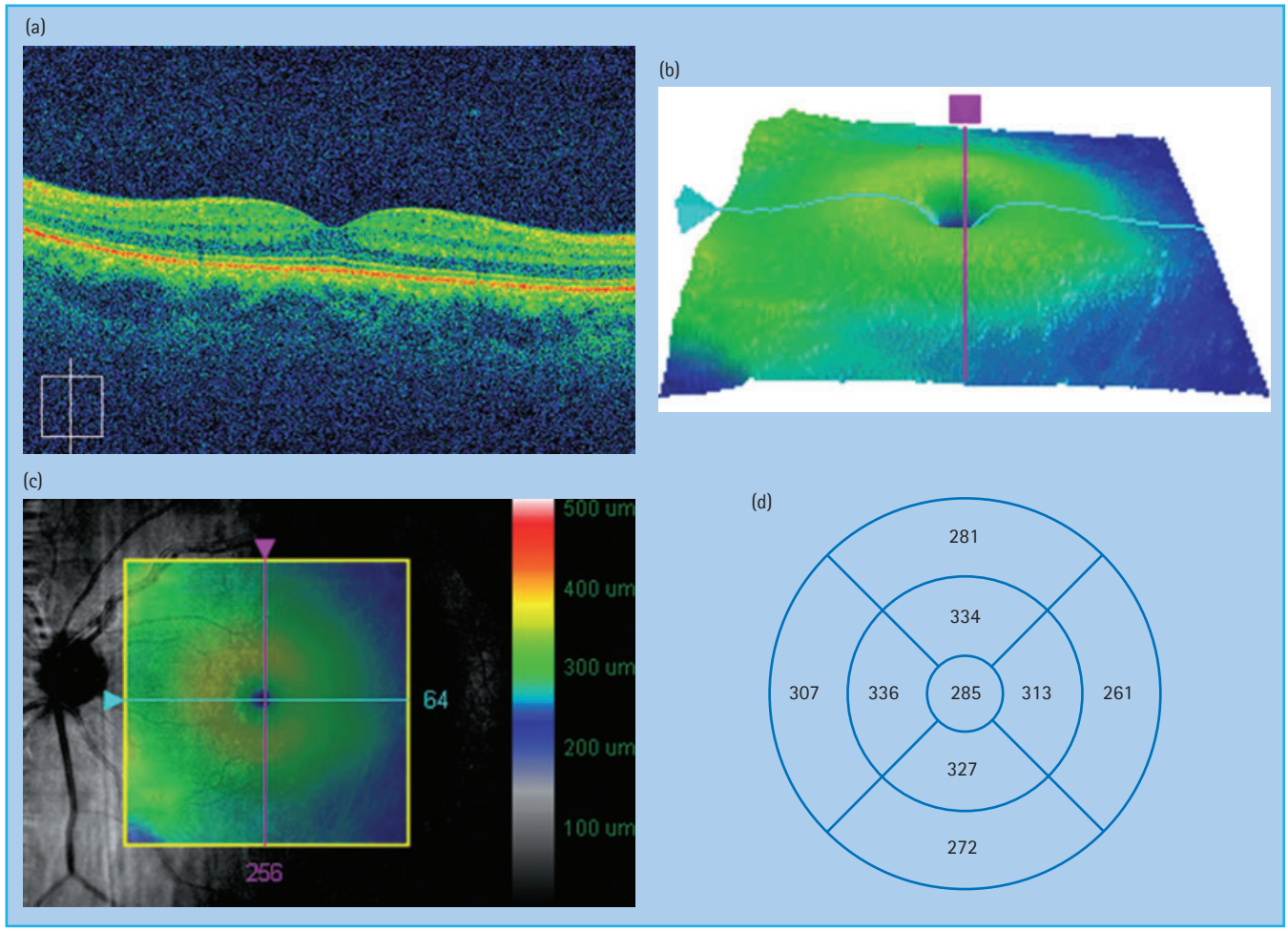


Figure 36.8 (a) Normal cross-sectional optical coherence tomography (OCT) image. (b) Topographic map of macular area. (c) Topographic map superimposed on red free image of macular area. (d) Measurements of thickness in macular area.

tive or suspicious findings must be referred to their physicians for diagnosis and necessary treatment."

Applying this definition to DR demonstrates that it is a very suitable condition for screening:

- Sight-threatening DR is an important public health problem [35,36].
- The incidence of sight-threatening DR is going to become an even greater public health problem; the International Diabetes Federation (IDF) has predicted a worldwide increase in diabetes and DR.
- Sight-threatening DR has a recognizable latent stage [19,37].
- Laser treatment for sight-threatening DR is effective [38,39] and agreed universally. Favorable long-term visual results have been reported [40–42] and there is also evidence that intensive control of blood glucose control [6,19] and systemic hypertension [10] reduces the risk of new onset DR and slows the progression of existing DR.
- A suitable and reliable screening test is available (digital photography) for sight-threatening DR [43–46], and is acceptable to both health care professionals and to the public.
- The costs of screening and effective treatment of sight-threatening DR balance economically in relation to total expenditure on health care [47–50], including the consequences of leaving the disease untreated.

Lesions and classifications of diabetic retinopathy

Microaneurysms and retinal hemorrhages

The lesions that the Early Treatment Diabetic Retinopathy Study (ETDRS) (Table 36.1) [51] described as critical to the stages of progression of DR were:

- *Microaneurysms* – a microaneurysm is defined as a red spot <125 μm (approximate width of vein at disc margin) and sharp margins.
- *Small retinal hemorrhages* – a hemorrhage is defined as a red spot, which has irregular margins and/or uneven density, particularly when surrounding a smaller central lesion considered to be a microaneurysm.

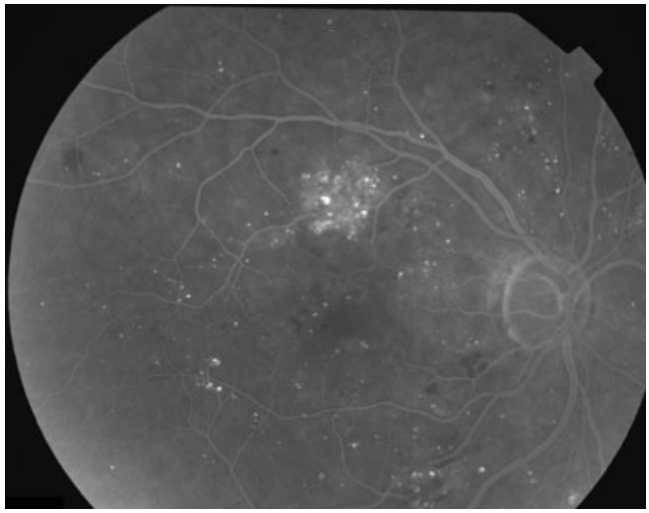


Figure 36.9 An example of the venous phase of a fluorescein angiogram showing small hemorrhages (dark), microaneurysms fluorescing, some of which are leaking shown by the fluffy edge.

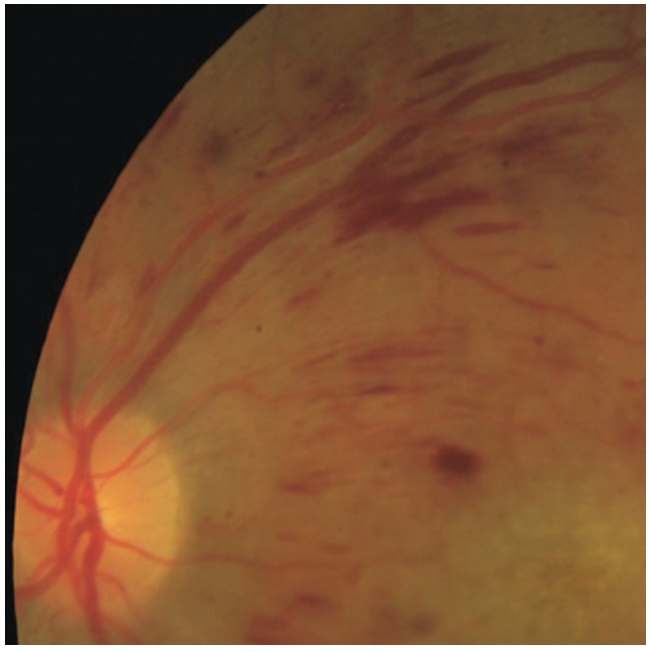


Figure 36.10 An example of more elongated lighter red flame hemorrhages and more oval and darker red blot hemorrhages.

• *Hemorrhage/microaneurysm* (HMa) – because the ETDRS recognized that it was very difficult to differentiate between microaneurysms and small hemorrhages, the concept of HMa was introduced, which is a small hemorrhage or microaneurysm (Figure 36.9).

Other larger retinal hemorrhages

• *Flame hemorrhages* – superficial hemorrhages just under the nerve fiber layer (Figure 36.10).

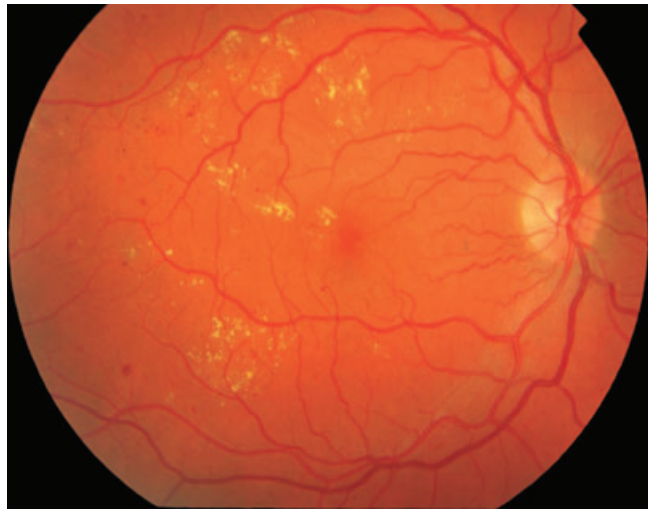


Figure 36.11 An example of exudates in the right macular area.

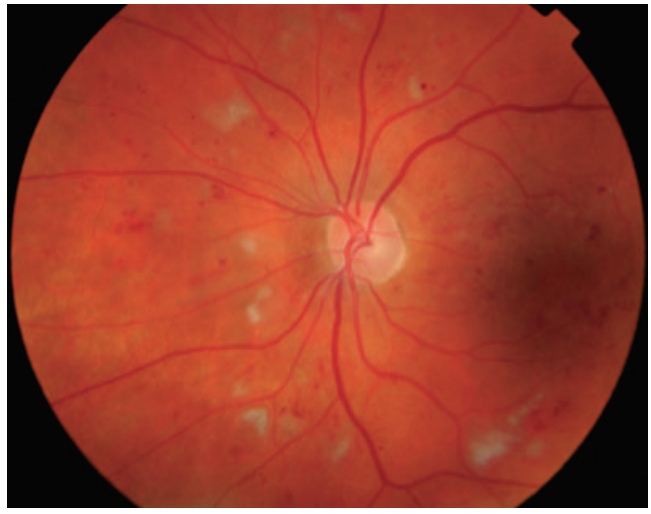


Figure 36.12 An example of cotton wool spots. Reproduced from Scanlon PH, Wilkinson CP, Aldington SJ, Matthews DR. *A Practical Manual of Diabetic Retinopathy Management*. Published 2009 by Blackwell Publishing.

• *Blot hemorrhages* – deeper hemorrhages, which are a sign of retinal ischemia in the area of the retina in which they occur.

Hard exudates

Hard exudates (sometimes now just referred to as exudates) are defined as small white or yellowish-white deposits with sharp margins, located typically in the outer layers of the retina, but they may be more superficial, particularly when retinal edema is present (Figure 36.11).

Cotton wool spots

Cotton wool spots (referred to as soft exudates in the ETDRS, but this term is now rarely used) are fluffy white opaque areas caused by an accumulation of axoplasm in the nerve fiber layer of the retina, which is caused by an arteriolar occlusion in that area of retina that is apparent on a fluorescein angiogram (Figure 36.12).

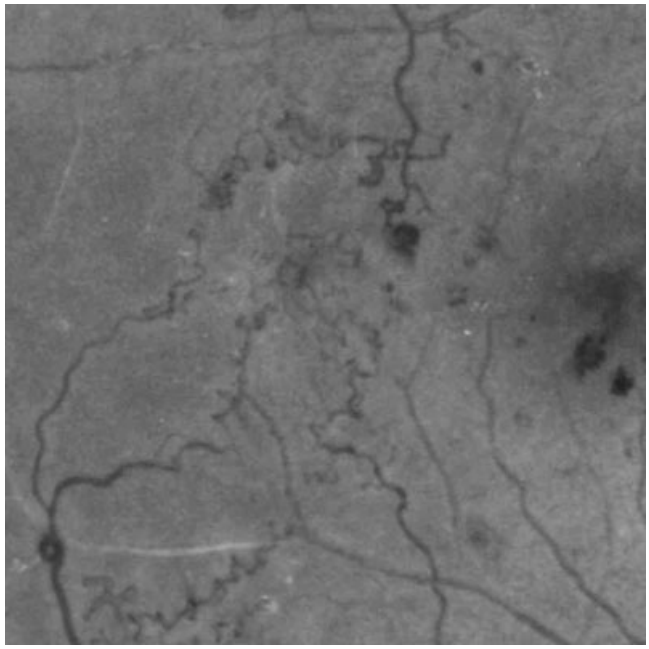


Figure 36.13 An example of intraretinal microvascular abnormality (IRMA) in the temporal retina of the right eye (the right macula is seen in the right side of this red free photograph).

Intraretinal microvascular abnormalities

IRMA are defined as tortuous intraretinal vascular segments, varying in caliber, derived from remodeling of the retinal capillaries and small collateral vessels in areas of microvascular occlusion and are therefore a sign of retinal ischemia (Figure 36.13).

Venous abnormalities

- *Venous loops* – abrupt curving deviations of a vein from its normal path (Figure 36.14).
- *Venous beading* – in the ETDRS, venous beading is described as a localized increase in caliber of the vein and the severity is dependent on the increase in caliber and the length of vein involved. It is associated with retinal ischemia (Figure 36.15).

Other venous changes that occur in DR are as follow:

- Venous dilatation;
- Venous narrowing;
- Opacification of the venous wall; and
- Perivenous exudate.

Arteriolar abnormalities

Other arteriolar changes that occur in DR are as follow:

- Arteriolar narrowing;
- Opacification of arteriolar walls; and
- Arteriovenous nipping.

Fibrous proliferation at the disc

Fibrous proliferation at the disc (FPD) usually occurs when new vessels at the disc start to regress and fibrosis occurs.

Fibrous proliferation elsewhere

Fibrous proliferation elsewhere (FPE) usually occurs when new vessels elsewhere start to regress and fibrosis occurs.

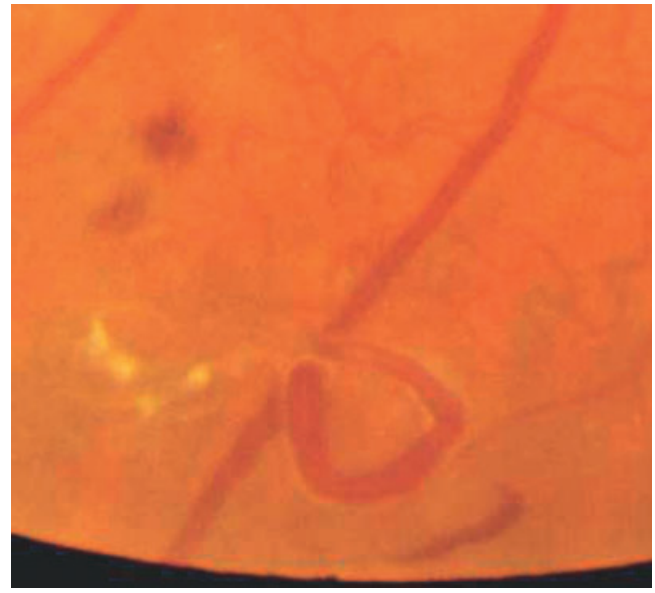


Figure 36.14 An example of a venous loop.

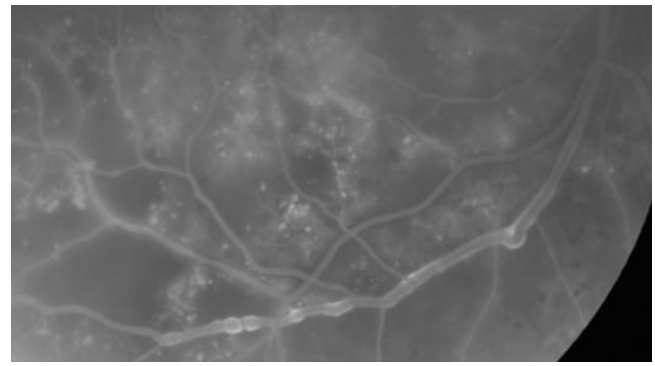


Figure 36.15 A fluorescein angiogram showing venous beading adjacent to an ischemic area of retina. Reproduced from Scanlon PH, Wilkinson CP, Aldington SJ, Matthews DR. *A Practical Manual of Diabetic Retinopathy Management.* Published 2009 by Blackwell Publishing.

New vessels on and/or within 1 disc diameter of the disc

For new vessels on and/or within 1 disc diameter (DD) of the disc (NVD), see Figure 36.16.

New vessels elsewhere

For new vessels elsewhere (NVE), see Figure 36.17.

Vitreous hemorrhage

Vitreous hemorrhage (VH) is a hemorrhage that is in the vitreous gel.

Preretinal hemorrhage

Preretinal hemorrhages (PRH) are boat-shaped hemorrhages and roughly round, confluent or linear patches of hemorrhage just anterior to the retina or under the internal limiting membrane (Figure 36.18).

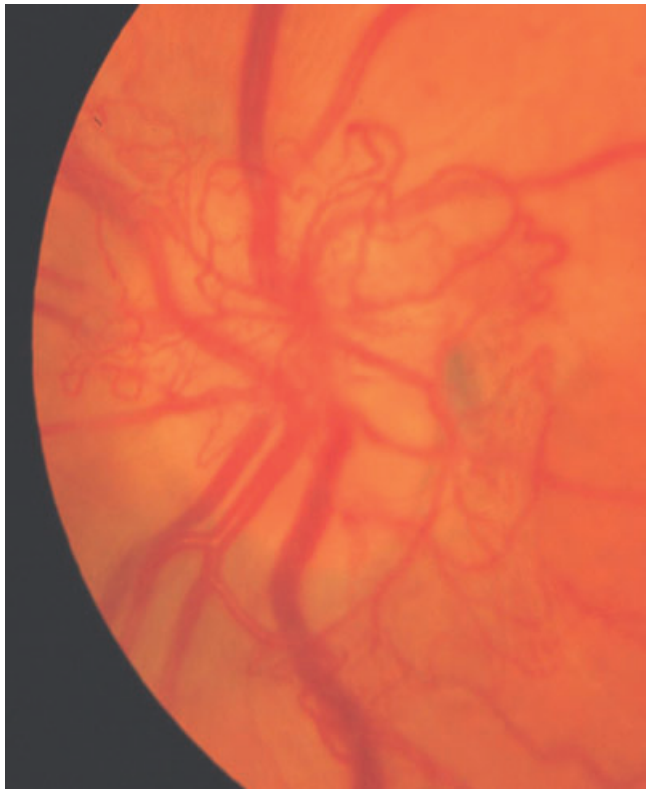


Figure 36.16 An example of new vessels on disc (NVD).

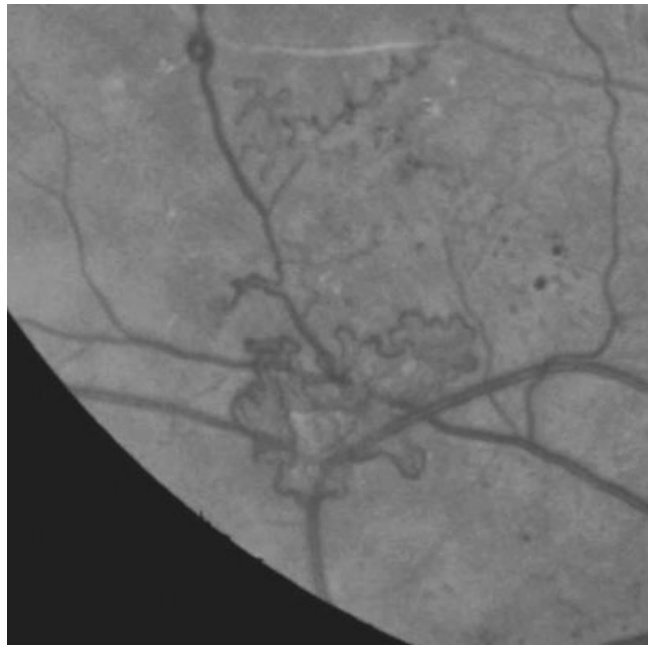


Figure 36.17 An example of new vessels elsewhere (NVE).

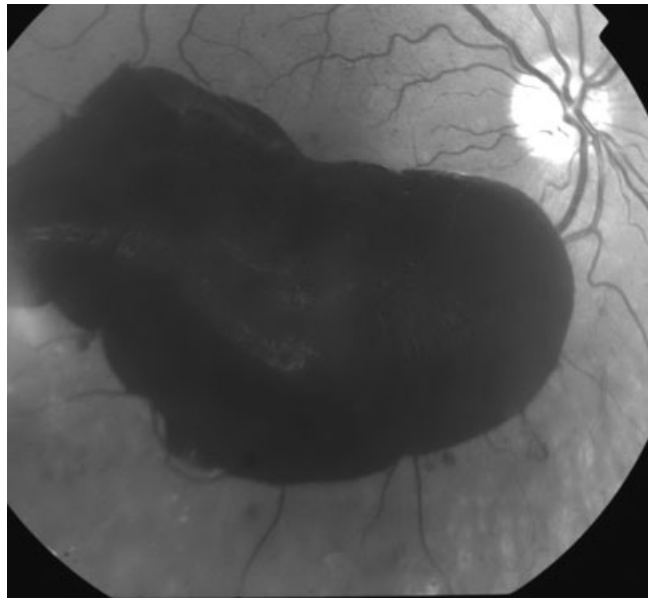


Figure 36.18 An example of preretinal hemorrhage.

Post laser treatment

Photocoagulation laser scars may be seen both after macular or panretinal laser treatment (Figure 36.19; Tables 36.1–36.4).

Maculopathy

Clinical classification of diabetic maculopathy

Diabetic maculopathy may be classified into focal (subdivided into focal exudates and focal/multifocal edema), diffuse and ischemic diabetic maculopathy (Tables 36.2 and 36.4).

Pathophysiology of macular edema

In focal macular edema, focal leakage tends to occur from microaneurysms, often with extravascular lipoprotein in a circinate pattern around the focal leakage [57].

In diffuse macular edema, there is a generalized breakdown of the blood–retina barrier and profuse early leakage from the entire capillary bed of the posterior pole [58] causing extracellular fluid accumulation, often accompanied by cystoid macular edema [57], which is caused by cellular swelling. In ischemic maculopathy, enlargement of the foveal avascular zone as a result of capillary closure is found.

The fluorescein angiographic appearance

In diabetic maculopathy, most leakage occurs in the venous phase of the angiogram and hence examples of venous phase angiograms are shown in Figure 36.20.

Optical coherence tomography

An example of diabetic maculopathy is shown in Figure 36.21. Macular traction can occur from contracture of fibrotic proliferations, particularly as new vessels regress after panretinal photocoagulation, and also from a taut posterior hyaloid. If macular traction is severe, surgical intervention is required (Figure 36.22).

Laser treatment for diabetic maculopathy

In 1985, the ETDRS [59] demonstrated that focal (direct/grid) laser photocoagulation reduces moderate vision loss caused by

Table 36.1 Early Treatment Diabetic Retinopathy Study (ETDRS) Research Group diabetic retinopathy classification of progression to proliferative diabetic retinopathy based on 7 × 30° field stereo photographs of each eye.

ETDRS final Retinopathy Severity Scale [37]	ETDRS (final) grade	Lesions	Risk of progression to PDR in 1 year (ETDRS Interim)	Practical clinic follow-up intervals (not ETDRS)
No apparent retinopathy	10	DR absent		1 year
	14, 15	DR questionable		
Mild NPDR	20	Microaneurysms only		1 year
	35	One or more of the following:	Level 30 = 6.2%	6–12 months
	a	Venous loops ≥ definite in 1 field		
	b	SE, IRMA, or VB questionable		
	c	Retinal hemorrhages present		
	d	HE ≥ definite in 1 field		
	e	SE ≥ definite in 1 field		
Moderate NPDR	43a	H/Ma moderate in 4-5 fields or severe in 1 field *or*	Level 41 = 11.3%	6 months
	b	IRMA definite in 1–3 fields		
Moderately severe NPDR	47	Both level 43 characteristics – H/Ma moderate in 4–5 fields	Level 45 = 20.7%	4 months
	a	or severe in 1 field and IRMA definite in 1–3 fields		
	b	*or* any one of the following:		
	c	IRMA in 4–5 fields		
	d	HMa severe in 2–3 fields		
		VB definite in 1 field		
Severe NPDR	53	One or more of the following:	Level 51 = 44.2%	3 months
	a	≥2 of the 3 level 47 characteristics		
	b	H/Ma severe in 4–5 fields		
	c	IRMA ≥ moderate in 1 field	Level 55 = 54.8%	
	d	VB ≥ definite in 2–3 fields		
Mild PDR	61a	FPD or FPE present with NVD absent *or*	1976. Diabetic Retinopathy Study [52] protocol changed to treat untreated eyes with high risk characteristics	
	b	NVE = definite		
Moderate PDR	65a	**1** NVE ≥ moderate in 1 field or definite NVD with VH and PRH absent or questionable *or*		
	b	**2** VH or PRH definite and NVE < moderate in 1 field and NVD absent	1981. Diabetic Retinopathy Study [53] recommendation to treat – eyes with new vessels on or within 1 DD of the optic disc (NVD) ≥0.25 –0.33 disc area, even in the absence of preretinal or vitreous hemorrhage. Photocoagulation, as used in the study, reduced the risk of severe visual loss by 50% or more	
High risk PDR	71	Any of the following:		
	a	**1** VH or PRH ≥ moderate in 1 field		
	b	**2** NVE ≥ moderate in 1 field and VH or PRH definite in 1 field		
	c	**3** NVD = 2 and VH or PRH definite in 1 field		
	d	**4** NVD ≥ moderate		
High risk PDR	75	NVD ≥ moderate and definite VH or PRH		
Advanced PDR	81	Retina obscured due to VH or PRH		

DD, disc diameter; DR, diabetic retinopathy; HE, hard exudate; HMa, small hemorrhage or microaneurysm; IRMA, intraretinal microvascular abnormality; NPDR, non-proliferative DR; NVD, new vessels on disc; NVE, new vessels elsewhere; PDR, proliferative diabetic retinopathy; PRH, preretinal hemorrhage; SE, soft exudate, a term that has now been replaced by cotton wool spot; VB, venous beading; VH, vitreous hemorrhage.

Table 36.2 Early Treatment Diabetic Retinopathy Study (ETDRS) maculopathy classification.

ETDRS	Outcome
Clinically significant macular edema [54] as defined by:	
• A zone or zones of retinal thickening one disc area or larger, any part of which is within one disc diameter of the center of the macula	Consider laser
• Retinal thickening at or within 500 μm of the center of the macula	Consider laser
• Hard exudates at or within 500 μm of the center of the macula, if associated with thickening of the adjacent retina (not residual hard exudates remaining after disappearance of retinal thickening)	Consider laser

Because of the difficulty in correlating 7 field stereo-photography to the clinical setting, two further simplified classifications have been developed (International Classification and the English Screening Classification).

Table 36.3 International and English retinopathy classifications.

International clinical classification of diabetic retinopathy severity or diabetic macular edema [55]	Recommended International outcome	English Screening program levels [56] and recommended outcome
Microaneurysms only	Optimize medical therapy, screen at least annually	**R0**: no DR Outcome: currently screen annually
More than just microaneurysms but less severe than severe NPDR	Refer to ophthalmologist	**R1**: background DR Microaneurysm(s) Retinal hemorrhage(s) ± any exudate Outcome: currently screen annually
Severe NPDR Any of the following: (a) Extensive intraretinal hemorrhage (>20) in 4 quadrants (b) Definite venous beading in 2+ quadrants (c) Prominent IRMA in 1+ quadrant *and* no signs of PDR	Consider scatter photocoagulation for T2DM	**R2**: preproliferative DR venous beading venous loop or reduplication IRMA, multiple deep, round or blot hemorrhages Outcome: refer to ophthalmologist
Neovascularization Vitreous/preretinal hemorrhage	Scatter Photocoagulation without delay for patients with vitreous hemorrhage or neovascularization within 1 DD of the optic nerve head	**R3:** proliferative NVD NVE Preretinal or vitreous hemorrhage Preretinal fibrosis ± tractional retinal detachment Outcome: urgent referral to ophthalmologist

DD, disc diameter; DR, diabetic retinopathy; IRMA, intraretinal microvascular abnormality; NPDR, non-proliferative DR; NVD, new vessels on disc; NVE, new vessels elsewhere; PDR, proliferative diabetic retinopathy.

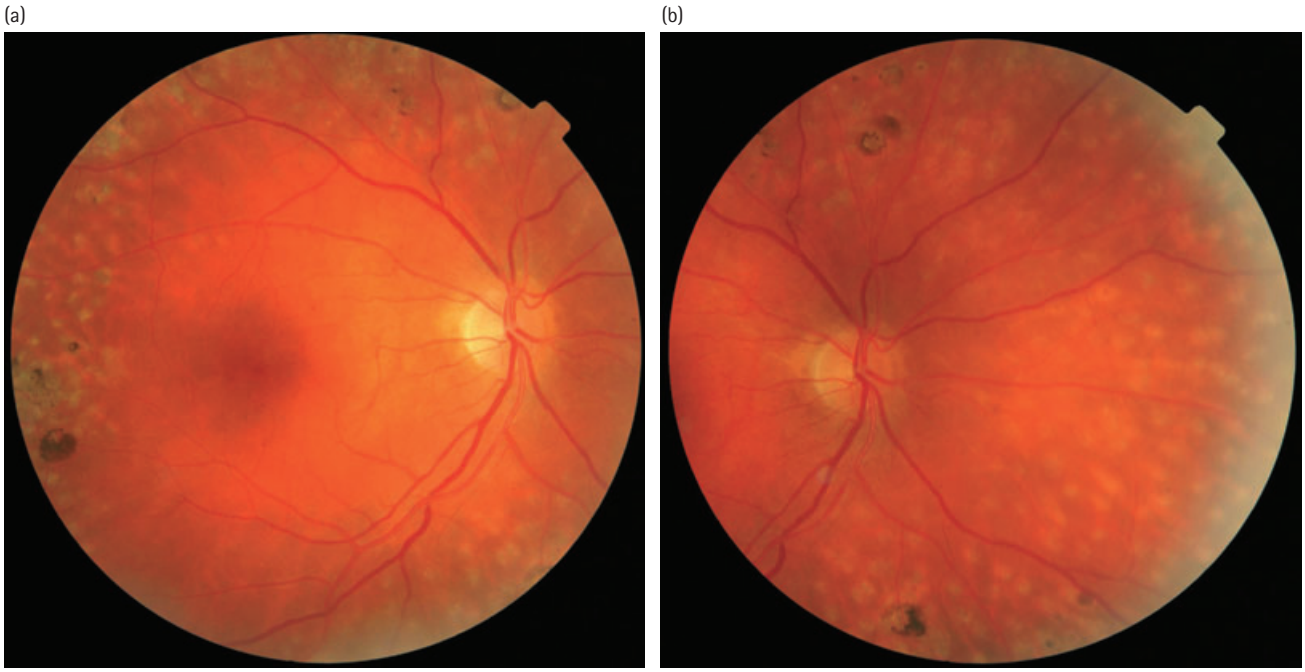


Figure 36.19 (a,b) Right macular and nasal views following panretinal photocoagulation to show laser treatment scars in the superior, inferior, temporal and nasal retina.

Table 36.4 International and English maculopathy classification.

International classification [55]	Outcome	English classification [56]	Outcome
Diabetic macular edema present as defined by some retinal thickening or hard exudates in the posterior pole and subclassified into:	Referral	Circinate or group of exudates within the macula (The macula is defined as that part of the retina that lies within a circle centered on the fovea whose radius is the distance between the center of the fovea and the temporal margin of the disc)	Referral
Mild diabetic macular edema: Some retinal thickening or hard exudates in the posterior pole but distant from the macula		Any microaneurysm or hemorrhage within 1 DD of the center of the fovea only if associated with a best VA of ≤6/12 (if no stereo)	Referral
Moderate diabetic macular edema: Retinal thickening or hard exudates approaching the center of the macula but not involving the center	Referral	Exudate within 1 DD of the center of the fovea	Referral
Severe diabetic macular edema: Retinal thickening or hard exudates involving the center of the macula	Referral	Retinal thickening within 1 DD of the center of the fovea (if stereo available)	Referral

DD, disc diameter; VA, visual acuity.

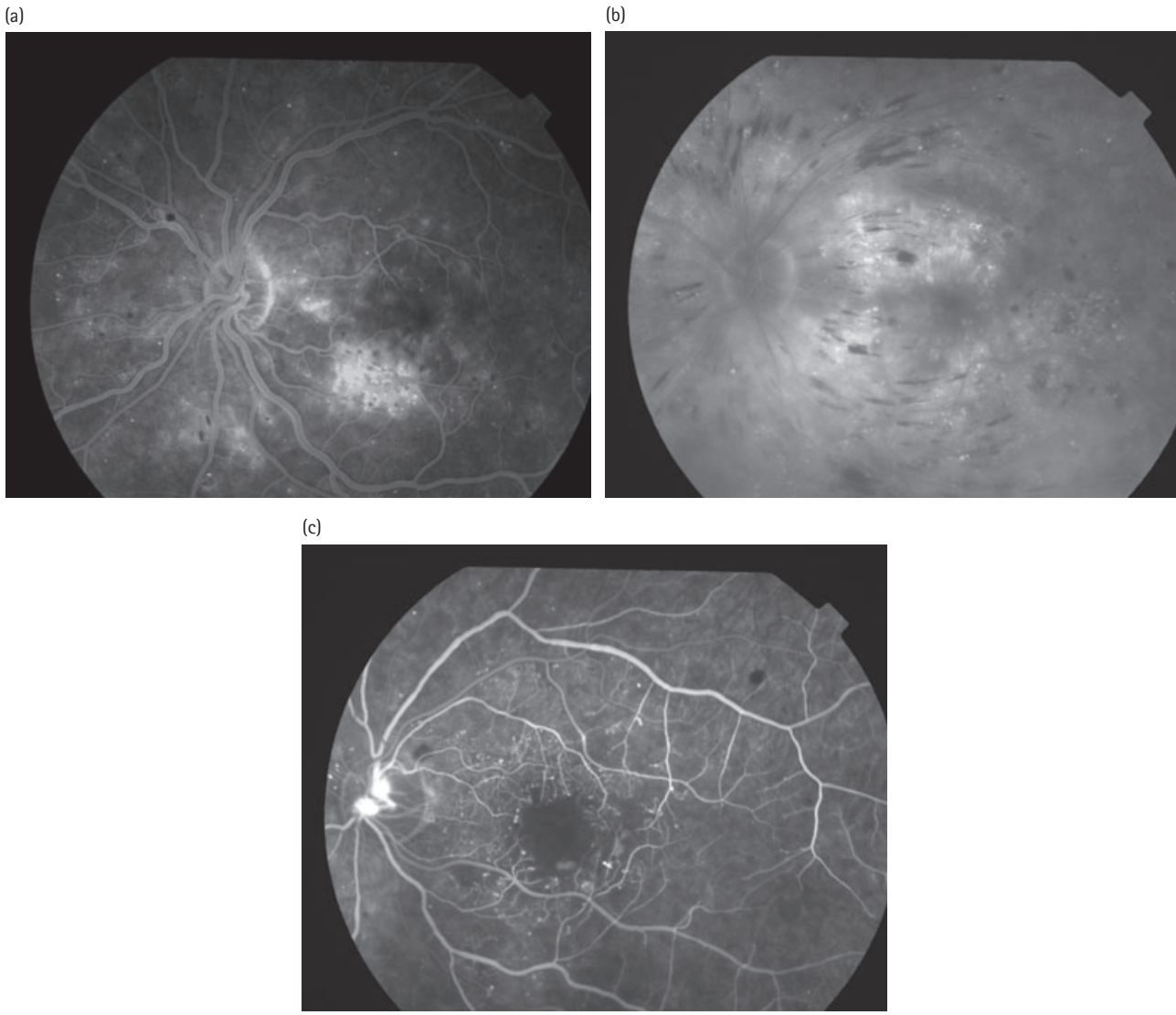


Figure 36.20 (a) Focal maculopathy. Reproduced from Scanlon PH, Wilkinson CP, Aldington SJ, Matthews DR. *A Practical Manual of Diabetic Retinopathy Management*. Published 2009 by Blackwell Publishing. (b) Diffuse maculopathy. Reproduced from Scanlon PH, Wilkinson CP, Aldington SJ, Matthews DR. *A Practical Manual of Diabetic Retinopathy Management*. Published 2009 by Blackwell Publishing. (c) Ischemic maculopathy. Reproduced from Scanlon PH, Wilkinson CP, Aldington SJ, Matthews DR. *A Practical Manual of Diabetic Retinopathy Management*. Published 2009 by Blackwell Publishing.

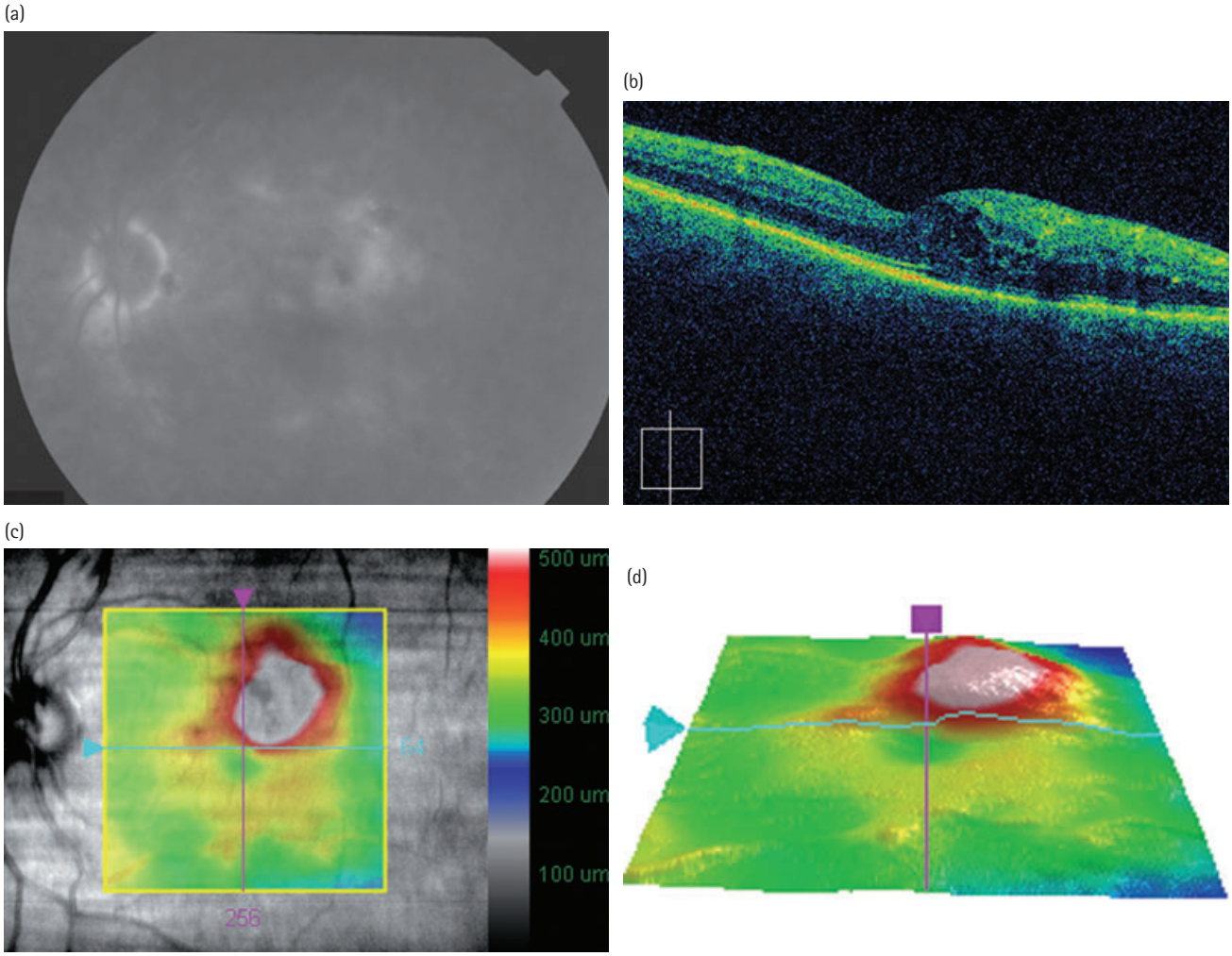


Figure 36.21 (a) Venous phase fluorescein angiogram showing leakage superotemporal to the macula. (b) Cross-sectional optical coherence tomography (OCT) image showing clinically significant macular edema. (c) Topographic map superimposed on red free photograph. (d) Topographic map of clinically significant macular edema.

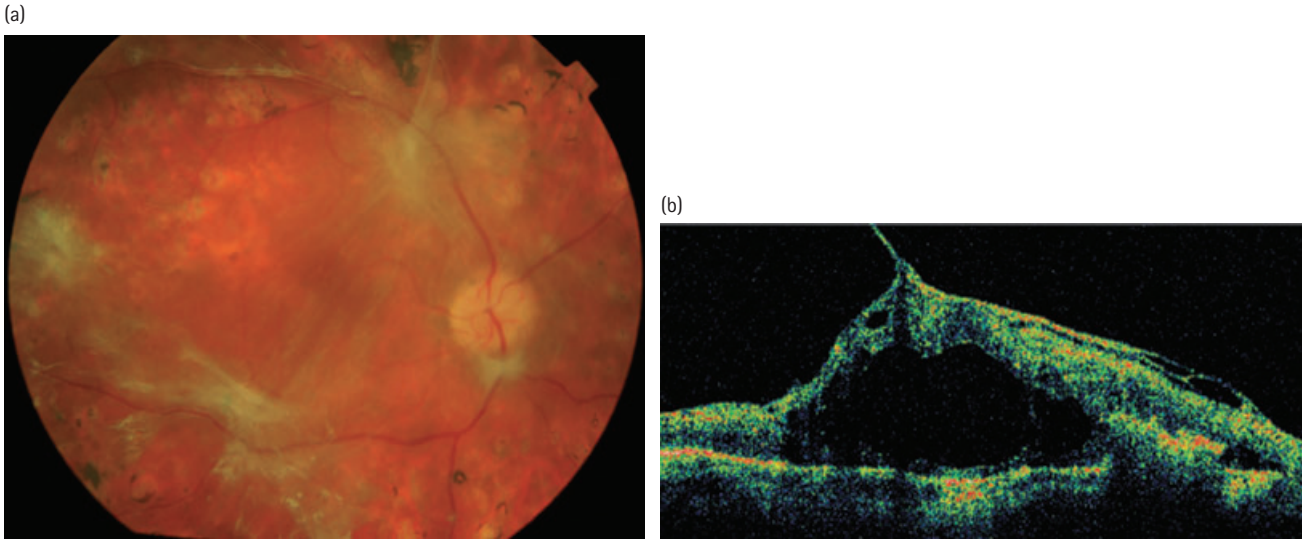


Figure 36.22 (a) Fibrotic proliferations causing macular traction following panretinal photocoagulation. Reproduced from Scanlon PH, Wilkinson CP, Aldington SJ, Matthews DR. *A Practical Manual of Diabetic Retinopathy Management*. Published 2009 by Blackwell Publishing. (b) A cross-sectional optical coherence tomography (OCT) image showing macular traction. Reproduced from Scanlon PH, Wilkinson CP, Aldington SJ, Matthews DR. *A Practical Manual of Diabetic Retinopathy Management*. Published 2009 by Blackwell Publishing.

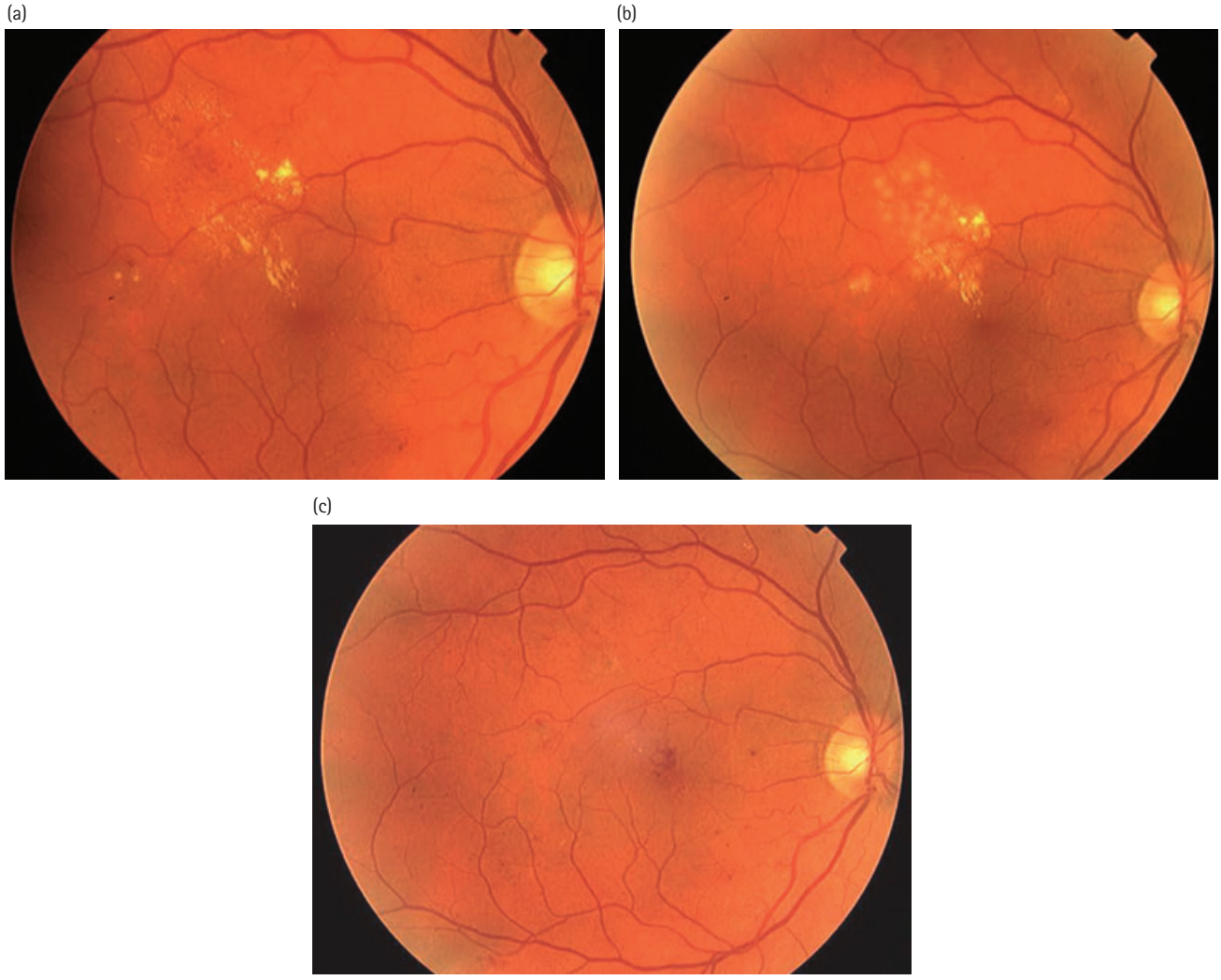


Figure 36.23 (a) Focal maculopathy pretreatment. (b) Focal maculopathy immediately after treatment showing blanching from laser treatment. (c) Focal maculopathy 6 months after treatment showing clearing of the exudate.

diabetic maculopathy edema by 50% or more. It also described "clinically significant macular edema," which defined the parameters for treatment as [54]:

- Thickening of the retina at or within 500 µm of the center of the macula;
- Hard exudates at or within 500 µm of the center of the fovea, if associated with thickening of the adjacent retina (not residual hard exudates remaining after disappearance of retinal thickening);
- A zone or zones of retinal thickening 1 disc area or larger, any part of which is within 1 DD of the center of the macula (Figure 36.23).

Mechanisms of action of laser for macular edema

The effectiveness of focal laser treatment may be caused, in part, by the closure of leaky microaneurysms. Other methods suggested have been histopathologic changes [60], biochemical changes [61] and the application of Starling's law and improved oxygenation [62].

Adverse effects of macular laser treatment

Potential side effects specific to macular laser are:

- Laser close to the central fovea, resulting in a drop in visual acuity. Laser burns may be associated with paracentral scotomas and may become larger than the original spot size [63] and encroach on fixation.
- Choroidal neovascular membrane developing in an area that has received laser treatment – this complication is extremely rare.

Intravitreal triamcinolone

Promising results in the short term for improving the vision in eyes with chronic diabetic macular edema unresponsive to conventional laser treatment, reducing macular thickness and induc-

ing reabsorption of hard exudates, have been described in numerous studies [64–67]. The effects are reported to last for 3–8 months, which may be partially dependent on the dose given, varying between 1 and 25 mg.

Serious side effects, however, have been reported such as early rapid increases in intraocular pressure requiring surgical intervention [68] and infectious endophthalmitis [69]. Randomized controlled trials utilizing varying doses of steroid are now required to assess the long-term efficacy, safety and to define optimum treatment regimens.

Vascular endothelial growth factor treatments

For anti-vascular endothelial growth factor (anti-VEGF) treatments, see the section on the use of intravitreal vascular endothelial growth factor inhibitors later in this chapter.

Mild non-proliferative diabetic retinopathy (ETDRS & International) and background diabetic retinopathy (English Screening)

The earliest sign of mild non-proliferative DR (mild NPDR) or background DR is microaneurysms.

Microaneurysms

Patients with no DR and microaneurysms only were not included in the ETDRS study. In the Wisconsin Epidemiological Study of Diabetic Retinopathy, the rate of progression to proliferative retinopathy 4 years after the initial evaluation showed "no DR" was 0.4% for young patients <30 years with T1DM, 0% for older patients ≥30 years with diabetes taking insulin and 0.6% for those not using insulin. For those with microaneurysms or one hemorrhage in one eye only, the rate of progression to proliferative retinopathy 4 years after the initial evaluation was 3.0% for young patients <30 years with T1DM, 0% for older patients ≥30 years with T1DM and 1.5% for those not using insulin.

The other signs of mild NPDR are one or more of the following:

- *Retinal hemorrhages*. In mild NPDR, retinal hemorrhages are usually small dot hemorrhages or flame-shaped hemorrhages (Figures 36.9 and 36.10). Because small retinal hemorrhages can be difficult to differentiate from microaneurysms they are commonly referred to as HMa.
- *Exudates* (or hard exudates) are a feature of mild NPDR (Figure 36.11).
- *Cotton wool spots* may be present in mild NPDR or background DR but are caused by an arteriolar occlusion in that area of retina, but despite this being the underlying cause, they are not a good sign of increasing retinal ischemia. They are often associated with hypertension (Figure 36.12).
- *A single venous loop*. The ETDRS included a single venous loop in their classification of mild NPDR; however, this rarely occurs in isolation without other significant signs of retinal ischemia and a venous loop is therefore not a feature of the English Screening definition of background DR (Figure 36.14).

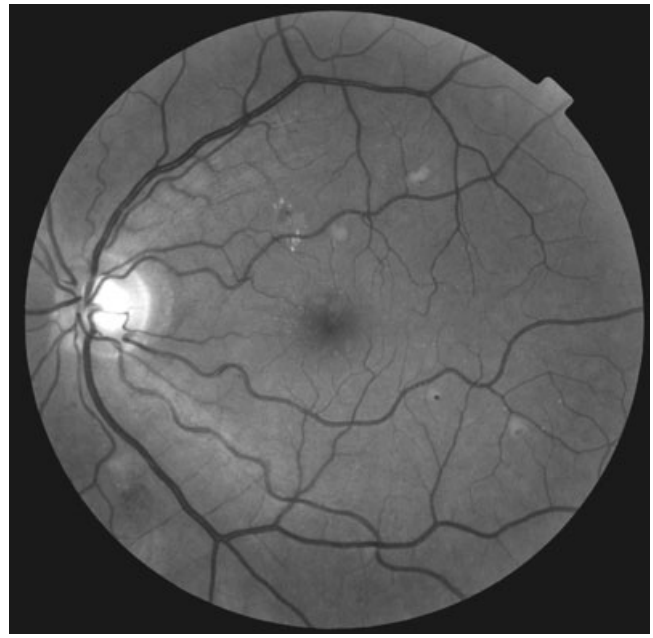


Figure 36.24 Red free photograph showing microaneurysms, hemorrhages, hard exudates and cotton wool spots.

For mild NPDR, there is a 6.2% risk of progression to proliferative retinopathy within 1 year.

The International classification of DR recommends that anyone who has a more severe disorder than microaneurysms is referred to an ophthalmologist [55]. In the UK, patients who are screened and who show signs of background DR are only rescreened annually. For the purposes of the English National Screening Programme, background DR is defined by the following lesions [56]:

- Microaneurysm(s); and
- Retinal hemorrhage(s) with or without any exudate (Figure 36.24).

Moderate and severe non-proliferative diabetic retinopathy (ETDRS & International) and pre-proliferative diabetic retinopathy (English Screening)

The main features that warrant classifying a DR level in the higher levels of moderate and severe NPDR [55] (or pre-proliferative DR [56]) are increasing signs of retinal ischemia.

Lesions associated with increasing retinal ischemia:

- Retinal hemorrhages especially blot hemorrhages (Figure 36.25).
- Intraretinal microvascular abnormality (Figure 36.25). Intraretinal microvascular abnormalities are derived from remodeling of the retinal capillaries and small collateral vessels in

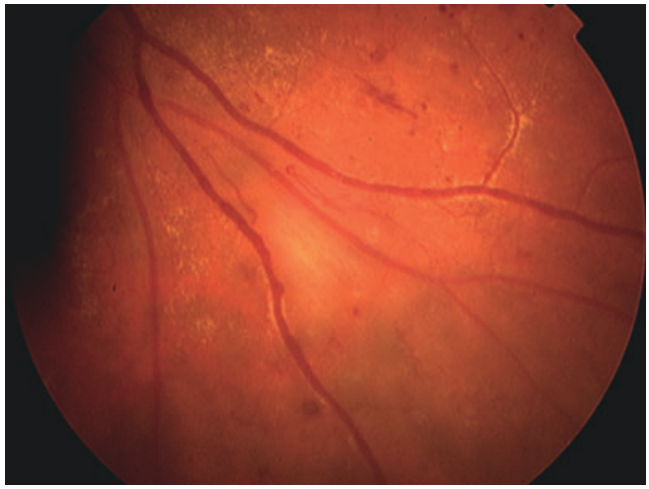


Figure 36.25 Photograph showing venous beading, intraretinal microvascular abnormality, perivenous exudate and a small number of blot hemorrhages. Reproduced from Scanlon PH, Wilkinson CP, Aldington SJ, Matthews DR. *A Practical Manual of Diabetic Retinopathy Management*. Published 2009 by Blackwell Publishing.

areas of microvascular occlusion. They are usually found on the borders of areas of non-perfused retina.

- Venous beading (VB; Figure 36.25) is found to be associated with retinal ischemia and is used for assessment of severity of DR.

With increasing ischemia, there is an increasing risk of progression to proliferative in 1 year. The risk increases from approximately 11.3% in the lower levels of moderate NPDR to 54.8% progression to proliferative in 1 year in the most severe NPDR level.

ETDRS definitions have been simplified to make them easier for everyday clinical use both in the International classification and in the English classification for screening.

The ETDRS "4:2:1 rule" indicates that the presence of severe hemorrhages in four quadrants (≥20), VB in two quadrants or IRMA in a single quadrant represents this severity of retinopathy, severe NPDR.

In the International classification, severe NPDR is defined by any of the following:

- Extensive intraretinal hemorrhages (>20) in four quadrants;
- Definite VB in two or more quadrants;
- Prominent IRMA in one or more quadrant, and no signs of PDR.

Moderate NPDR is classified in the International classification as more than "microaneurysms only" and less severe than the 4:2:1 rule.

In the English Screening classification, pre-proliferative DR is defined by any of the following:

- VB;
- Venous loop or reduplication;
- IRMA; or
- Multiple deep, round or blot hemorrhages.

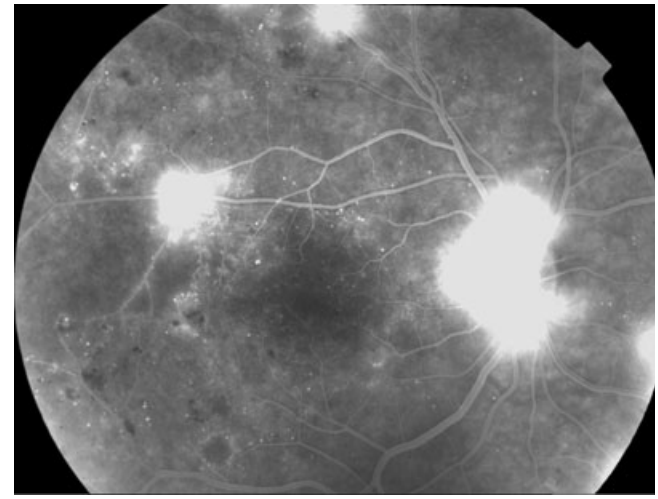


Figure 36.26 Profuse leakage of fluorescein from new vessels on disc (NVD) and new vessels elsewhere (NVE) in the arteriovenous phase of this angiogram.

Proliferative diabetic retinopathy and advanced diabetic retinopathy

Pathogenesis of retinal angiogenesis (new vessel formation)

New vessels arise from the post capillary venule in areas of ischemic retina. New vessel growth originates either within 1 DD of the optic disc (new vessels at the disc [NVD]) or developing from retinal vessels more than 1 DD away from the edge of the optic disc (new vessels elsewhere [NVE]).

The central role of growth factors in retinal neovascularization was suggested as early as 1948 by Michaelson [70], who proposed that a diffusible factor released from the ischemic retina was responsible for angiogenesis. The growth factors that have been extensively studied are fibroblast-derived growth factor (FDGF) [71], insulin-like growth factor I (IGF-I) [72], platelet-derived growth factor (PDGF) [73], hepatocyte growth factor (HGF) [74] and VEGF [75]. Another consequence of generalized retinal ischemia can be neovascularization in the anterior chamber on the iris (rubeosis iridis).

Fluorescein angiographic appearance

The characteristic appearance of new vessels on the fluorescein angiogram, once they have penetrated the internal limiting membrane, is leakage appearing in the arteriovenous phase of the angiogram and increasing through the angiogram (Figure 36.26).

Presentation

Some patients present asymptomatically from screening, others with visual loss arising from hemorrhage from new vessels.

Laser treatment for proliferative diabetic retinopathy

For laser treatment for proliferative diabetic retinopathy (PDR), see Figure 36.27.

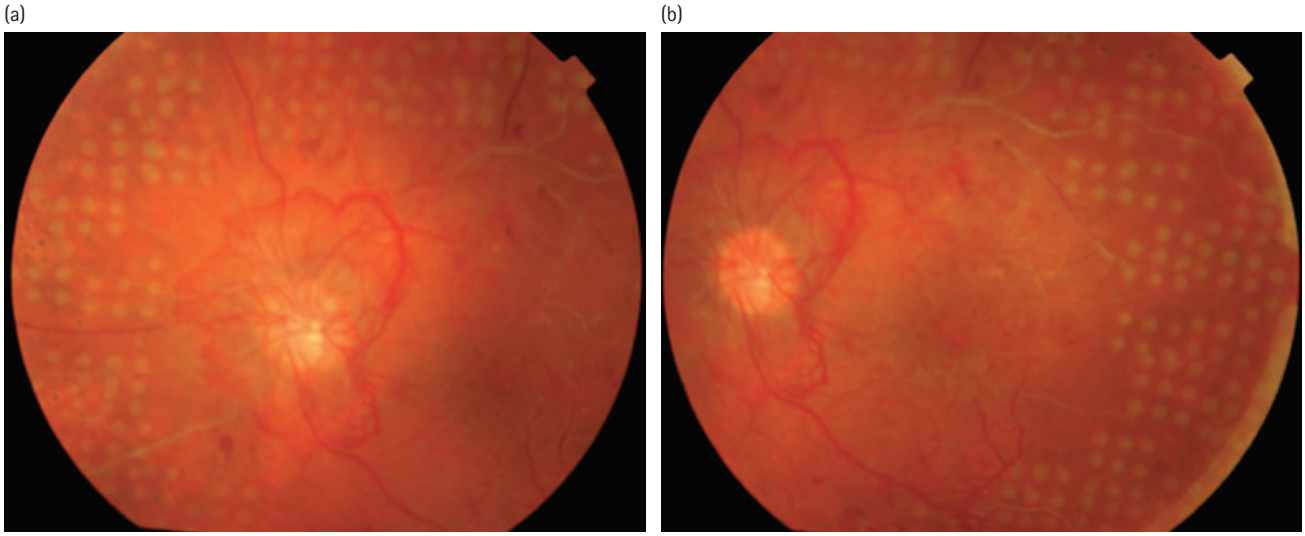


Figure 36.27 Disc and macular photographs taken immediately after panretinal laser treatment on a patient with proliferative diabetic retinopathy. Reproduced from Scanlon PH, Wilkinson CP, Aldington SJ, Matthews DR. *A Practical Manual of Diabetic Retinopathy Management.* Published 2009 by Blackwell Publishing.

Diabetic Retinopathy Study

The Diabetic Retinopathy Study (DRS) [53] recommended prompt treatment in the presence of DRS high-risk characteristics, which reduced the 2-year risk of severe visual loss by 50% or more and were defined by:

- Presence of preretinal or vitreous hemorrhage;
- Eyes with NVD equalling or exceeding one-quarter to one-third disc area in extent with no hemorrhage;
- NVE equalling more than half disc area with hemorrhage.

Untreated, eyes with high risk characteristics had a 25.6–36.9% chance of severe visual loss within 2 years, depending on the size and location of the new vessels and whether or not hemorrhage was present.

"Low risk" proliferative patients

In eyes with PDR without high risk characteristics, there were still the following risks of severe visual loss:

- Untreated: 2 year 7.0%, 4 years 20.9%;
- Treated: 2 year 3.2%, 4 years 7.4%.

These risks need to be balanced against the potential adverse effects of laser treatment.

Adverse effects of laser treatment

Adverse effects of laser treatment described in the DRS [76] and other studies are as follow:

- Loss of peripheral areas of visual field was attributed to argon laser in approximately 10% of eyes and field loss was nearly three times more common in the xenon arc treated group.
- Visual acuity loss at the 6-week follow-up visit was assumed to be brought about by treatment. Among eyes with NPDR, 14.3% more argon-treated and 29.7% of xenon-treated eyes than control subjects had an early persistent loss of one or more lines.

Other possible adverse effects of panretinal laser treatment are as follow:

- Unintended laser absorption (e.g. to the lens) or uptake of laser from a flame-shaped hemorrhage, which may result in a burn and destruction of the nerve fiber layer that lies on its surface.
- Inadvertent coagulation (e.g. to the fovea).
- Choroidal detachment is usually as a result of a large dose of laser treatment being applied in a single session, which usually resolves spontaneously within 10 days.

Risks to the ophthalmologist

There has been some concern in the past that the ophthalmologist is exposed to excessive amounts of reflected light, particularly blue light; however, modern technology with appropriate filters has significantly reduced this risk.

Risks to an observer

The risk to an observer is extremely small but, as a precaution, it is advised that any observer wears the appropriate spectacle protection.

Factors other than high risk characteristics influencing the decision to laser

Anterior segment neovascularization

Extensive neovascularization in the anterior chamber angle is an urgent indication for scatter laser photocoagulation, if it is feasible (Figure 36.28).

Signs of ischemia

Large IRMA, VB in more than one quadrant, extensive retinal hemorrhages and opaque small arteriolar branches are signs suggesting severe retinal ischemia.

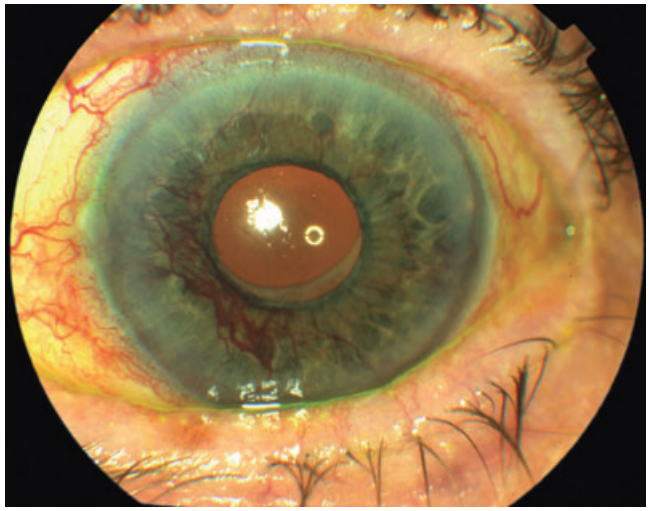


Figure 36.28 Iris neovascularization.

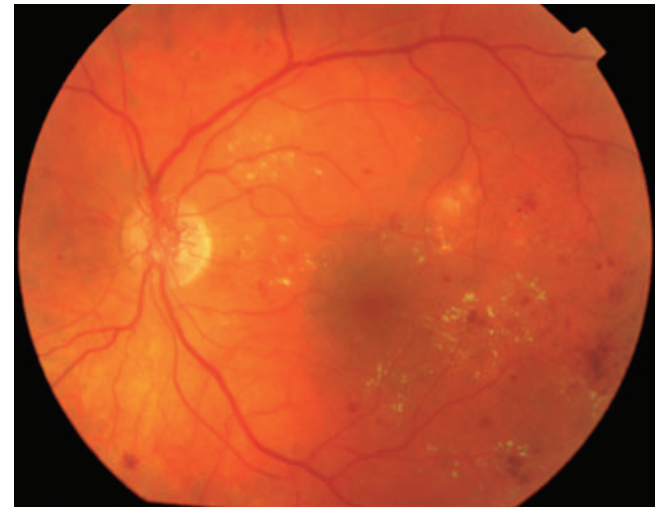


Figure 36.29 Proliferative diabetic retinopathy and concurrent maculopathy.

Macular edema
See the section on laser for PDR and concurrent diabetic maculopathy.

Pregnancy
See the section on pregnancy and DR (below).

Renal failure
Treatment needs to coincide with renal dialysis or transplantation. It is also important to control hypertension.

Past history
The past history of retinopathy, both in the eye for which scatter laser photocoagulation and in the fellow eye, needs to be considered.

Duration of the laser burn
There has been an increasing tendency in the last year for operators to reduce the duration of the burn and increase the power to produce an apparently similar mild bleaching because of the clinical impression that this is more comfortable for the patient.

Pattern scan laser
With conventional methods of retinal laser photocoagulation, the ophthalmologist uses a mechanical joystick and foot pedal to deliver single 100-ms laser pulses to the peripheral retina. With the pattern scan laser, the laser pulse time is reduced from 100 ms to just 10–20 ms, and automated multiple spots are produced with each depression of the foot pedal. Higher power is required for shorter burns. Predetermined pattern types can administer up to 25 spots at a time for scatter laser treatment.

Stage R3 with M1: proliferative diabetic retinopathy with maculopathy

The ETDRS [77] compared giving immediate panretinal photocoagulation with either simultaneous or delayed focal treatment. The conclusion was that, where possible, clinically significant macular edema should be treated by applying focal/grid photocoagulation for macular edema before beginning scatter laser treatment. When the risk of vitreous hemorrhage or neovascular glaucoma seems high, combine treatment of clinically significant macular edema by applying focal/grid photocoagulation for macular edema with panretinal photocoagulation to the inferior half of the peripheral retina, followed 2 weeks later by panretinal photocoagulation to the superior half.

Hamilton *et al.* [78] recommended an exception to this approach for young patients with T1DM who have rapidly accelerating peripheral ischemia associated with macular edema that may resolve following panretinal photocoagulation (Figure 36.29).

Use of intravitreal vascular endothelial growth factor inhibitors

Ocular neovascularization (angiogenesis) and increased vascular permeability have been associated with VEGF, which does also has a neuroprotective effect. There are three potential VEGF inhibitors:

1 Pegaptanib (Macugen);
2 Ranibizumab (Lucentis);
3 Bevacizumab (Avastin).

Ranibizumab (Lucentis) is an antibody fragment derived from bevacizumab (Avastin), which is a full-length humanized monoclonal antibody against human VEGF.

There are reports of reduction in macular thickness using intravitreal injections of these agents [79]; however, the effect does not last and repeated injections would be required to sustain any beneficial effects.

Favorable results have been reported with some regression of neovascularization and reduction in fluorescein leakage in some studies using bevacizumab [80,81] and using pegaptanib [82] but the effect is only transient (2–11 weeks [81]).

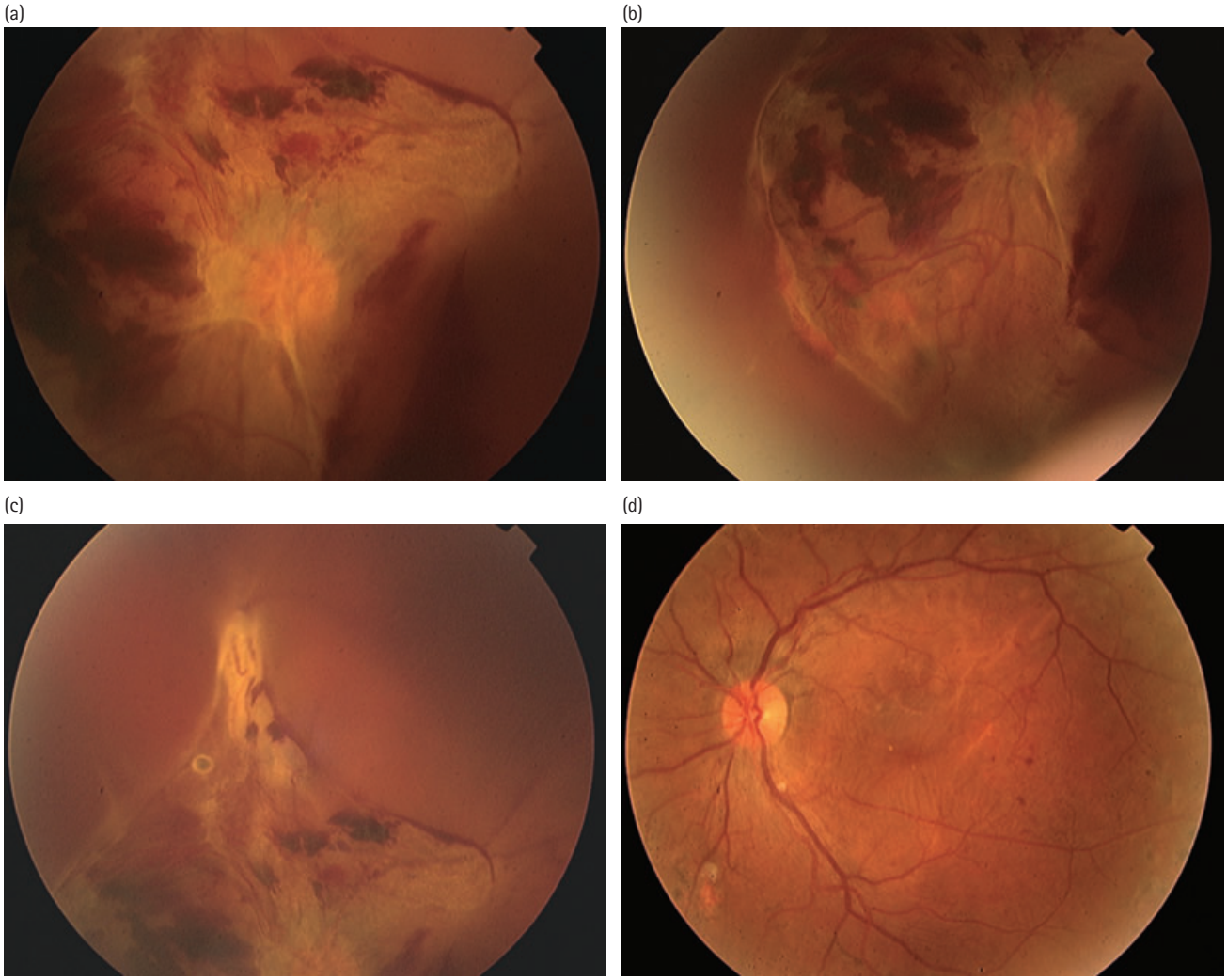


Figure 36.30 Vitrectomy for tractional detachment shown in (a–c) with postoperative photograph in (d). Reproduced from Scanlon PH, Wilkinson CP, Aldington SJ, Matthews DR. *A Practical Manual of Diabetic Retinopathy Management*. Published 2009 by Blackwell Publishing.

Intravitreal injection is an effective means of delivering anti-VEGF drugs to the retina but has the potential complications of endophthalmitis and retinal detachment. Randomized controlled trials utilizing varying doses of the VEGF inhibitors are required to assess the long-term efficacy, safety and to define optimum treatment regimens.

Vitrectomy

Smiddy and Flynn [83] wrote an excellent review where they noted that, according to the ETDRS, at least 5% of eyes receiving optimal medical treatment will still have progressive retinopathy that requires laser treatment and pars plana vitrectomy.

Two recent reports of vitrectomy case series have demonstrated that the most common reason for vitrectomy for DR is vitreous hemorrhage [84,85]. In the latter study, the indications for vitrectomy were:

- Vitreous hemorrhage in 80 patients (86.1%);
- Tractional retinal detachment in three patients (3.2%); and
- Vitreous hemorrhage associated with tractional retinal detachment in 10 patients (10.7%).

Lewis [86] suggested that for clinically significant macular edema, OCT should be performed to test for posterior hyaloid thickening and vitrectomy should be considered when a shallow macular detachment is found. Studies by Okamoto *et al.* [87] and Emi *et al.* [88] have shown that vitrectomy is effective in increasing the quality of life of patients with DR (Figure 36.30).

Pregnancy and the diabetic eye

Risk factors for progression of diabetic retinopathy in pregnancy

The known risk factors for progression of DR in pregnancy are:

• Pregnancy itself is independently associated with progression of DR [89,90];
• Baseline severity of DR [91–93];
• Poor metabolic control at conception [91];
• Rapid improvement of glycemic control [90–93];
• Poor metabolic control during pregnancy or the early postpartum period [89,90,93,94];
• Duration of diabetes [93,95,96]; and
• Chronic hypertension and pregnancy-induced hypertension [93].

Recommendations for patients

• Plan pregnancies early in life – women with T1DM should be encouraged to plan pregnancies early in life [94].
• Improving metabolic control before conception is recommended both for the mother and infant [91].
• Improving metabolic control during pregnancy is recommended both for the mother and infant [89,90,93,94].
• Control of hypertension both before conception and during pregnancy is recommended both for the mother and infant [93].
• Photocoagulation before conception and during pregnancy [95]. It is recommended that, if a patient is found to have significant retinopathy before conception, pregnancy is delayed where possible until appropriate laser treatment has been applied and good metabolic control has been achieved for a 9-month period to overcome any effects of the early worsening phenomenon [7]. Photocoagulation before pregnancy may protect against rapidly progressive PDR. Aggressive treatment of PDR developing in pregnancy may prevent further progression of the disease.

Low vision and blindness from diabetic retinopathy

In 2001, Cunningham [97] reported that 45 million people worldwide fulfil the WHO criteria for blindness. Twenty-four percent of all blindness, affecting people in both developed and developing nations, is caused by a combination of DR and macular degeneration with a small contribution from other eye diseases. In 2002, Kocur and Resnikoff [36] reported that in people of working age in Europe, DR is the most frequently reported cause of serious visual loss, confirmed in the UK by two studies [98,99].

In 2004, Fong *et al.* [100] reported that DR is a leading cause of adult blindness in the USA, resulting in blindness for more than 10 000 people per year.

The most progress in reduction of blindness has been made in Iceland [2] where the prevalence of legal blindness from DR dropped from 4.0% to 0.5% over 15 years, beginning in 1980.

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