CHAPTER 2

THE HUMAN EYE

The human eye is often compared to a camera. Incoming light reflected from objects is focused on to the retina after passing through cornea, pupil and lens, which is similar to the mechanism of a camera. A camera uses the photographic film or a CCD panel to create a picture, whereas the eye uses a specialized layer of cells, called the retina, to produce an image. The incoming information is processed by photoreceptor cells in the retina and transmitted to the brain through optic nerve. The eye's amazing ability to focus on a wide range of objects having different sizes, luminosity and contrast at a very high speed is more powerful than those of currently available cameras.

2.1 FEATURES IN THE HUMAN EYE

Figure 2.1 shows a sagittal section of an adult human eye. Iris is the coloured part of the eye which controls the amount of light that enters the eye. It is able to contract and dilate in order to control the size of the pupil depending on the light intensity. Cornea is the transparent part in the front of the eye that refracts light entering the eye onto the lens, while sclera is the outer white part of the eye that protects the inner structures. Light reaches the eye by first passing through the cornea which filters it, and begins focusing

the image. The anterior chamber contains a viscous fluid called aqueous humour, that keeps the front of the eye firm and slightly curved. Light traverses through the pupil, which compensates for changing light conditions by shrinking or relaxing. The muscles responsible for these movements are in the iris. Subsequently, the lens focuses the rays of light on to the retina. The interior surface of the eye, opposite the lens, is known as the fundus. The landmark features present in the physiology of the retina include optic disc, macula and blood vessels which are also seen in the sectional view. The retina is a multi-layered sensory tissue that lies on the back of the eye. It contains millions of photoreceptors that capture light rays and convert them into electrical impulses. These impulses traverse through the optic nerve to the brain where they are converted into images. The retinal vasculature supply oxygen and other nutrients to the inner and outer layers of the retina, the former is visible from the vitreous humour, the latter is not visible since they are situated in the choroid beneath the retina. Mainly two types of photoreceptors are there in the retina, the rods and cones, named after their shape. Rod cells are very sensitive to changes in contrast even at low light levels, hence are able to detect movement, but they are imprecise and insensitive to colour. They are generally located in the periphery of the retina and are used for scotopic vision (night vision). Cones, on the other hand, are high precision cells capable of detecting colours. They are mainly concentrated in the macula, the area responsible for photopic vision (day vision). The central portion of the macula is called the fovea, which is responsible for our sharpest vision.

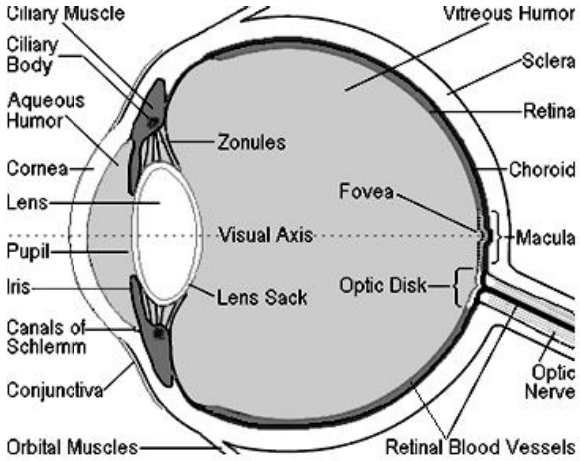


Figure 2.1 Sagittal section of an adult human eye

A fundus camera is used to capture the images of the interior surface of the retina. With its digital imaging capabilities, the images may be enhanced, stored and retrieved more easily than film, and images may be transferred electronically to other sites for a trained optical technician or an expert ophthalmologist to detect or diagnose diseases for a patient at a remote location. In the fundus image of a healthy human subject, features such as optic disc, retinal vasculature and macula are visible as shown in Fig 2.2. There are two kinds of quality problems in the fundus images: noise pixels and pixels whose color is distorted. Both seem to exist in regions where illumination has been inadequate. Since illumination is usually adequate in the center of the image, poor image quality regions are located near the edge of the fundus.

2.1.1 Optic disc

The optic disc (OD) is the entrance of the vessels and the optic nerve into the retina. It appears in color fundus images as a bright yellowish or white region. Its shape is more or less circular, interrupted by the incoming and outgoing vessels. Sometimes the optic disc has the form of an ellipse

because of a non negligible angle between image plane and object plane. The size of optic disc varies from patient to patient; its diameter lies between 40 and 60 pixels in 640× 480 color photographs. There are no sensory cells here, making it as a blind spot. Each eye covers for the blind spot of the other eye and the brain fills in the missing information. Optic disc is a major landmark for retinal fundus image registration and is indispensible for the quick understanding of retinal images. The diameter of the optic disc delivers a calibration of measurements that are done and it determines approximately the location of macula, the centre of vision. Its detection and segmentation is inevitable for the detection of exudates, since the optic disc has similar attributes in terms of brightness, color and contrast, and most algorithms make use of these characteristics for the detection of exudates .The detection of exudates is a key in identifying diabetic retinopathy.

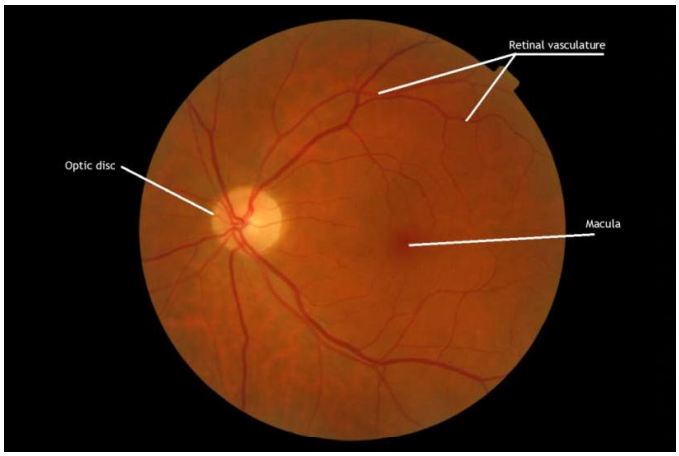


Figure 2.2 Fundus photograph of a human retina

2.1.2 Macula

The *macula lutea* or macula is a yellow spot near the center of the retina. In retinal fundus images, the macula appears as a dark region nearby the centre of the image. It is responsible for our central, or reading vision. This part of the retina gives us 20/20 vision. Near the centre of the macula is

the fovea, a tiny area responsible for our central, sharpest vision. Unlike the peripheral retina, it has no blood vessels; instead, it has a very high concentration of cones, allowing for the appreciation of colour. It is the darkest part in most fundus images; in some images it is not obvious to human eyes due to bright lighting or being covered by lesions. The diagnosis of age related macular degeneration (AMD) is typically undertaken through the inspection of macula. Macular oedema is a special case of diabetic retinopathy caused by leakage of blood vessels in the macular region. The location of macula, the centre of vision, is of great importance, as lesions in the macular region can immediately affect vision.

2.1.3 The retinal vasculature

Eye fundus is the only part of the human body where both the circulation and the nerve tissue can be inspected non-invasively. It is visible in retinal fundus photographs as tree like structure. Abnormal blood vessel growth and leaking blood vessels are the cause of vision loss in eye conditions like Diabetic Retinopathy (DR), Retinopathy of Prematurity (ROP), and Macular Degeneration (MD). Information on the retinal vasculature can be used in grading disease severity or as part of the process of automated diagnosis of several ophthalmic pathologies. Appearance of the blood vessels in the retina can provide information on pathological changes caused by some diseases including diabetes, hypertension, arteriosclerosis and retinopathy of prematurity. Furthermore, segmentation of the vascular tree in the retina seems to be the most appropriate representation for image registration applications due to the following reasons:

1) it maps the whole retina;

2) it does not move except in the case of a few diseases;

3) it contains enough information for the localization of some anchor points.

2.2 EYE EXAMINATION

The diagnosis of eye related pathologies are normally performed through periodic eye examinations by an expert ophthalmologist. The rapid increase in pathologies in this area pushes the limits of the current screening capabilities in populous developing countries like India. In the screening of abnormalities like diabetic retinopathy, the health care specialist uses direct ophthalmoscope or fundus photography to investigate the state of retina.

2.2.1 Clinical Eye Examination

Direct or indirect ophthalmoscope and biomicroscope with indirect lenses are commonly used for direct eye examinations. The opthalmoscope consists of an illumination source and suitable optics which are included in a headband, through which a specialist can observe the eye of a patient. The biomicroscope comprises of an observation system and illumination system, where the observation system is a biomicroscope capable of wide range of magnifications and the illumination system emits focal light into the patient's eye that can be controlled with slit mechanism and apertures. Combined with wide field lenses it can be used to visualize large areas of the retina. The main disadvantage of this approach is that no hard copy is produced for investigation at a later date or by a second expert. Moreover the requirement of an expert's time to examine all patients is needed in this.

2.2.2 Fundus Photography

The eye fundus photography is considered to be the most preferred diagnostic modality today by ophthalmologists. Fundus photography was first

described by Jackman and Webster way back in 1886. In contrast to traditional ophthalmoscopy, it records diagnostic data. Due to recent developments in digital image processing and storage capabilities, these images can be used for automatic screening by an expert system. A typical fundus photograph of both eyes is shown in Figure 2.3. Fundus photographs of the right eye (Figure 2.3 (a)) and left eye (Figure 2.3 (b)) are seen from front side of the eyes so that left in each image is the person's right eye. No sign of disease or pathology is visible from these images. The gaze is into the camera, so in each picture the macula is in the center of the image, and the optic disk is located towards the nose of the subject. Compared to ophthalmoscopy, fundus photography generally needs a considerably larger instrument, but has the advantage of availing the image to be examined by a specialist at another location and/or time, as well as providing photo documentation for future reference. This image can be made available for automatic screening also. Modern fundus photographs generally recreate considerably larger areas of the fundus than what can be seen at any one time with handheld ophthalmoscopes.

Fundus photography is performed by using a fundus camera, which basically consists of a specialized low power microscope with an attached camera. The optical design of fundus camera is based on the principle of monocular indirect ophthalmoscopy. A fundus camera provides an upright, magnified view of the fundus. A typical camera views 30 to 50° of retinal area, with a magnification of 2.5x, and allows some modification of this relationship through zoom or auxiliary lenses from 15°, which provides 5x magnification, to 140° with a wide angle lens.

(a) (b)

Figure 2.3 Fundus images of both eyes

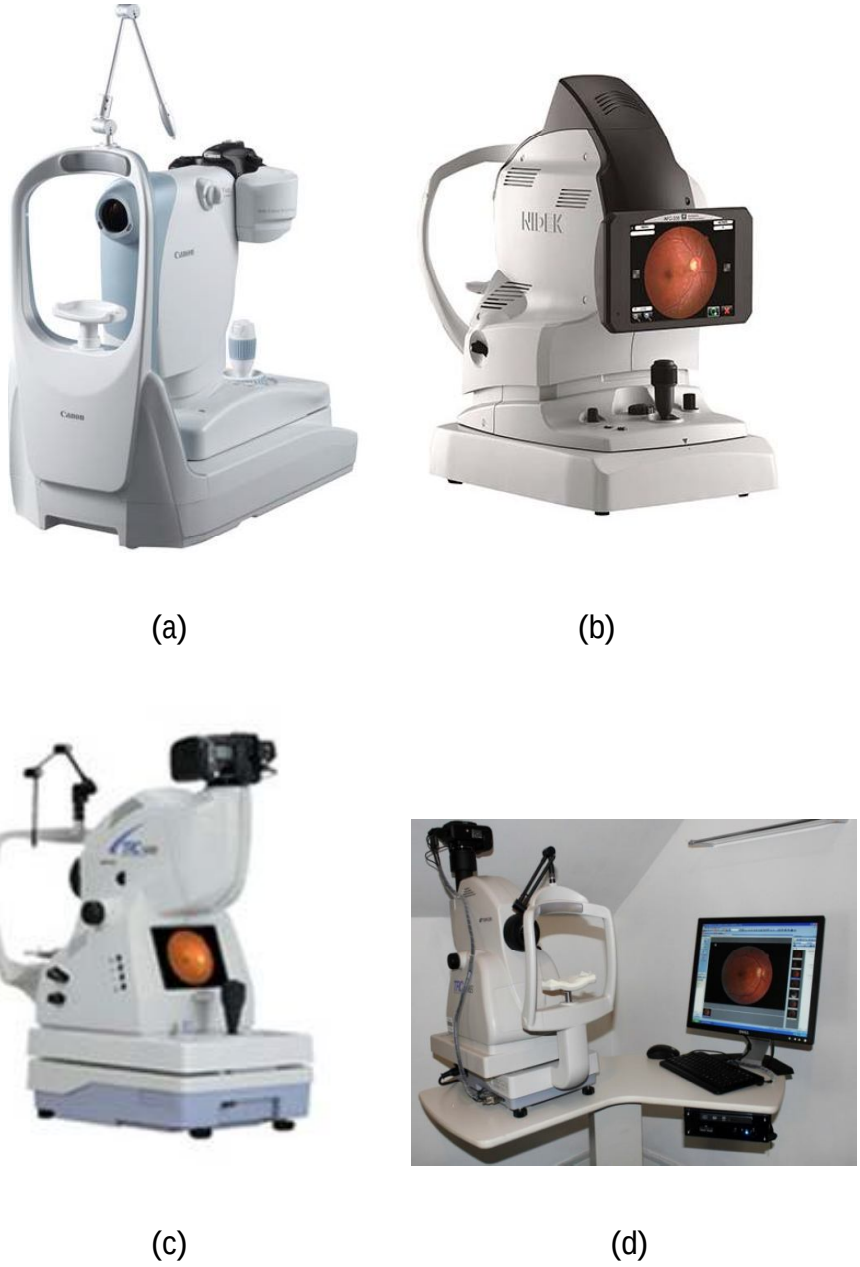
The optics of the fundus camera is similar to those of an indirect ophthalmoscope in that the observation and illumination systems follow dissimilar paths. The observation light is focused via a series of lenses through a doughnut shaped aperture, which then passes through a central aperture to form an annulus, before passing through the camera objective lens and through the cornea onto the retina (Saine 2006). The light reflected from the retina passes through the non-illuminated hole in the doughnut formed by the illumination system. As the light paths of the two systems are independent, there are minimal reflections of the light source in the captured image. The rays with which image is formed continue to pass towards the low powered telescopic eyepiece. When the button is pressed to take a picture, a mirror interrupts the path of the illumination system to allow the light from the flash bulb to pass into the eye. Simultaneously, a mirror falls in front of the observation telescope, which redirects the light onto the capturing medium, which is generally a film or a CCD. Because of the eye's tendency to accommodate while looking through a telescope, it is imperative that the exiting vergence is parallel in order for an in focus image to be formed on the

capturing medium. Since these instruments are complex in design and difficult to manufacture to clinical standards, only a few manufacturers exist, like Topcon, Zeiss, Canon, Nidek, Kowa, CSO and CenterVue.

Practical instruments for fundus photography perform the following modes of examination:

- Color photography, where the retina is illuminated by white light and examined in full color.
- Red-free photography, where the imaging light is filtered to remove red color, improving contrast of vessels and other structures.
- Angiography, where the vessels are brought into high contrast by intravenous injection of a fluorescent dye.

There are two types of fundus photography, mydriatic and non-mydriatic. Mydriatic denotes the dilation of pupil with suitable eye drops. Non mydriatic fundus photography may be used in mass screening, while mydriatic photography can be used for accurate diagnosis. Four models of fundus cameras are shown in Figure 2.4. Figure 2.4 (a) shows Canon CR2 plus nonmydriatic retinal camera, Figure 2.4 (b) shows NIDEK AFC-330 fundus camera, Figure 2.4 (c) shows TOPCON TRC NW-8 nonmydriatic fundus camera and Figure 2.4 (d) shows KANGHUA APS-AER nonmydriatic fundus camera.



(a) (b)

(c) (d)

Figure 2.4 Fundus cameras

2.2.3 Alternate Diagnostic Modalities

In addition to opthalmoscopy and fundus photography, there exist methods like fluorescein angiography (FA) and optical coherence tomography (OCT), which are also playing a significant role in the diagnosis of several

eye related pathologies. In fluorescein angiography, a fluorescent dye is injected in the systemic circulation of the patient and by emitting light into patient's eye in specific wavelengths, the fluorescent properties of the dye are activated. The emitted light excite the dye molecules into a higher energy level and as the molecules return to the original state they emit lower energy light that is captured using fundus photography. The image thus obtained is called angiogram. Since the dye circulates in the ocular vasculature, the fluorescein angiography provides valuable information for diseases pertaining to retinal vasculature. Specific methods include sodium fluorescein angiography (FA or FAG) and indocyanine green (ICG) angiography. The disadvantages of this approach are the requirement of injection and in rare cases, side effects such as nausea.

Optical coherence tomography (OCT) produces a two-dimensional cross-sectional image of ocular tissue structures, where the dimensions are propagation direction of the light and the perpendicular spatial direction. A broadband beam of light (LASER) is scanned across the ocular tissue and due to transparent structures of the retina the time of propagation is longer from the deeper tissue layers. Optical coherence tomography collects the reflected light and use the low coherence interferometer to measure the time of flight delay. The final optical coherence tomography image is composed of several axial scans and using several OCT images, a computational three-dimensional reconstruction of the retina can be devised. In diabetic retinopathy it is mainly used to provide accurate information about macular swelling and its type.

Abramoff et al. (2010) add the following imaging modalities also to a broader category of fundus imaging:

Stereo fundus photography: Two or more view angles of the fundus are acquired by this instrument at the same time. This allows the perception of the depth by the ophthalmologist.

Hyperspectral imaging: It is a fundus camera that does not employ the visible light only, but can select specific wavelength bands. This allows particular applications such as oximetry, the quantification of oxygen levels in the bloodstream.

Scanning laser ophthalmoscope (SLO): An instrument that uses low power LASER to image the retina or choroid. It uses a very narrow moving beam of light which can bypass most ocular media opacities (i.e. corneal scars, cataracts, vitreous hemorrhage) to reach the surface of the retina and record its surface detail. With SLO, the optics of the eye serves as the objective lens. Confocal SLO is SLO equipped with a confocal aperture. Adaptive optics SLO optically corrects the laser reflections by modeling the aberrations in its wavefront

Other modalities used in eye examination are adaptive optics ophthalmoscopy, colour Doppler imaging, computed tomography, magnetic resonance, ophthalmic ultrasound, retinal thickness analyzer and scanning laser polarimetry.

2.3 ABNORMALITIES IN RETINAL IMAGES

The vascular changes in diabetic retinopathy produce lesions, which hinder the working of the photoreceptive neurons lining the retina. Specific spatial regions exist in the retina, like the fovea, containing high concentration of photosensitive cells and are devoid of vasculature. Diabetic retinopathy leads to the risk of vision loss if vascular changes occur near such regions. DR presence can be detected by examining the vasculature in the retina for its characteristic features.

2.3.1 Microaneurysms

Microaneurysms appear due to local weakening of the vessel walls of the capillaries, causing them to swell. In some cases they will burst causing hemorrhages. Retinal microaneurysms are the most characteristic lesion of diabetic retinopathy, which are also present in other pathologies that affect the microvessels. Micoraneurysms are a small dilation of a capillary wall. In retinal fluorescein angiography they appear as bright spots, whereas in colour fundus images they appear as round, red spots. They are indistinguishable from small hemorrhages of the same dimension, since they both are small round regions, with a dark red colour. Figure 2.5(a) shows micro aneurysms.

2.3.2 Hemorrhages

Retinal hemorrhages are blood deposits in the retina. Hemorrhages disappear as the blood is reabsorbed with time. They are due to the breaking of a vessel wall or of a microaneurysm, and the increase in their presence is a clear sign of retinal damage. They have very different shapes, going from the round red spot with sharp margins to the blot hemorrhage. As the blood is reabsorbed, hemorrhage margins fade and the characteristic red colour turns in to a faint greyish-red before disappearing completely. Figure 2.5(b) shows hemorrhages.

2.3.3 Hard exudates

As the disease and damage to the vasculature progresses, larger hemorrhages will appear. In addition to leaking blood, the vessels will also leak lipids and proteins causing exudates to appear. They appear as white or yellowish-white areas with sharp margins. They may be arranged as individual dots, confluent patches or in partial or complete rings surrounding microanaeurysms or zones of retinal edema. In the more severe cases of

hypertensive retinopathy, they appear as a confluent ring around the macula (the macular star). Figure 2.5(c) shows hard exudates.

2.3.4 Soft exudates

Soft exudates are also known as cotton wool spots. These are the consequence of retinal ischemic events, due to precapillary arterioles stenosis. This causes a swelling of the nerve fiber layer, with local deposit of cytoplasmatic material. They are round or oval in shape with soft and feathery edges and white or pale yellow in colour. They usually appear along the major vessel arcades, parallel to the nerve fibers, and are sometimes accompanied by the presence of microaneurysms. Figure 2.5(d) shows soft exudates.

2.3.5 Drusen

Drusen is deposit associated with thinning or hypopigmentation of the retinal pigment epithelium. They appear as deep, yellowish-white dots. To distinguish drusen from hard exudates, good stereoscopic view would be necessary, since drusen appear very deep while hard exudates are slightly more superficial. Drusen are usually scattered diffusely or scattered near the center of the macula. They are usually round in shape, while hard exudates are usually irregular in shape. Finally, drusen often has a faint border of pigment.

2.3.6 Neovascularizations

As the retinal damage progresses, a few small regions of the retina become ischemic (deprived of blood). These ischemic areas are visible on the retina as fluffy whitish blobs called cotton-wool spots. As a response to the appearance of ischemic areas in the retina, the eye will start growing new

vessels to supply the retina with more oxygen and nutrients. These vessels, called neovascularizations, have a greater risk of rupturing and causing large hemorrhages than normal vessels and even retinal detachment.

Diabetic retinopathy is commonly categorized in to the following stages

- **Mild Nonproliferative Retinopathy:** At this earliest stage, microaneurysms occur. They are small areas of balloon-like swelling in the retina's tiny blood vessels.

- **Moderate Nonproliferative Retinopathy:** As the disease progresses, some blood vessels that nourish the retina are blocked.

- **Severe Nonproliferative Diabetic Retinopathy (NDR):** Many more blood vessels are blocked, depriving several areas of the retina with their blood supply. These areas of the retina send signals to the body to grow new blood vessels for nourishment.

- **Proliferative Diabetic Retinopathy (PDR):** At this advanced stage, the signals sent by the retina for nourishment trigger the growth of new blood vessels. These new blood vessels are abnormal and fragile. They grow in the retina and along the surface of the clear, vitreous gel that fills the inside of the eye. By themselves, these blood vessels do not cause symptoms or vision loss. However, they have thin, fragile walls. If they leak, vision loss and blindness can result.

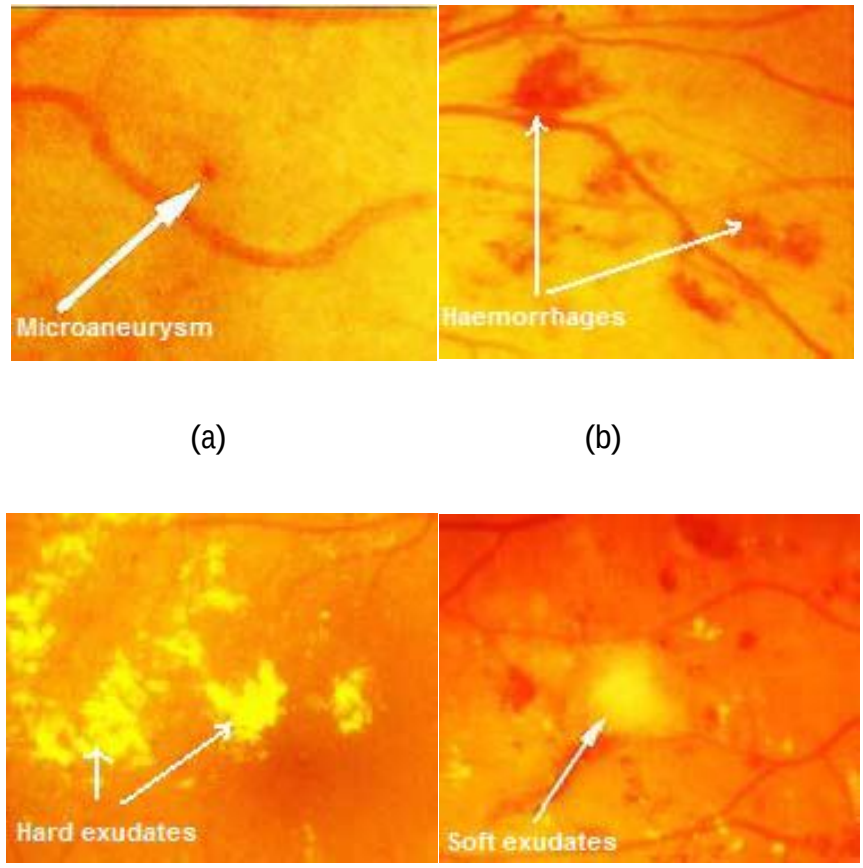
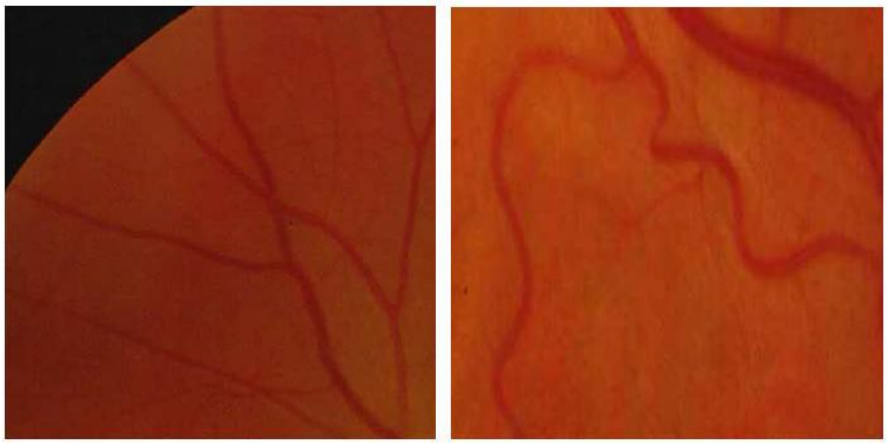


Figure 2.5 Abnormalities in retinal images

Other vascular abnormalities visible in retinal images include tortuousity, arteriolar narrowing, bifurcation abnormalities and crossing abnormalities. Vessel tortuousity is caused by increased blood pressure. In presence of hypertension, vessels may increase in length and vessel walls thicken, and as a result they become increasingly tortuous. This is first visible in arteries, and in more severe stages of retinopathy, they also appear in veins. Figure 2.6 (a) shows a normal vessel course in the retina while Figure 2.6 (b) shows a tortuous vessel course.



(a) (b)

Figure 2.6 Abnormalities in the vessel course

The earliest fundus change due to high blood pressure is the thinning of retinal arterioles. Narrowing of the arterioles is usually proportional to the degree of elevation of blood pressure. In severe hypertension states, irregularities in the caliber of blood vessels may appear. In arterioles, they are due to localized spasm and contraction of the wall. They appear as a focal thinning of the blood column. The narrowing continues until the vessels become thread-like. Arterial diameters and topography at branch points are believed to conform to design principles that optimize circulatory efficiency and maintain constant shear stress across the network (Murray 1926). It is suggested that arterial diameters at a bifurcation should conform to a power relationship, and arterial branches in various circulation have been shown to obey to this design.

It is seen that bifurcation angles are reduced with increasing hypertension, probably because the atheroma fibrosis of the central artery is displaced by contraction of the arteries towards the disk. Although the mechanisms of bifurcation changes are not understood clearly, both branching angles and also the value of the junction exponent seems to deviate from its

optimal values with age (Stanton et al. 1995). The abnormal changes in arteriovenous crossings result from the thickening of the wall of the arterioles due to hypertension and sclerosis, and associated changes in the veins at the crossings. The first appearance of crossing abnormalities is the compression of the vein by the artery, which may vary in severity from a slight indentation to complete interruption of the vein where the artery crosses. When the sclerotic process in the artery extends to the adventitia of the vein, the blood column in the vein will be partially obscured and will appear tapered on each side of the crossing. Constriction and compression of the veins may impede the blood return, so that the veins become distended for some distance peripheral to the crossing. This is known as Gunns sign. The arterial sclerosis may cause detection of the vein from its normal course at the point where the artery crosses. The veins may be detected both vertically or laterally. In the second case, instead of crossing the artery obliquely, the vein does so at right angles and appears as a S-shaped structure at the bend, which is referred to as the Salus sign.

2.3.7 Glucoma

Glaucoma is not a retinopathy but a neuropathy. Nevertheless, it affects the retina by damaging ganglion cells and their axons. The disease is characterized by an increased pressure on the optic nerve which slowly affects it, resulting in a peripheral visual field loss. Because of the peripheral damages, it is often unnoticed and it has become the second leading cause of blindness in the world (Resnikoff et al. 2004). Glaucoma can be diagnosed by analyzing the 3-D shape of the optic nerve head, the optic cup and the optic disc. In their review, Abramoff et al. (2010) present various methods to accomplish this task with fundus and OCT images.

The optic disc has the same pixel brightness as the exudates and thus has to be localized before establishing the presence of the exudates. Similarly the blood vessel tree and macular region have to be subtracted from the retinal image before diagnosing microaneurysms and hemorrhages, which are considered to be unequivocal signs of diabetic retinopathy. The extraction of retinal vasculature is of paramount importance in detecting vascular abnormalities also. Moreover, the detection and extraction of these important normal features of the retina are indispensible for image registration applications. Hence, the localization and extraction of these landmark retinal features are of great importance in the context of automatic fundus image screening, registration and analysis.