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Ten years experience with choroidal angiography using indocyanine green dye: a new routine examination or an epilogue?

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Abstract. The choroidal circulation can be studied by an angiographic technique which utilizes near-infrared light wavelengths and a biocompatible dye, indocyanine green (Cardiogreen^{R}). Near-infrared light is less absorbed than visible light by the pigment epithelium and the macular xanthophyll, and indocyanine green (ICG) dye doesn't leak from the choriocapillaris as sodium fluorescein dye typically does. Due to the high rate of choroidal blood flow, a fundus camera adapted with special filters and a continuous light source was used in order to make angiograms at the rate of 10 per second.

Our experience at the Wilmer Institute and the Eye Clinic at St. Gallen includes 180 choroidal angiograms of normal volunteers and approximately 500 choroidal angiograms of patients with several fundus diseases, mainly senile macular degeneration, diabetic retinopathy and choroidal tumors. Although many of our results are preliminary, we present them to demonstrate the potential applications of this method in ophthalmology. Some factors which may have inhibited an extensive propagation of clinical choroidal angiography in the past are also discussed.

Introduction

Since the invention of the ophthalmoscope by Helmholtz in 1851, the unique possibility has existed to study human blood vessels in vivo in the eye. The fundus oculi can be seen because it reflects a significant fraction of the light incident on it. The optical properties of the eye are such that this reflected light forms an exact image of the fundus outside of the eye. The image is real and can either be seen by the eye of an observer (ophthalmoscope) or it can be documented on photographic film (fundus photography). Using visible light, the retinal vessels may be readily observed while the choroidal vessels are almost entirely hidden behind the pigment epithelium and by the pigment in the choroid itself. Therefore, the ophthalmologist generally knows much more about the retinal vasculature than that of the choroidal.

The difficulties associated with routinely observing the choroidal vessels do not *a priori* imply that they lack importance to physiologic and pathologic conditions of the eye. Consider for instance that about 90% of the blood

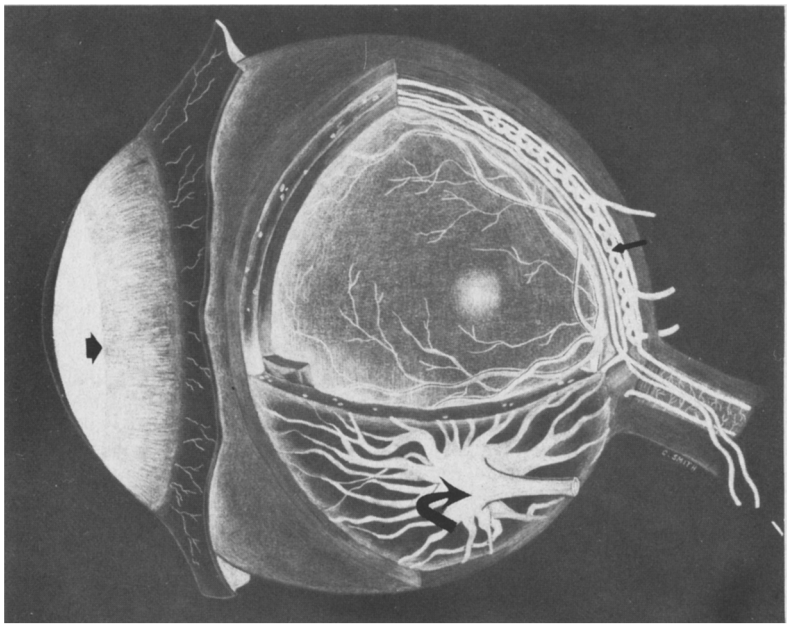

Figure 1.1. Schematic representation of the blood supply of the eye. The choroid (small arrow) is highly vascularized. 10–20 short posterior ciliary arteries (below the arrow) and 2 long posterior ciliary arteries (above the arrow) supply the choroid with blood. Four large vortex veins (curved arrow) drain blood from the uveal circulation, including the iris (thick arrow). The retina has an independent circulation with its central artery and the central vein both following a course along the optic nerve.

entering the eye circulates in the uveal vessels (Figure 1.1). Of all organs in the body, the choroid appears to be relatively best supplied with blood (Alm, 1983). The importance of the choroid to maintain the human eye is furthermore evidenced by the fact that the avascular outer retinal layers, including the photoreceptors, apparently are entirely supported by the choroidal ciculation. With the advent of choroidal angiography, however, choroidal vessels now also can be visualized routinely in man. In order to better understand the possibilities and limits of this new technique, some anatomic and physiologic principles shall be reviewed briefly.

The basic anatomy of the choroid has been known since the last century (Donders, 1855; Müller, 1956; Sattler, 1876), but more recent studies have added important physiological information (Hayreh, 1975; Bill, 1981; Alm, 1983).

Deriving from 2 major branches that leave the ophthalmic artery in the posterior orbit, between 10 and 20 short ciliary arteries enter the globe at the posterior pole. After a slightly oblique entrance through the sclera these arteries turn radially toward the equator after branching at the posterior pole (Figure 1.2). Twenty to 90 μm diameter choroidal arteries give off short

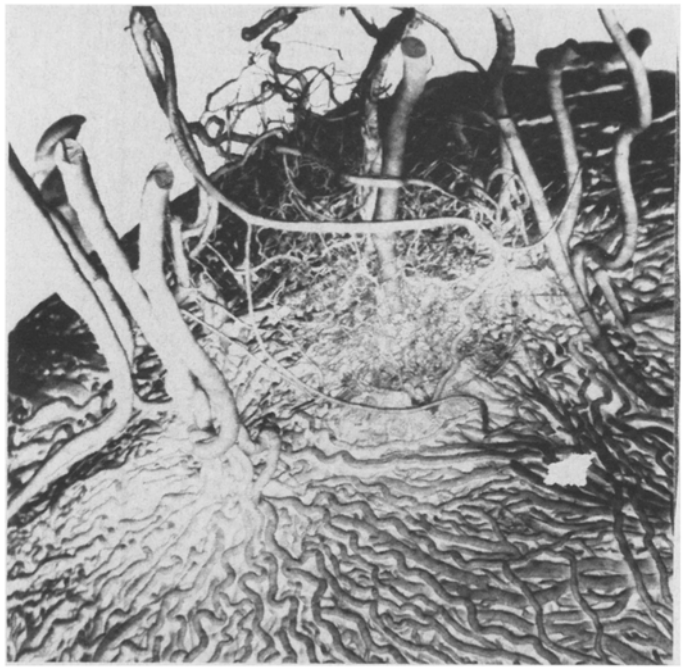

Figure 1.2. Posterior ciliary arteries and choroidal vessels. Scanning electron microscopic view on a corrosion cast of a monkey eye from behind. Note the ciliary arteries and the multiple nearby parallel choroidal vessels. From 'Risco JM, Grimson BS and Johnson PT (1981) Angioarchitecture of the ciliary artery circulation of the posterior pole. Arch Ophthal 99:864–868'. Copyright 1981, American Medical Association.

arterioles which join the choriocapillaris almost perpendicularly (Hogan, 1961). Anterior to the equator the choroid is supplied by branches from the anterior ciliary arteries and from the 2 long posterior ciliary arteries.

The *choriocapillaris* is a monolayer network consisting of 10 to 30 μm wide capillaries separated by very small intercapillary spaces (Sattler, 1876; Leber, 1903; Wolff, 1976). While some anatomical studies suggested the existence of anastomosis between arterioles (Shimizu and Ujiie, 1978) or within the choriocapillaris (Wybar, 1954; Ring and Fujiono, 1967; Araki, 1976), it is currently believed that, at least functionally, the choriocapillaris is organized in a segmental way (Krey, 1975; Hayreh, 1975). The basic choriocapillaris unit has a diameter of about 1/4 that of the optic disc. A clinical manifestation of this basic structure may be present in the Elschnig's spots, found in hypertensive patients. These small white spots can be correlated with the occlusion of choroidal arterioles and subsequent atrophy of the individual choriocapillaris units, at least in the animal model (De Venecia et al., 1980). The choriocapillaris is also a monolayer endothelial network having a close relationship to Bruch's membrane (Figure 1.3). The endothelial walls of the choriocapillaris are fenestrated, and the basement

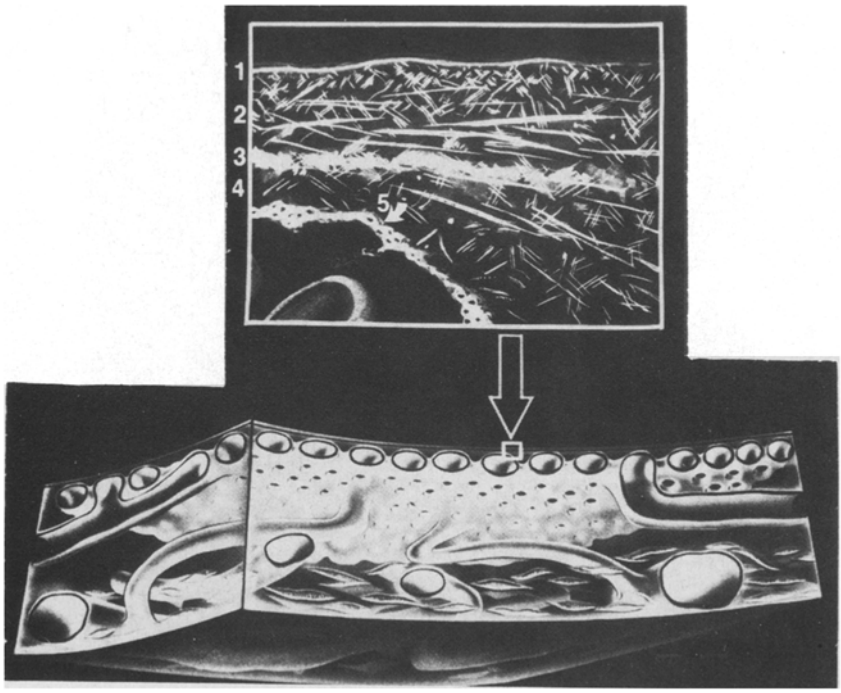

Figure 1.3. Schematic representation of the choroid and Bruch's membrane. Arterioles and venules are connected to the choriocapillaris (lower picture). Bruch's membrane (upper picture) consists of different layers: (1) basal membrane of the retinal pigment epithelium, (2) collagen fibers, (3) elastic tissue, (4) other collagen and (5) basal membrane of the choriocapillaris. From "Torczynski E (1982) Choroid and Suprachoroid. In: Duane TD and Jaeger EA (eds): Biomedical Foundations of Ophthalmology. Philadelphia, Harper & Row, Vol. 1, chap. 22:1–33"

membrane is discontinuous. Fenestrated capillaries are generally found in tissues where secretion or absorption is a major function, as for instance in the ciliary body of the eye, the endocrine glands, the gallbladder, and, as mentioned before, the choriocapillaris. The fenestra apparently facilitate passage of small molecules such as fluorescein, and to a much lesser extent even small proteins (Spitznas, 1974). By comparison, the endothelial walls of choroidal arteries and veins and the retinal capillaries are not fenestrated and therefore form a barrier for molecules larger than 300 daltons (Tripathi, 1974; Garner, 1982).

The *choroidal veins* are 20 to 100 μm wide (Hogan, 1961) and form multiple, almost parallel pathways to the 4 vortex veins. While venous anastomoses certainly exist in the choroid (Wolff, 1976), fluorescein angiographic studies in rhesus monkeys (Hayreh and Baines, 1973) and clinical experience (Amalric, 1974) suggest existence of a functionally well defined segmental distribution for each vortex vein.

The 10 to 20 short posterior *ciliary nerves* enter the eye at the posterior

pole in a close relationship to the posterior ciliary arteries (Potts, 1966). They consist of at least 3 different parts:
(1) Sympathetic postganglionary fibers, originating from the superior cervical ganglia.
(2) Parasympathetic fibers that take a common course with the facial nerve, pass the ganglion pterygopalatinum and finally synapse with the ciliary nerves in the ciliary ganglia.
(3) Sensory fibers from the trigeminus nerve.

Is there a special anatomical configuration of the *submacular choroid*? Confirmation of the postulated existence of a special macular artery (Hepburn, 1912) has been offered only once (Ernest, 1977). The hemodynamic situation of the submacular choroid is nevertheless unique and may account for the predilection of some diseases for the macular area. First, the pressure gradient in the submacular precapillary arterioles may be higher than elsewhere in the choroid (Potts, 1966) because most ciliary arteries enter the sclera at the posterior pole. The presumed high pressure within the submacular arterioles may increase the risk for local embolization, and it may, in case of failing arteriolar vasoconstriction, lead to high blood flow in the adjacent choriocapillaries, vessel wall distention, and subsequent leakage of fluid under the pigment epithelium and retina.

In regard to *choroidal angiography* three conclusions can be made from these anatomic considerations:

(1) Compared to the relatively planar retinal vasculature, the choroidal vasculature is three dimensional. Consequently, whereas the wavefront of an injected dye moves through the retinal vessels perpendicular to the optic axis of the eye, that which moves through the choroid does so parallel to the optic axis. This is true either for both choroidal arterial filling and for venous drainage from the choriocapillaris. If one attempts to study choroidal blood flow, this blood flow configuration necessitates performance of high-speed angiography (part 2.2).

(2) In order to be useful in choroidal angiography, the injected dye must either be a very big molecule or it must be bound to big molecules such as plasma proteins; the dye would otherwise leak rapidly from the choriocapillaris and obliterate the underlying choroidal vessels as is the case when fluorescein dye is injected.

(3) In order to visualize choroidal vessels, wavelengths of light longer than those of visible light must be used to better penetrate the pigmented layers of the retina.

The introduction of *fluorescein angiography* (Novotny and Alvis, 1961) led to marked increase in knowledge of the retinal circulation by demonstrating morphological as well as functional changes in the form of pathologic filling patterns or pathologic dye leakage from ocular blood vessels. With regard to

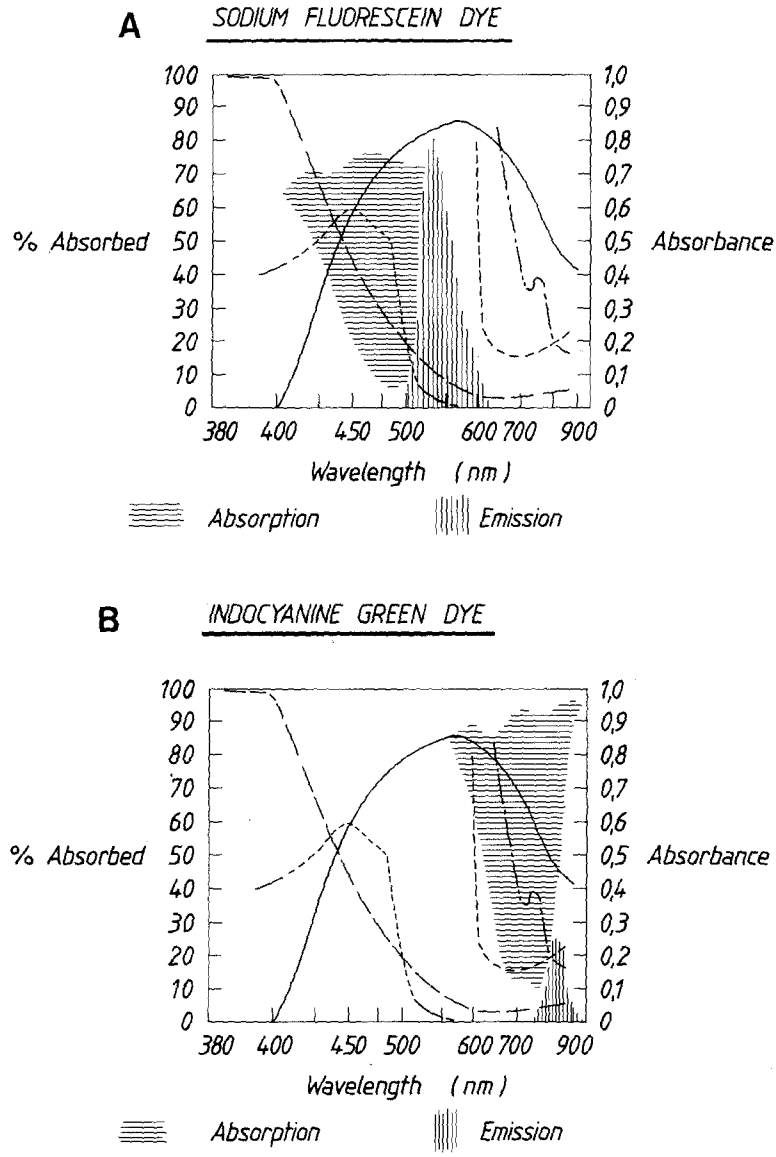

Figure 1.4A. Fluorescein-fluorescence and absorption characteristics of the eye.
Figure 1.4B. Indocyanine green-fluorescence and absorption characteristics of the eye.
Figure 1.4(A & B). ——— Percentage of absorption in the pigment epithelium and the choroid (Geeraets et al., 1960). — — — Percentage of absorption in the transparent media of the eye (Geeraets et al., 1960) – – – – – Absorption of macular xanthophyll (Wald, 1949). - - - - - - Absorption of HbO_2. - — - Absorption of Hb.

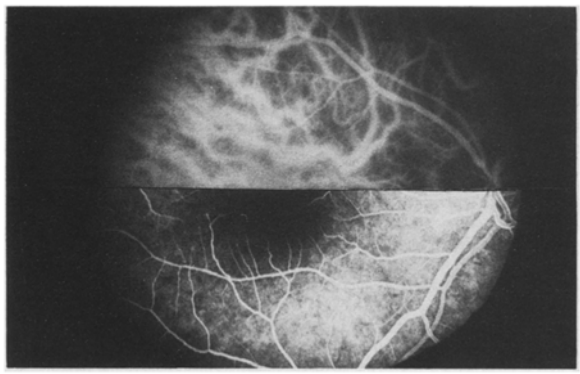

Figure 1.5. Comparison of ICG- and fluorescein angiograms. Two corresponding halves of negatives (ICG-angiogram above, fluorescein angiogram below) have been put together to demonstrate the differences between them. Instead of a diffuse fluorescein background fluorescence (below) the choroidal veins are clearly visible with ICG fluorescence (above). Instead of a 'black macula' (below) multiple vessels are visible in the submacular choroid (above). The contrast is superior in the fluorescein angiogram.

the choroidal circulation, however, this technique has produced only limited information (Hyvärinen et al., 1969; Archer et al., 1970). The blue-green fluorescein excitation wavelengths are absorbed and scattered by the pigmented layers of the fundus and by macular xanthophyll (Figure 1.4A), producing the 'black macula' in the fluorescein angiograms. Moreover, only 60% to 80% of injected fluorescein dye is bound to plasma albumin (Bloome, 1980), while the free fluorescein leaks rapidly out of the fenestrated choriocapillaris, producing the diffuse 'background staining' that obscures visualizing of the deeper choroidal vessels.

The introduction of a new angiographic technique, infrared fluorescein *choroidal angiography*, in 1970 (part 2) made it possible for the first time to routinely examine the choroidal circulation in human patients (Figure 1.5). Compared to fluorescein angiography, two basic differences of the new technique made this possible, namely the use of near-infrared light and use of a blood protein-bound dye, indocyanine green dye.

The light used for choroidal angiography. consists mainly of near-infrared wavelengths (Figure 1.4B), which are able to better penetrate the pigmented layers of the fundus, including macular xanthophyl (Wald, 1949; Geeraets et al., 1960; Behrendt and Wilson, 1965). Several characteristics of the near-infrared light used in choroidal angiography, should be briefly mentioned:

(1) In contrast to the excitation light used in fluorescein angiography, that used in choroidal angiography is perceived by patients to be a faintly visible red light. Consequently, angiography of photophobic patients may be readily performed.

(2) Infrared light is potentially less harmful to the retina than light of shorter wavelengths (part 2.3) making feasible the use of a continuous light source for high-speed angiography.

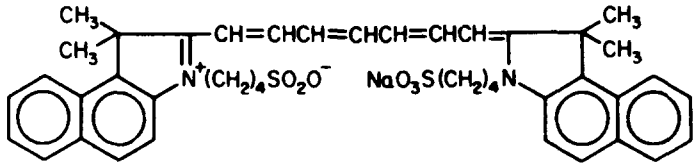

Figure 1.6. Structure of indocyanine green.

(3) Since shorter wavelengths of light are less scattered than long ones, near-infrared photography may be performed in patients with diffuse, not too dense opacities, in whom the blue excitation light used in fluorescein angiography would be significantly scattered.

(4) In addition to insertion of special filters, the fundus camera must also be modified slightly in order to correct the chromatic aberration (redshift) (part 2.1).

(5) A limiting factor for this technique is the relatively low sensitivity of infrared film.

Indocyanine Green (ICG) dye (Figure 1.6) absorbs light in the near-infrared region of the spectrum (maximum absorption is approximately at 790 nm). ICG also fluoresces in the near-infrared region with the maximum emission occurring at approximately 835 nm (Flower and Hochhemimer, 1976; Benson and Kues, 1978) (Figure 1.4B). Approximately 98% of ICG is bound to plasma proteins (Cherrick et al., 1960) and, therefore, does not 'leak' from the choriocapillaris. Another advantage of ICG is its rapid removal from the blood by the liver; the dye is essentially removed from circulating blood within the first few minutes after intravenous injection (Wheeler et al., 1958; Ketterer et al., 1960). As a consequence, there is no significant staining with ICG of the ocular tissues (Ansari et al., 1975); this permits repitition of ICG-angiography after only a few minutes following the first angiography.

ICG is manufactured primarily by Hynson, Westcott and Dunning, Inc, Baltimore, Maryland (USA) and sold with the brandname 'Cardio-Green' in 25 and 50 mg vials in crystallized form, providing a long shelf-life for the dye. Before the injection, the dye is dissolved in an aqueous soluent provided in the commercial package. To prevent recrystallization, Cardio-Green contains a trace of sodium iodide never exceeding 5% (*U.S. Pharmacopeia, 1980*); this precludes its use in patients allergic to iodide. Generally, ICG is considered nontoxic and has proven its safety in several hundred thousand applications for cardiologic and hepatic studies (part 2.3).

The present study provides an overview of the extensive experience with choroidal angiography at the Wilmer Ophthalmological Institute in Baltimore, Maryland where the major technological developments took place. We have reviewed earlier choroidal angiograms of about 180 normal volunteers and 220 patients with different fundus diseases. We will present a summary of these results together with recent angiographic findings from St. Gallen,

Switzerland (currently consisting of approximately 280 patients) by discussing the normal (part 3) and some pathologic (part 4) choroidal vascular patterns. By so doing, we aim to demonstrate the currently realized possibilities and limitations of this examination method. We also will present in detail the technical aspects of this type of angiography and thereby hope to encourage other clinicians to utilize this method (part 2.1).

With regard to choroidal angiography we are currently in the interesting situation wherein the major technical problems have been essentially solved but where the clinical significance of this method still must be explored completely (part 5).

2. Technical aspects of choroidal angiography with Indocyanine Green

Choroidal angiography with ICG is a relatively new method and has undergone several improvements in the last decade. In order to better understand the equipment used (2.1) and the dye injection procedure (2.2), an overview of the history of this technique is given first.

Infrared angiography, using ICG as an absorbing dye, was first applied in the study of pial vessels in dogs (Kogure and Choromokos, 1969). Later, the same authors injected ICG into the carotid artery of a monkey and photographed its fundus, using infrared color film. They were able to demonstrate for the first time filling of the choroidal veins but could not resolve choroidal arteries or capillaries (Kogure et al., 1970). In some human patients that underwent carotid angiography for various reasons, between 25–50 mg ICG were injected into the carotid artery, and the choroidal veins were successfully photographed. It was not possible, however, to photograph choroidal vessels after intravenous injection of the dye (David, 1971).

An important step toward developing a clinically useful procedure was the use of infrared-sensitive black and white film instead of infrared color film and use of better photographic filters. It then became possible to photograph choroidal veins in the cat following *intravenous* dye injection (Hochheimer, 1971). Using that same technique, successful choroidal angiography in humans was reported using intravenous injection of ICG (Flower and Hochheimer, 1972).

This marked the beginning of clinical use of *ICG-absorption angiography* in Baltimore. It was based on the absorption spectrum of ICG dye which lies in the near-infrared region. If the fundus is illuminated with infrared light and photographs are taken through a bandpass filter whose peak transmission wavelength matches the peak absorption wavelength of the injected dye, then the light reflected by the sclera exposes the photographic film, but areas corresponding to the largest choroidal vessels which contain enough circulating dye to absorb all the incident light are not exposed. Those vessels appear white on the photographic film negative but black on the photographic print (Figure 2.1). The principal drawback to this method is its

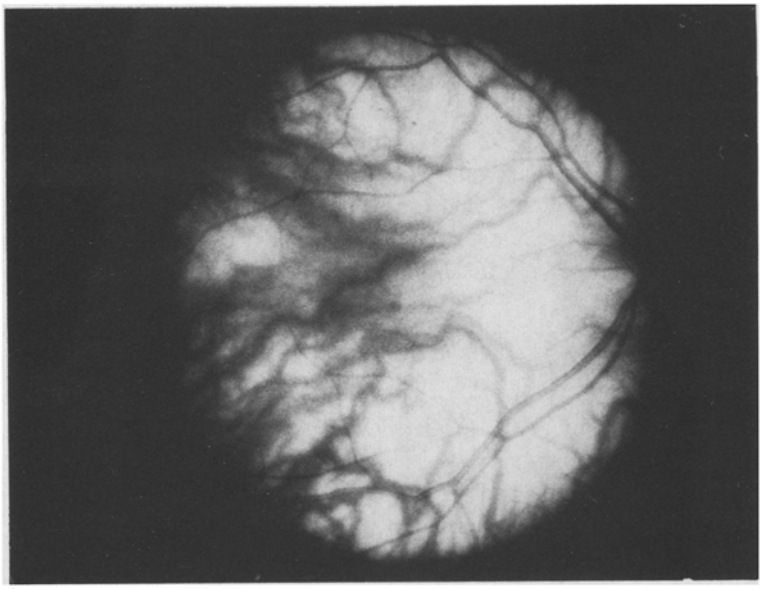

Figure 2.1. ICB absorption angiogram. Twenty-six year old normal volunteer, right eye, 4.9 seconds. In this angiogram the choroidal veins appear black; because the intravascular ICG absorbed the infrared light thereby preventing its reflection from the sclera.

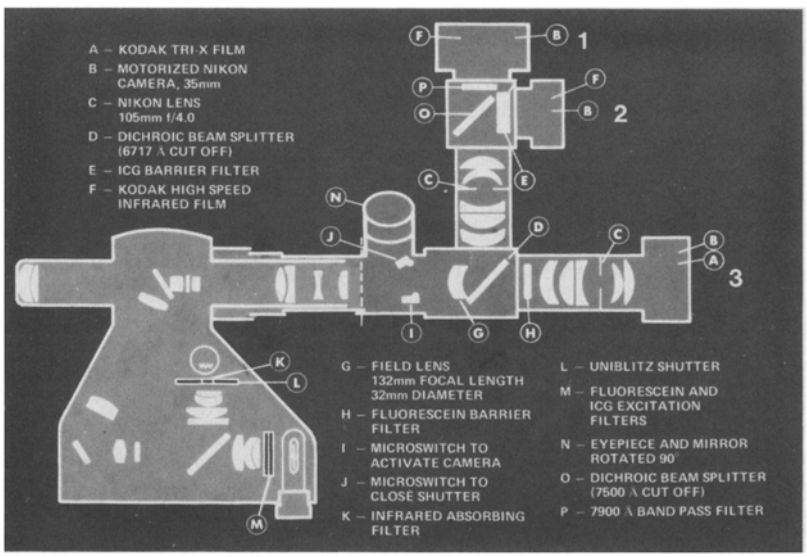

Figure 2.2. Multispectral fundus camera (Baltimore 1973–1975). Simultaneously, 3 different examinations could be performed: (1) ICG absorption angiography; (2) ICG fluorescence angiography; (3) Fluorescein angiography.

inability to demonstrate the smaller diameter choroidal vessels including the arteries and choriocapillaries.

By taking advantage of another property of ICG, namely its fluorescence, *ICG-fluorescence angiography* was performed in 1973 and proved to be the superior technique (Flower and Hochheimer, 1973). By this technique, the vessels become as 'selfluminous bodies', and the choroidal arteries also can be photographed routinely. It's still difficult to resolve the choriocapillaris using this method because of its anatomical structure, wherein spaces between the vessels are smaller than the vessels themselves. With correct excitation and barrier filters in a fundus camera, only light from the fluorescent vessels exposes the photographic film, while the excitation light reflected from the fundus is blocked by the barrier filter. On the photographic print, however, the vessels appear white and the background black (as is demonstrated in the parts 3 and 4).

Originally in order to facilitate interpretation of the choroidal ICG dye-filling sequence, choroidal ICG dye filling was correlated to simultaneously occurring retinal fluorescein dye filling. Between 1973–1975 a multispectral fundus camera was developed and used in Baltimore capable of simultaneously performing ICG-fluorescence, ICG-absorption and fluorescein-fluorescence angiography (Figure 2.2) (Flower, 1974; Flower and Hochheimer, 1976). 40–80 mg ICG, solved in 1–2 ml 25% fluorescein (equivalent to 250–500 mg sodium fluorescein) were injected into an antecubital vein, followed by a 5 ml saline flush. Three synchronized Nikon 35 mm photocameras were used. The xenon flash generator employed at this time limited the frequency of the angiograms to 1 frame per 0.7 seconds.

In 1976, two reports summarized the clinical results obtained with that multispectral camera (Patz et al., 1976, Orth et al., 1976). Both authors considered their results only preliminary and could not at that time adequately determine the clinical significance of the method. They did, however, recommend its application for differential diagnosis between choroidal hemangiomas and other tumors and for further clinical studies of choroidal blood flow. They also mentioned some advantages of ICG-vs fluorescein-angiography in patients with an allergy to fluorescein, with slightly hazy media or with photophobia.

In order to improve the spatial and temporal resolutions of choroidal angiograms, the multispectral camera was abandoned in 1975 in favor of a fundus camera built exclusively for ICG-fluorescence angiography and thereby optimized for this one examination technique. Instead of the relatively slow flash generator, a continuous light source was employed, and the photocamera was replaced by a 35 mm movie camera.

In order to compensate for the relatively low level of ICG-fluorescence intensity, the image size on the film was reduced from the 28 mm originally used in the standard Zeiss fundus camera to approximately 17 mm (Flower, 1977). Following anti-reflection coating of all the camera lens surfaces and

installation of a stronger continuous light source in 1978, it became possible to forego the image size reduction and yet still obtain sufficient film exposure even at 10–20 frames per second. With that equipment it became possible to observe choriocapillaris dye transit in young monkeys (Flower, 1980), but in humans the choriocapillaris is still not readily resolvable.

The first clinical results obtained using that new equipment were published in 1980 (Hyvärinen and Flower, 1980). Surprisingly, after performing about 400 choroidal angiograms in the years 1972–1976, between 1979 and 1981 no further studies were done in humans. Since 1982, however, we again started studying human patients using this same equipment (part 4).

According to the ophthalmic literature, ICG-fluorescence angiography has been performed only in a few European countries (Craandijk and van Beek, 1976; Chopdar et al., 1978; Hyvärinen and Flower, 1980) and in Japan (Hayashi et al., 1982). Some French investigators proceeded with the earlier mentioned ICG-absorption angiography using color infrared film. There are, however, serious drawbacks reported with that approach: color film is less sensitive than black and white film, it is more difficult to determine correct exposure from patient to patient, and it must be developed by special laboratories. Moreover, the resolution of smaller choroidal vessels, such as the choroidal arteries, is most often impossible with absorption angiography, and finally the dosage of ICG needed for absorption angiography is much higher than in the fluorescence technique, in humans normally 200 mg ICG are given intravenously (Buffet et al., 1979; François et al., 1977; Habozit, 1976).

2.1 Adaption of a Zeiss-fundus camera for choroidal angiography

Our experience is limited to the *Zeiss*-fundus camera, consequently we will discuss only the necessary modifications for this widely used type of camera. There is no reason, however, why the same modifications cannot be made to another fundus camera for choroidal angiography.

At the present time, there is no commercially available choroidal angiography equipment. The various components needed to modify a standard fundus camera, including filters and continuous light source, must be obtained individually. Consequently, three main modalities are possible for someone deserving to perform choroidal angiography. If one plans only a few such studies and intends to use a fundus camera mostly for fluorescein angiography the simplest and cheapest way, described below as the '*minimal solution*' is best. This modality allows one to gain some initial experience with the new method without having to invest much time or money, but this is accomplished by sacrificing temporal resolution which ultimately may be critical in assessing circulatory diseases of the choroid.

At the opposite end of the spectrum of modalities is the '*maximal solution*'. With it the attempt is made to optimize transmission of infrared light along the optical pathways and to gain the maximum exposure of the

photographic film. This involves use of an elaborate 35 mm high-speed movie camera, a strong continuous light source, special anti-reflection coating of the lenses and special optical surfaces suited to infrared wavelengths.

Between these extremes, however, there is a third *'compromise solution'*, whereby one tries to do acceptable choroidal angiography and yet use relatively simple equipment. One may install a continuous light source and a relatively inexpensive 35 mm photocamera with motordrive to obtain a frequency of about 4 exposures per second, which may prove to be sufficient for many clinical applications.

Maximal solution. As one example of an elaborate modification of a Zeiss-fundus camera for choroidal angiography, the camera developed by Flower and currently used in St. Gallen, Switzerland will be described here.

Compared to the usual Zeiss-camera, several changes are evident as one looks at this camera from the outside (Figure 2.3): the relatively large white movie camera (1), a TV-camera with monitors (2), the hydraulic system (3) which is necessary to balance the heavy 35 mm camera, the electronic equipment (4) and finally two smaller details, a filter inserting device (5) and an external ventilator (6). Other changes become visible only after removing the side of the camera (Figure 2.4): the new light source (7) and a special shutter (8) to block the background illumination. There are other important changes which cannot be seen on these photographs such as the recoating of all lens surfaces, and mirrors (9) and the special filters (10). These 10 changes shall be discussed below in detail in as much as they are important to other investigators who may be interested in making similar fundus camera modifications.

(1) *Movie camera*: The currently used 35 mm movie camera (Flight Research Model IV-CXS Multidata Camera, Giannini Scientific Corporation, Richmond, VA, USA) allows angiograms to be made at a frequency of between 1 to 40 frames per second. The maximum shutter opening time for this camera is relatively long; for example, it is more than 1/30 second at 10 frames per second and 1/50 second at 20 frames/sec.

(2) *TV-camera*: This black and white TV-camera is integrated in the observation optical pathway by a beam splitter. However, producing relatively poor spatial resolution, there is no regular use for a TV-camera in routine choroidal angiography, but it is used at the end of an angiographic sequence to confirm that the intravenously injected dye reached the eye.

(3) *Hydraulic system*: When a heavy movie camera is added to a fundus camera, the additional weight must be balanced. A simple device by which this may be accomplished is a counterbalance consisting of a wire rope attached to the movie camera and running through a ceiling-mounted pulley to a counterweight. While cheap, such a simple device quite markedly reduces the mobility of the fundus camera, therefore, instead in our system, a special hydraulic balance system has been built which guarantees unrestricted movement of the camera.

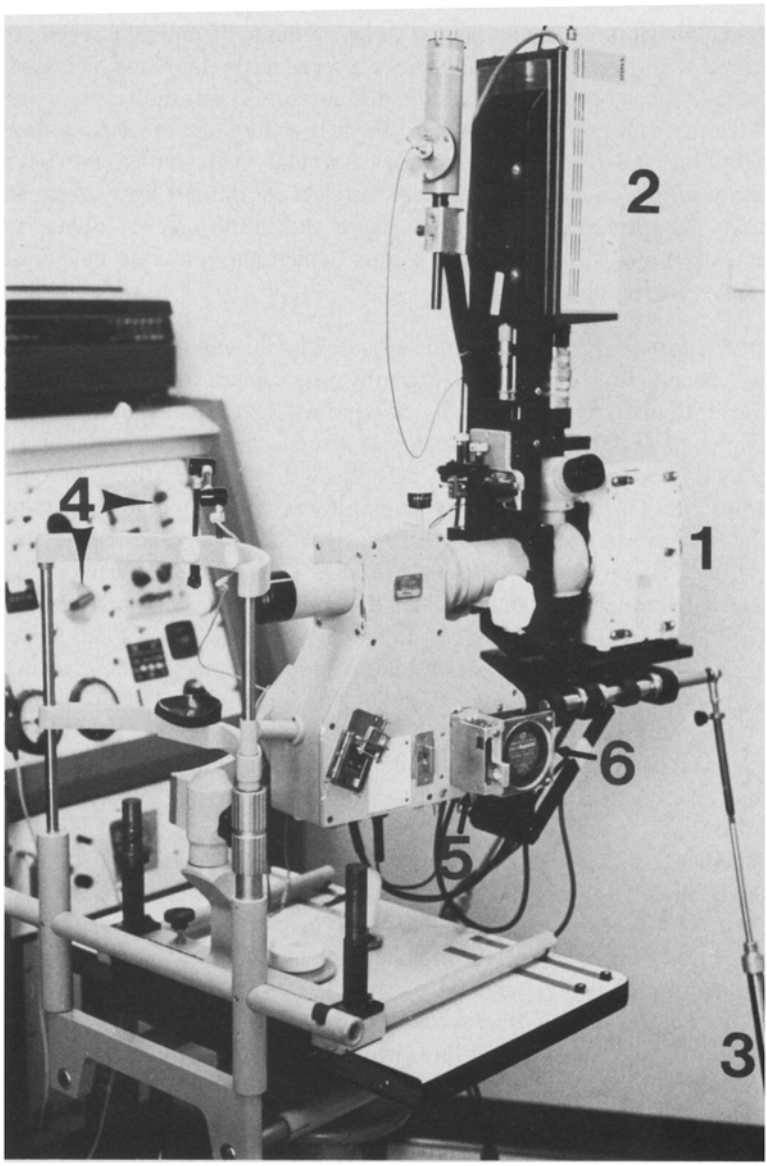

Figure 2.3. Picture of a Zeiss fundus camera adapted for choroidal angiography (R.W. Flower). (1) 35 mm movie camera; (2) TV camera (black and white); (3) Part of the hydraulic support system; (4) Electronic control unit; (5) Inserting device for the ICG-excitation filters; (6) Ventilator to cool the light source.

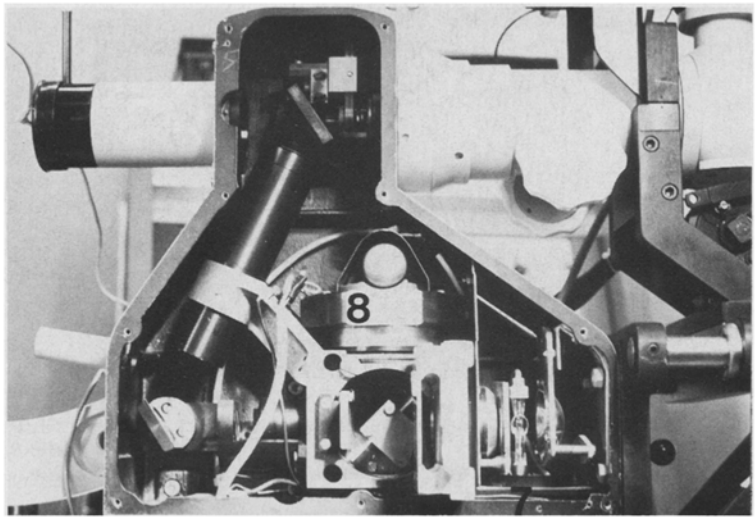

Figure 2.4. Picture of the camera body, sidewall open. (7) Illumination system; (8) Shutter to block the background illumination during the photography.

(4) *Electronic equipment*: A central unit controls the following functions:

– A computerized timing system preheats the continuous light source for 90 seconds before use, allows the firing of the movie camera for another 150 seconds and finally assures cooling of the light source by the external ventilator mentioned earlier.

– While exposing angiograms, a metal-shutter inserted between the light source and the filters is opened automatically.

– Also while the 35 mm movie camera operates, the background illumination is excluded from the illumination beam by automatically closing a second shutter.

– The movie camera itself starts running at the end of a preset interval after the photographer or the physician making the dye injection presses on a foot-switch. The total filming time also is preset.

– The camera mode may be easily changed from "continuous" to 'single frame' operation, and also the choice may be made between movie and the TV camera.

(5) *Filter inserting device*: The excitation filters should both be placed in the usual filter holder of the Zeiss-fundus camera when using a strong continuous light source. The light converges to a focus there, and the heat produced can damage the filters, possibly exposing the patients to dangerous unfiltered light. The filters, therefore, must be installed in such a manner that essentially parallel light from the light source passes through them; this evenly distributes the light energy over a large filter area, thereby avoiding excessive heating of the filter material. The best place to install the filters is behind the

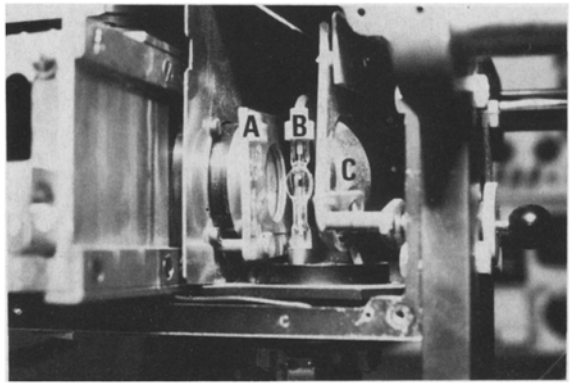

Figure 2.5. Higher magnification view of the illumination system. (A) Metal shutter for the protection of the filters before and after the photography; (B) 300 watt indium iodide lamp, part of the 'MARC-300 high brightness lighting system'; (C) Concave mirror for intensification of the light emission.

diagonal mirror which reflects background illumination into the eye. A special filter inserting device has been built and placed in the fundus camera between the diagonal mirror and the light source (see Figure 2.5).

(6) *Ventilator*: As is the case with slide projectors, the special fundus camera continuous light source must be cooled constantly. In order to attach the necessary small ventilator, a hole was made in the removable side plates of the Zeiss fundus camera body in such a way that circulating air passes over the lamp. Also a small air exit post was installed on the opposite side of the fundus camera body.

(7) *Light source*: (Figure 2.5). To obtain the maximum amount of infrared light, the filtered output of a continuous 300 watt indium iodide lamp is used (MARC-300 high brightness lighting system, General Electric). A concave mirror was mounted behind the lamp so that the back image of the lamp is focussed onto the arc thereby increasing the amount of energy collected by the fundus camera optics. It was also necessary to insert a metal-shutter between the lamp and the filters in order to prevent unnecessary filter heating and also to prevent light exposure of the patients's fundus prior to filming the dye passage.

(8) *Background focussing illumination*: While necessary for the initial adjusting and focussing of the camera, this illumination is excluded from the light entering the patients's eye during filming by means of a shutter interposed between the background illumination source and the diagonal beam-splitter location just in front of the excitation filters.

(9) *Lenses and mirrors*: In order to optimize infrared light transmission along the optical pathways, all 14 lens surfaces of the fundus camera (except for the aspheric objective lens) were antireflection coated for best transmission of the infrared light. This resulted in 40% greater transmission

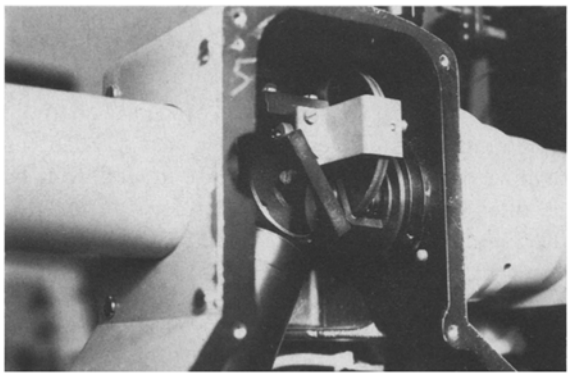

Figure 2.6. Higher magnification view of the upper diagonal mirror. The central hole has a diameter of 10 instead of 5 mm.

than was available using the original lens coatings (Hyvärinen and Flower, 1980). In addition, the diagonal mirrors were recoated with quartz-clad silver which improved the light transmission by another 25%. The most important step in increasing the amount of ICG fluorescent light emitted by the eye available for exposing the film was doubling of the diameter of the aperture hole in the upper diagonal mirror form 5 mm to 1 cm (Figure 2.6). This resulted in a four times increase in fluorescence light energy impinging on the photographic film. Unfortunately, this change also produces a small circular reflex which is always present on the angiograms as an artifact. It is noteworthy that although an increase in spherical aberration and a reduction in depth of field are produced as a result of this modification, no such significant changes in camera function were observed.

(10) *Filters*: Optimal filters generally have narrow bandwidths and high transmission of the center wavelength of light for which they are designed. With regard to the excitation and emission spectrum associated with ICG-fluorescence, these center wavelengths range around 795 nm and 835 nm, respectively. The following combination of filters has proved to be best suited for our type of modified camera and continuous light source:

– *Excitation filters*: The following combination of three filters, placed side-by-side, used in the filter inserting device near the light source:

a) Cold mirror (Melles Griot, Irvine, CA). This element reflects light with wavelengths below 700 nm and transmits those of higher wavelengths.

b) ICG-Exciter filter (Ditric Optics, Inc, Marlboro, MA). This filter excludes wavelengths between 700 and 730 nm and between 850 and 1000 nm.

c) Corning 7-69 red filter (Corning Med. & Scientific Glass Works, Medfield, MA). This filter blocks a substantial amount of infrared wavelengths above 1000 nm.

– *Barrier filter*: This filter must be placed between the fundus camera

body and the 35 mm camera body using a small filter adapter. Consequently, the film plane is moved back a little bit, and the viewfinding of the 35 mm camera is obstructed. It is necessary therefore, to readjust the film plane to match the focus of the ocular in the fundus camera. Also in order to correct the chromatic aberration of infrared vs. visible light wavelengths (redshift), it is necessary to move the film plane back. We use the following barrier filter:

ICG-Barrier filter (Ditric Optics, Inc, Marlboro, MA). This filter has a relatively wide transmission band between 800 and 900 nm. In combination with the reduced film sensitivity which exists above 800 nm, however, a relatively narrow bandwidth is effectively produced.

Compromise solution. A compromise can be made between the above clinically proven but complex and expensive camera system and some simplified camera system for use by other clinicians and investigators without significant sacrifice of information about choroidal circulation.

The use of a standard 35 mm camera with a motordrive instead of an expensive and heavy high-speed movie camera would lower the cost significantly, there would also be no need for a hydraulic balance system. One must, however, be aware that a minimal exposure time of approximately 1/60 second per frame is necessary for infrared photography with a continuous light source. With currently available motordrives, a maximum frequency of about 4–5 frames per second can be obtained; that might satisfy most clinical needs. Moreover, future improvements in cameras and motordrives can be expected which might allow still higher frequencies with such equipment.

An additional TV-camera is not necessary for clinical purposes, and the amount of electronic equipment may be reduced, requiring however that the photographer manually perform all the necessary steps for the filter insertion, pre-heating of the light source, etc.

Changes similarly to those mentioned in the paragraphs about the 'maximum solution' which must be made are the following:

– continuous light source (7) and ventilator (6)

– new placement of the filter inserting device (5)

– blocking of the background illumination (8)

– changes in lenses and mirrors. While a recoating of all the lens surfaces would be difficult and expensive to perform, only recoating of the mirrors and the enlargement of the mirror aperture are recommended in this approach (9).

While it would be feasible to make all these adaptions in a way that they could be quickly and reversibly implemented, it would be much easier to assign one fundus camera only for ICG-angiography and to use a second camera for standard fundus photography and fluorescein angiography. For performing ICG-angiography there is really no need for the newest model of a Zeiss fundus camera; an older model camera can be used as long as its optics are intact.

Minimum solution. If the aim to achieve a moderate to high time frequency is abandoned but the desire to photograph the choroidal vessels in certain patients remains, the original xenon flash light source can be used, and most other features mentioned here, such as replacement of filters or changes in mirror apertures need not be included. Only the following readily reversible adaptions of a Zeiss fundus camera need be made to perform choroidal angiography (in addition, that is, to use ICG as the dye and infrared sensitive film).

1. *New filters:*

a) *ICG-Exciter filter* (Ditric Optics, Inc, Marlboro, MA) This filter may be placed in the illumination light pathway of the Zeiss fundus camera at any point where the beam is nearly parallel and left there temporarily or even permanently, since it does not influence visible wavelengths below 700 nm (Flower, 1977).

b) *Kodak Wratten Filter #88A or 25* (Eastman Kodak Co, Rochester, NY). It may be put in the original filter inserting device or filter wheel of the Zeiss camera. It blocks visible light and, therefore, has to be removed for the focussing of the patient's eye.

c) *ICG-Barrier filter* (Ditric Optics). This filter must be installed between the fundus camera and the photographic film; additionally, the film plane must be adjusted somewhat.

Film, film development. While there is currently no other good choice, we have always used 'High Speed Infrared (black and white) Film' from Eastman Kodak Co. Its ASA speed is 125, but it may be pushed by prolongated development time up to about 400. Its *theoretical* resolution, compared to Kodak Tri-X film which is often used for fluorescein angiography is only about 50% (63–80 lines/mm).

Being infrared-sensitive, the film must be handled in total darkness before it is developed. In our hands, the following development times and chemicals have proven to be best suited for ICG angiograms:

– 15 min development at a temperature of 68 °F (19 °C) with Kodak liquid X-ray developer and replenisher, Cat. 1465327.

– 2 min fixation with Kodak rapid fixer, Cat. 1464106.

– about 5 min washing ('Permawash' and water).

2.2 Procedure for high-speed choroidal angiography

Besides the right equipment, an optimal conduct of the photographic procedure is crucial in choroidal angiography. The use of the infrared light, for instance, precludes the photographer from concomitantly observing the fundus and from timing the beginning of filming so that it corresponds to the first appearance of dye in the eye. The timing, therefore, must be based on a mean arm-retina time of about 10 seconds in young, and about 12–14 seconds in older patients (Bloome, 1980). Also an optimal injection

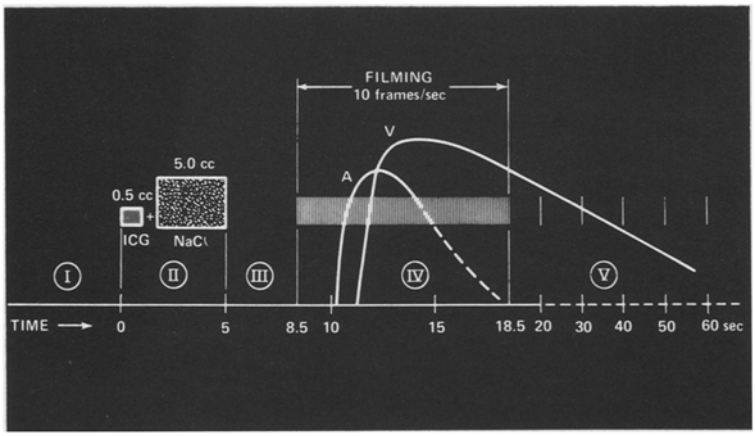

Figure 2.7. Schematic representation of choroidal angiography in relation to time. (I) Preparations; (II) ICG injection; (III) Interval (details in the text); (IV) Filming; (V) Late single frame pictures; (A) ICG-concentration in choroidal arteries; (V) ICG-concentration in choroidal veins.

technique is very important (Flower, 1973). To obtain maximum fluorescence of ICG in blood requires a dye concentration of 0.03 mg/ml. Since the dye is diluted after the injection in the cubital vein by about 600 times before it reaches the eye, approximately 20 mg ICG/ml have to be injected rapidly and be followed by a saline flush. In detail, our procedure is as follows (Figure 2.7):

(I) Preparations: Before the patient is seated in front of the camera, some security checks are recommended. With regard to the camera, a quick safety check of the filter system is necessary if one uses a continuous light source. We hold a sheet of white paper in front of the fundus camera – if a faint red ring appears, the filters are intact and in place. If, however, white light is visible, then there is not sufficient filtration, and the retina could be damaged. Based on the extant report of patients side effects observed with ICG, the following contraindications have to be considered: Allergy to iodide, uremic or hemodialysed patients and a general allergic diathesis that may increase the risk for an anaphylactic reaction. If ICG is not contraindicated, the patient may then be seated before the fundus camera which must be focussed on the fundus using visible light. The procedure must be explained in detail to the patient, with attention to 10 seconds of the filming period during which he must keep his eye open and steady. Finally, the light source may be preheated for about 90 seconds before the dye injection takes place.

(II) ICG injection: We inject the following dosage of the dye and saline flush into an antecubital vein using a four way stock and 2 syringes:

– 25 mg Cardiogreen in 0.5 ml aqueous solvent
– 5 ml physiological saline solution.

The total injection time is about 5 seconds.

(III) Interval between dye injection and beginning of the filming period: After the injection, the physician, or the photographer, activate a footswitch. 3.5 seconds later the camera begins to fire. With most patients, the dye appears about 2 to 4 seconds after beginning of the film period, but if the injection was made slowly, the initial dye-wavefront was sometimes missed as it moved through the choroidal vessels.

(IV) Filming: Currently we use a camera speed between 8 and 10 frames per second over a period of 10 seconds. During that period, the photographer can only adjust the camera to track major movements of the patient's eye, by carefully observing the red ring on the cornea. He is not able to observe the fundus during filming.

(V) Late single frame pictures: In order to recognize a potential dye leakage and to examine, at least in the late venous phase, other regions of the fundus, including the posterior pole and the periphery, several photographs can be made during the 2–3 minutes following filming of the initial dye passage.

2.3 Limits and side effects of choroidal angiography

Not only technical but also anatomical factors limit the resolution of choroidal vessels.

– The theoretical optical resolution of the Zeiss fundus camera is excellent, about 5 μm, while the currently available film can resolve only about 20 μm at near infrared wavelengths. The theoretical optical resolution of the human eye itself has been calculated to be 11 μm at 830 nm (Flower, 1976).

– The fluorescence intensity of ICG in blood is small, about 25 times less than that of fluorescein. A slightly different dye with a fluorescence three times stronger than ICG but with otherwise identical properties, dibenzodicarbocyanine, has been successfully tested in animals (Hochheimer, 1979), but it is not yet approved for human application.

– The anatomy of the ocular fundus itself, however, is the main obstacle to obtaining a sharp photographic image of choroidal vessels. The melanin in the pigment epithelium and the choroid also scatters infrared light, and the choriocapillaris, when filled with the dye forms a sort of neutral density filter. In a myopic eye with only slight pigmentation, for instance, the choroidal arteries are far better visualized in the angiograms than normally (Figure 3.1). Moreover, the three-dimensional structure of the choroidal circulation, with a blood flow sometimes directed parallel to the optic axis, will never be resolvable to the same extent as the nearly two-dimensional, more superficial retinal circulation.

While some technical problems. such as the relatively poor resolution of infrared film may be solved in the future, the anatomical factors will persist. The choroidal angiograms need not to be judged by their aesthetical

appearence but by the information they uniquely provide about the choroidal circulation.

With regard to possible *side effects of choroidal angiography*, two questions have to be answered: (1) How safe is the intravenously injected dye? (2) Is the infrared light toxic to the eye?

(1) Toxicity of ICG. There are enough data to answer this question because the dye has been widely used for cardiologic and hepatic studies since 1956. Also since 1972 we have had additional experience as a result of performing choroidal angiography.

Animal experiments have shown that ICG is nontoxic in dogs and rabbits (Fox and Wood, 1960), also in mice if given intravenously at a dosage below 35 mg/kg (Lutty, 1978) or intraperitoneally below 50 mg/kg (Lutty, 1979). In monkeys, circulatory and respiratory parameters remained normal up to a dose of 10 mg/kg (Tokoro et al., 1976). More important than results of animal experiments are data about side effects observed in humans. In chronological order we will list the significant data we have found in the literature:

– Fox and Wood (1960) reported on cardiologic studies in about 1000 patients. Using a dosage between 2 and 5 mg/kg they never observed any side effects.

– Cherrick et al. (1960) had the same experience with their hepatic studies. The inadvertent subcutaneous injection of ICG in one case did not damage the tissue.

– Leevy et al. (1976) recommended ICG for hepatic studies, toxic and idiosyncratic reactions being neglectable. They seldom found a vesicular rash after the injection of the dye.

– Habozit (1976) reported 62 choroidal angiographies performed without any complication, using the high dose of 150 or 200 mg ICG per patient.

– Carski et al. (1978) reviewed all side effects reported to the producer of the dye. They estimated a total of 240,000 ICG injections having been done by that time. In the earlier years, while it was not yet widely known that Cardiogreen contains up to 5% iodide, some complications occurred in patients allergic to jodide. In addition, 4 patients treated in 4 different hospitals suffered the following adverse reactions:

Seventy year old female; 5 min after the injection of 5 mg/kg ICG urticaria began, but disappeared with Benadryl. Allergologic tests were negative for ICG.

Sixty-six year old male with a history of asthma; shortly after the injection of 5 mg ICG in a cardiac catheter, an anaphylactic reaction occurred with nausea, respiratory distress and general vasodilation. Immediate therapy with cortisone, adrenergic and antihistaminic drugs was successful.

Forty-six old male with a history of allergy to penicillin and sulfonamides; immediately following the injection of 5 mg ICG in the superior vena cava, a

severe anaphylactic reaction was noted with nausea, heat sensation, dyspnea, tachycardia and low blood pressure. That patient died. It is noteworthy, that he had taken several other medications during the preceding 24 hours, namely Inderal, Aldomet, Hydrodiuril, Isordil, Lithiumcarbonate, potassium chlorid, Nembutal, Demerol and Atropine.

Forty-eight year old male; shortly after intravenous injection of 27 mg ICG also had a severe anaphylactic reaction, but immediate and rigorous treatment was successful.

– Shabetai and Adolph (1980) found no cardiovascular side effects of ICG in their cardiologic studies.

– Iseki et al. (1980) studied circulatory parameters in 43 patients that underwent chronic hemodialysis. Three patients suffered from nausea, and one patient with a history of asthma had a fully reversible anaphylactic reaction.

– Bacin et al. (1981) reported an inadvertent subcutaneous injection of ICG. Beside the some weeks notable skin discoloration there were no consequences. They overviewed 40 choroidal angiographies using their high dose of 200 mg ICG, but they never saw any adverse reactions.

Reviewing our own experience with about 700 human choroidal angiograms we never saw any side effects. Compared to fluorescein, ICG did not disturb the patients at all, particularly there was no nausea. One inadvertent subcutaneous injection led only to discoloration of the skin for several weeks.

In conclusion, ICG dye is relatively nontoxic, but one must be aware of the risk of rare but severe anaphylactic reaction. In comparison to the risk with fluorescein, where 5–20% of the patients suffer from nausea, headache or dizziness, 5–10% exhibit allergic reactions (Bloome, 1980), and where a life threatening complication has been calculated to occur in 1 out of 20,000 injections (Enzmann and Rupredit, 1982), the risk with ICG seems to be minor. It is however necessary to be prepared with medications and equipment to immediately treat any anaphylactic reaction. This requires the same equipment that should be ready in every laboratory that performs routine fluorescein angiography. Moreover, angiography should not be performed in patients with a history of severe allergies or in the especially sensitive uremic patient.

(2) Toxicity of infrared light. The modified Zeiss fundus camera with a continuous light source, produces 200 mW of power. Therefore, retinal light exposition is below 200 mW/cm_2. Because the light is focussed on the lens, light exposition there is higher; it is 1 W/cm_2 maximum. Using our filter combination this light mainly consists of wavelengths between 730–850 nm. The duration of exposition is 10–15 seconds.

(2a) Retinal damage from infrared light. Retinal light damage may be produced mechanically (high energy lasers), thermally (after absorption in the

pigmented layers of the fundus) or photochemically (blue light damage) (Sliney, 1982). In ICG angiography, we only consider the possibility of thermal damage. Acute retinal damage is to be expected when the retinal temperature rises about 10 °C; this is possible only with light energies above 1 W/cm_2 (Sliney and Wolbarsht, 1980). While no standards exist which precisely address retinal exposure by a narrow-band multiwavelength continuous light source like we use, a worse-case approximation can be made in order to apply safety standards for laser light exposure. Considering the light emission of the camera to be like a laser source of 730 nm wavelength (the shortest wavelength emitted by our camera system), according to the exposure level recommended by the *American National Standards Institute (ANSI), 1976*, the safe exposure time would be at least 20 seconds (Hyvärinen and Flower, 1980). Therefore, the risk of retinal damage is neglectable when using appropriate camera filters and the recommended exposure time of about 10 seconds. One must, however, be aware that the risk increases significantly if the filters are not placed correctly. The energy of the unfiltered light from the continuous light source amounts to about 1W/cm_2 on the retina and contains harmful short wavelengths of the visible spectrum.

(2b) Lens damage by infrared light. Since Wenzel (1786) first mentioned the high incidence of cataracts in glassblowers, several experiments have shown that infrared light may cause cataract formation, either directly (Vogt, 1919; Wagner, 1938) or indirectly by heating the iris (Goldmann, 1932). In rabbits, cataract formation was initiated with a CW-Neodynium-YAG-Laser (emission at 1065 nm) when the dose exceeded 100 Joules (Wolbarsht, 1980). Another study in rabbits and monkeys suggested an exposure safety level of about 4000 Joule/cm_2 (Pitts et al., 1980). Our exposure amounts to 1 Watt/cm_2 maximum during 10 seconds, or 10 Joule/cm_2. The risk from choroidal angiography for the lens is therefore neglectable.

3. Normal choroidal vascular patterns

Since the ophthalmologist always examines the retinal vessels with the ophthalmoscope, understanding fluorescein angiograms of the retina is not too difficult. However, initially choroidal angiograms are difficult for the investigator to interpret because there is usually no such familiarity with the choroidal circulation. Moreover, the choroid is a three-dimensional vascular network in which blood flow is often perpendicular to the film plane of the fundus camera. Finally, the resolution of choroidal angiograms seems poor compared to the usually crisp retinal fluorescein angiograms (part 2.3). Nevertheless, with experience, one will learn to gain more and more information about the choroid from these angiograms, information that may prove to be as valuable as information taken from a fluorescein angiogram.

Up to now about 180 choroidal angiograms have been performed in 105 normal volunteers. In 1974 a series of studies with the multispectral camera was done, in which simultaneously made ICG-fluorescence-angiograms, ICG-absorption angiograms and fluorescein angiograms could be compared; these were made, however, at a relatively slow frequency of 1 picture per 0.7 seconds. The age of the volunteers ranged between 15 and 39 years with a mean of about 24 years. Both morphological and dynamical criteria were used to interpret choroidal angiographic studies. Besides the pattern, the thickness of the layers of the choroidal arteries and veins, the filling pattern of the choroid must also be considered. Often a regional or general delay of choroidal filling may prove to be the only sign of a pathologic choroidal process.

3.1 Morphology of the choroidal vasculature in the ICG-angiogram

Deriving from the short posterior ciliary arteries, the *choroidal arteries* originate at the posterior pole, mainly around the macula and nasally to the disc. They then lead almost radially toward the equator of the eye (Figure 3.1). Sometimes the arteries divide near their origin into two branches, but there is no regular dichotomic branching as in the retina. In comparison to the veins, the arteries are somewhat smaller and appear less fluorescent and more meandering. The individual vessels of the *choriocapillaris* are not resolved with our technique (part 2.3). However, the filling pattern of the choriocapillaris can be recognized as a faint and diffuse fluorescence. The *choroidal veins* are more impressive on the angiograms than the arteries. About 2–4 seconds after the first filling of choroidal arteries, the veins at the posterior pole are well visible. These veins lead in the direction of the 4 vortex veins (Figure 3.2), which may even be visualized by this technique. While in most eyes some veins pass through the submacular choroid, sometimes the border between superior and inferior veins form a raphe.

3.2 Normal choroidal filling pattern

Results of high-speed choroidal angiography clearly show that the choroidal arteries fill earlier than the central retinal artery. In a small series of young volunteers this filling time difference ranged between 0.5–1.0 seconds, calculated from angiograms made at a frequency of 8 frames/second. The early choroidal filling, compared to retinal filling, may be due to a higher velocity of blood flow in the short posterior ciliary arteries than in the central retinal artery. The difference in distances between the ophthalmic artery and the choroid and the opthalmic artery and the disc cannot along explain this different filling between choroid and retina (Parr et al., 1968). The earliest detectable arteries are most often those between the macula and the disc, sometimes those temporal to the macula. The highest blood perfusion pressure of the eye has been shown to be in these vessels (Flower, 1972).

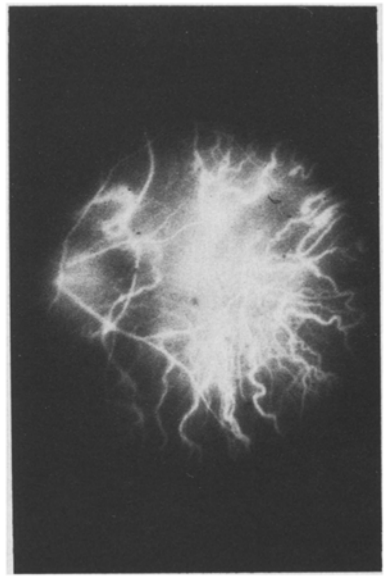

Figure 3.1. ICG angiogram showing the choroidal arteries. Young myopic patient, left eye, 3.0 sec. The choroidal arteries derive from the posterior ciliary arteries which enter the eye at the posterior pole. They extend radially toward the equator.

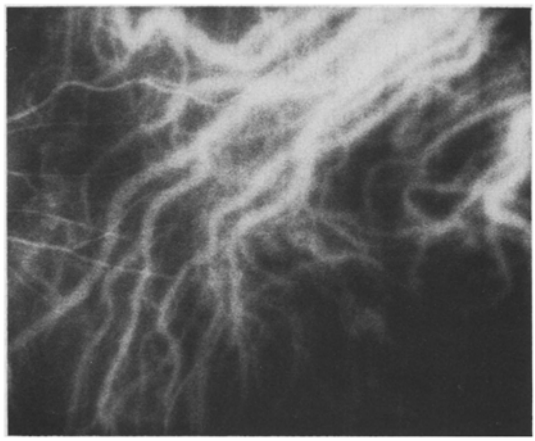

Figure 3.2. ICG angiogram showing the choroid veins. Seventy-one year old normal volunteer, left eye, 6.0 sec. Multiple rows of choroidal veins extend toward the four vortex veins.

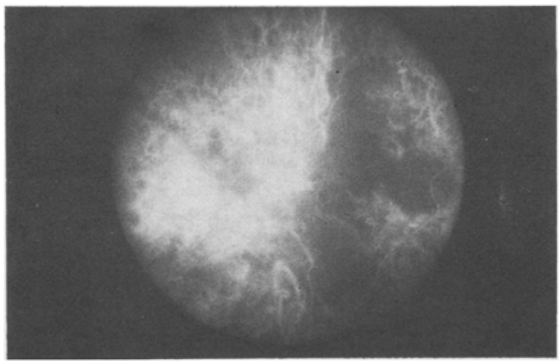

Figure 3.3A. ICG angiogram 0.7 sec. Choroidal arteries are visible at the posterior pole, beginning choriocapillaris filling in the submacular choroid.

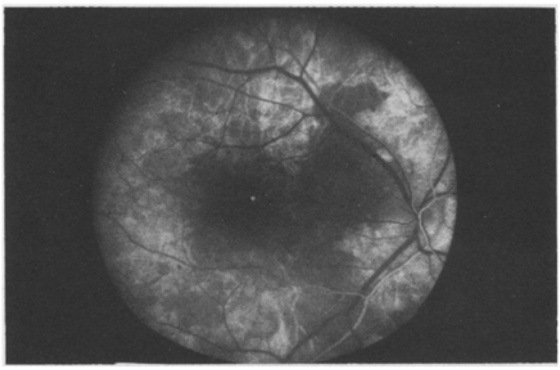

Figure 3.3B. Fluorescein angiogram 0.7 sec. Early filling of the main retinal arteries. The macula appears black (due to absorption by xanthophyll), but around the macular some choroidal arteries are visible.

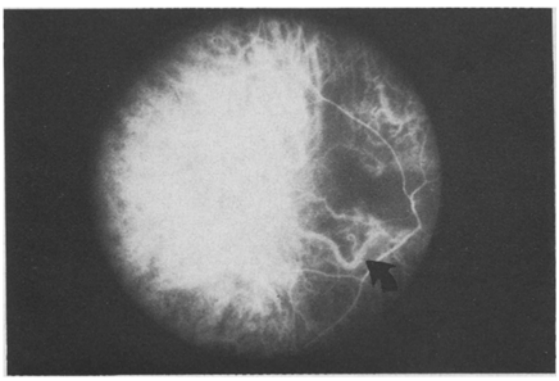

Figure 3.3C. ICG angiogram 1.4 sec. Early venous phase in the choroid. In one vein temporal to the disc (arrow) laminar flow is visible.

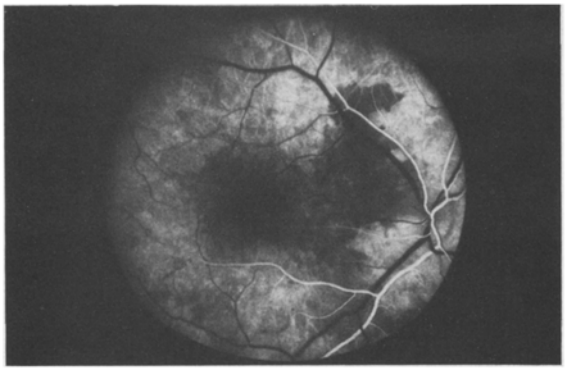

Figure 3.3D. Fluorescein angiogram 1.4 sec. Arterial phase in the retina. Leakage from the choriocapillaris masks already filled underlying choroidal vessels except in a region temporal to the disc, where the choriocapillaris has not yet filled (patchy filling of the choriocapillaris).

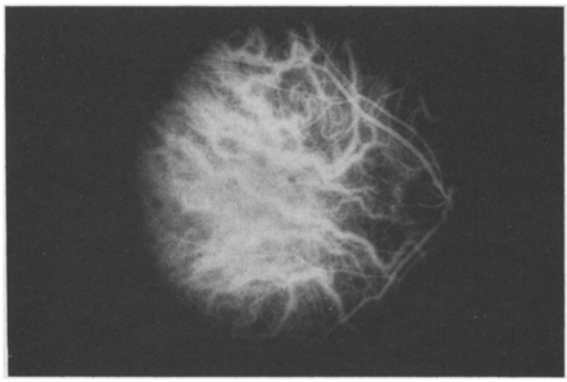

Figure 3.3E. ICG angiogram 6.3 sec Good filling of the choroidal veins. The main retinal vessels are visible in this angiogram too, but the resolution of smaller retinal vessels is poor.

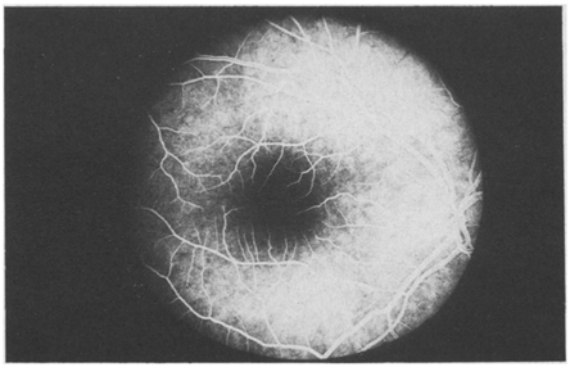

Figure 3.3F. Fluorescein angiogram 6.3 sec. Retinal venous phase. All veins are filled, but the retinal arteries are still visible. Uniform background fluorescence. Note the 'black macula'.

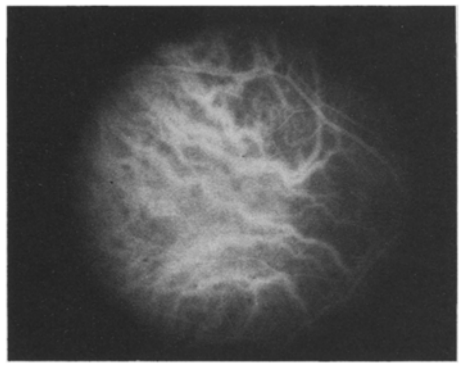

Figure 3.3G. ICG angiogram 14.0 sec. Late venous choroidal phase. The choroidal veins are still visible, but they are less filled with ICG than earlier. No leakage of the dye may be seen.

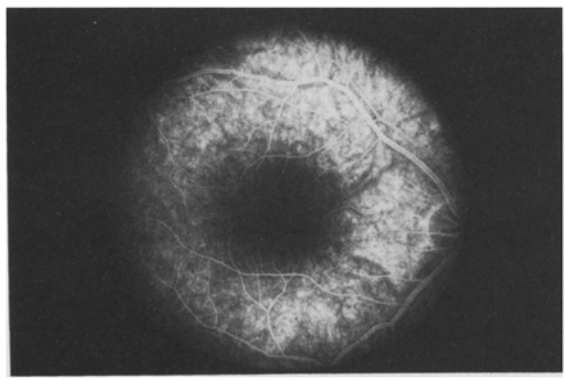

Figure 3.3H. Fluorescein angiogram 14.0 sec. Late venous retinal phase. Reduced concentration of fluorescein in the retina and the choroid, where some large choroidal vessels become visible (negative contrast).

Figure 3.3. Comparison of the normal filling characteristics between ICG- and fluorescein angiography. Twenty-six year old normal volunteer, right eye (simultaneous photography).

The different phases of a normal choroidal angiogram are presented in comparison to the simultaneously-made fluorescein angiogram in Figure 3.3. We found the following mean intervals in 21 normal volunteers studies with the multispectral camera:

choroidal artery
– choroidal vein: 1.8 sec.
central retinal artery
– retinal vein laminar: 2.0 sec.
Central retinal artery
– retinal vein full: 6.2 sec.

Some variation can be found in very young and in black individuals. The submacular choroid is only faintly visible in young eyes, probably because of the extensive pigmentation and a dense choriocapillaris. In black individuals, with their dense fundus pigmentation, we seldom produced choroidal angiograms of good quality, the vessels all being appearing faint. Therefore, the value of ICG-angiography in blacks seems to be limited.

3.3 Relation between ICG- and fluorescein-angiography

A comparison of these two angiographic techniques which use similar equipment demonstrates the information about retinal and choroidal vessels produced by each of them. Does one or the other type angiogram produce enough data to forego the other type? Or must both types of angiography be combined to understand the circulation in the fundus oculi? We will consider the information we get from fluorescein studies about the choroid (1) and from ICG studies about the retina (2). Then some remarks about the combination of both will be made (3).

(1) What information does fluorescein-angiography give about the choroid?. Three factors limit the value of fluorescein angiography for studies of the choroidal circulation:

Pigment in the pigment epithelium as well as in the choroid markedly absorbs and scatters visible light wavelengths (Figure 1.4A).

Xanthophyll in the macula absorbs the blue light wavelengths necessary for the excitation of fluorescein fluorescence. Therefore, a 'black-macula' prevents the study of the important submacular choroid when fluorescein is used.

Only about 80% of injected fluorescein is bound to plasma proteins. The circulating unbound molecules leave the fenestrated endothelial walls of the choriocapillaris, causing a diffuse interstitial fluorescence which masks the deeper lying choroidal vessels. The angiograms of a patient with a pigment epithelial defect (Figure 3.4) and such a defect combined with a loss of the choriocapillaris (Figure 3.5) demonstrate that the deep choroidal vessels would be visible on fluorescein angiograms were it not for the three mentioned obstacles.

Also in normal eyes, fluorescein angiography provides some limited information about the choroid. In very early pictures of not too heavily pigmented eyes, individual choroidal arteries may be visible (Figure 3.3B). Often patchy filling of the choriocapillaris is seen (Figure 3.3D). this is considered to be normal (Hyvärinen et al., 1969), Archer et al., 1970). Aside from these relatively unimportant aspects, in normal eyes fluorescein angiography does not provide much information about the choroid. In diseased eyes the changes in the pigment epithelium may lead, for instance, to a 'window defect' which more clearly shows the diffuse filling of the choriocapillaris. The deeper choroidal vessels, however, usually remain invisible. There is the

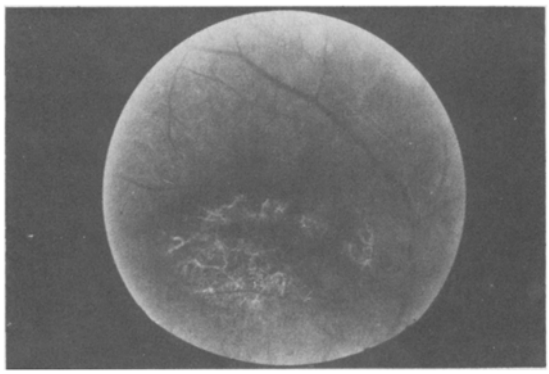

Figure 3.4A. '0' sec: (First appearence of dye in the eye): The central choroidal arteries and those in a peripapillary cone are visible.

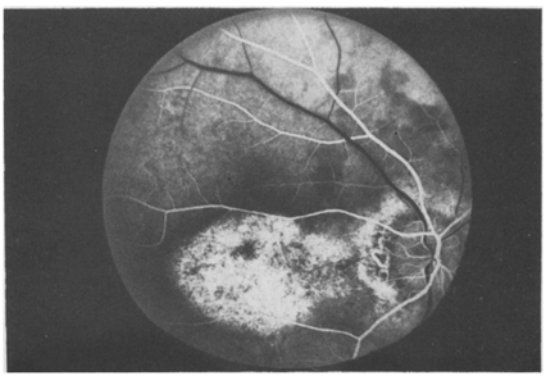

Figure 3.4B. 2.8 sec: Due to the leakage of fluorescein from the choriocapillaris, the deep choroidal vessels are masked. Some background fluorescence in the whole fundus, but less visible than centrally.

final consideration that the risk of phototoxic retinal damage by the blue light needed for fluorescein angiography is too high to allow the installation of a continuous light source needed for high-speed angiography.

(2) What information does ICG-angiography produce about the retina? There is no question that ICG fluoresces in the retinal circulation and that retinal vessels are also present on a so-called 'choroidal' angiogram. Therefore, could ICG-angiography alone produce enough data by which to examine the choroid as well as the retina? This is not the case. The retinal capillaries and

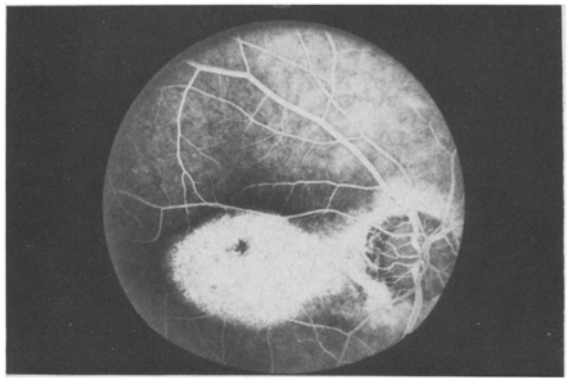

Figure 3.4C. 9.1 Sec: Venous retinal phase. Diffuse background fluorescence in the choroid.

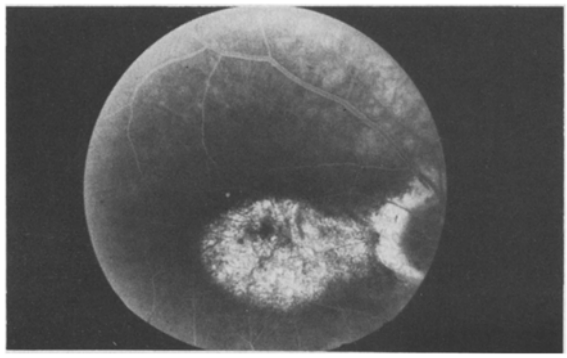

Figure 3.4D. Late picture: The central deep choroidal vessels are visible now as 'negative contrasts' since they don't contain any dye, yet some fluorescein remains in the choroidal tissue.

Figure 3.4. Fluorescein angiograms of a pateint with pigment epithelial defect (chloroquine retinopathy).

the smaller retinal arteries and veins are sometimes masked by the fluorescence arising from the underlying choroidal veins. There are, however, situations, where fluorescein angiography cannot be performed, for instance in photophobic patients and in case of a discrete vitreous hemorrhage. In such patients ICG-angiography does provide at least some information about the major retinal arteries and veins (Patz et al., 1976).

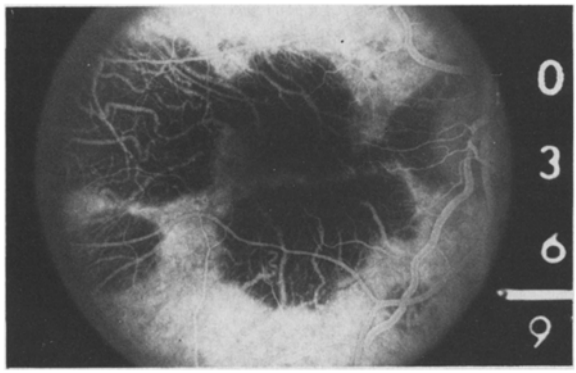

Figure 3.5. Fluorescein angiogram of a patient with pigment epithelial defect and loss of choriocapillaris. Sixty year old hypertensive patient, right eye. This example clearly shows that fluorescein doesn't leak from the large vessels. Therefore, if pigment epithelium and choriocapillaris don't mask these vessels, fluorescein angiography could be used for choroidal angiography too. In addition to the patchy regions of choroidal atrophy, the usual background fluorescence is visible.

(3) Combination of ICG- and fluorescein angiography. While each technique provides unique information, a combination of both of them seems to be necessary in all diseases of the fundus where a pathology may occur not just in the retina or just in the choroid, but possibly in both circulations. Should a multispectral camera comparable to the one used in Baltimore between 1973 and 1975 be used (part 2)? From the standpoint of convenience of the patient as well as the information about the ocular circulation obtained, such a combination would be ideal. At present, such a combination does not allow the best choroidal angiography, mainly because of the impossibility of high-speed filming whereby the amount of which would require phototoxic levels of blue light.

We recommend a sequential procedure in which the patient undergoes only one venous puncture. Two fundus cameras should be placed in the same examination room, one for ICG- one for fluorescein angiography. After the initial ICG-angiography which takes only about 1–2 min, the patient may move to the second camera for the injection of fluorescein, using the same intravenous catheter. If one uses two Zeiss cameras for the two studies, magnification of the two types of angiograms is the same. Negatives of ICG and fluorescein angiograms may also be overlaid to localize a subretinal neovascularization for instance.

4. Pathological choroidal patterns

The interpretation of pathologic choroidal angiograms is easy in the sense

that one need not first study several books and innumerable publications to find the correct and exact terminology and classification of the data obtained. The lack of a textbook and atlas of choroidal angiography, however, makes it sometimes rather difficult to separate important from unimportant findings. Therefore, dealing with a choroidal angiogram may sometimes be frustrating, especially when one cannot arrive at a clear interpretation to a given angiogram, but more often one may be fascinated by surprising new aspects about the relatively unknown choroidal circulation.

The results and angiograms presented in that chapter are based on the critical review of approximately 500 old and new studies performed at the Wilmer Institute in Baltimore since 1972 and in St. Gallen since 1983. Covering mainly changes found in senile macular degeneration, diabetic retinopathy and choroidal tumors, some typical pathologic choroidal patterns found in these diseases will be discussed. With regard to the relatively small number of patients in each group, these results do not pretend to be complete or always conclusive. On the other hand, they provide each reader with enough information to judge himself whether the interest in the choroid is really justified and, therefore, choroidal angiography should be added to his diagnostic tools or not.

4.1 Senile macular degeneration (SMD)

In correlation to the higher life expectancy, age-related disorders become more and more important. In ophthalmology, SMD is the main cause for legal blindness in the more than 65 year old population of the United States (*Macular Photocoagulation Study Group, 1982*). The prevalence of SMD has been calculated in the Framingham eye study. It ranges between 1.2% (52–64 years), 6.4% (65–74 years) and 19.7% (75–85 years) (Leibowitz et al., 1980). Despite its frequency, SMD is neither a uniform and well defined disease nor is its etiology and pathogenesis exactly known.

In most patients the so-called 'dry' type of SMD is present, ophthalmoscopically characterized by drusen and irregularities in the pigment epithelium. Five to ten percent of all patients with SMD, however, suffer from the 'wet' or exudative type (Leibowitz et al., 1980) with a detachment of the pigment epithelium, sometimes an edema of the sensory retina or even hemorrhage below and within the retina. The central visual acuity may be lost within a few days and a macular scar will finally result. In the last years laser treatment has proved to be helpful at least in some early stages of exudative SMD (*Macular Photocoagulation Study Group, 1982*), leading to a new interest of the ophthalmologists in early diagnosis of this disease. Fluorescein angiographic studies suggested and histopathologic specimens confirmed that often subpigment epithelial neovascularization occurs in these patients (Green, 1980). New vessels growing from the choriocapillaris through holes in Bruch's membrane are believed to cause hemorrhage and to be responsible for the bad prognosis at all. Early photocoagulation of such a neovascular network can sometimes prevent is progression.

It is still not clear why so many, especially degenerative diseases are located in the macular region. Is there any anatomical or physiological particularity to explain this strange predisposition? Several hypotheses have been made. For instance, the light exposition and the high activity of the foveal photoreceptors could play an important role. Age-related primary changes in Bruch's membrane could reduce the supply of oxygen and other substances to the retina at the posterior pole and so give rise to the outgrowth of new vessels (Wise et al., 1971, Green 1980). Finally, anatomical properties of the submacular choroidal vasculature could also be responsible for the common location of diseases in the macular region, probably mediated by one of the two following mechanisms:

(1) High arterial pressure: In the submacular choroid only short arteries and arterioles are interponed between the ciliary arteries and the choriocapillaris. In these arterioles that enter the choriocapillaris almost perpendicularly, high pressure and rapid blood flow can be expected (Ring and Fujino, 1967; Flower, 1972). Age-related loss of contractility in the vessel wall (Garner, 1982) could lead to a huge blood flow and a pressure rise in the adjacent choriocapillaris with consequent exudation of fluid through Bruch's membrane (Potts, 1966), hemorrhage or even subretinal neovascularization (Bischoff and Flower, 1983). In histopathologic specimens taken from a survey of patients with SMD (Green, 1980), we found several wide, dilated arteries in the submacular choroid (Figure 4.1). More extensive studies are necessary to distinguish between physiologic age-related changes and true pathologic vasodilation.

(2) The macula in the center of 'watershed-zones': The segmental organization of both arterial and venous side of the choroidal circulation could explain the susceptibility of the macular against chronic and general ischemic disorders, because the borders or the watersheds between those segments join in the macular region (Hayreh, 1975). One might suggest that in the dry type of SMD such a mechanism could play a role. Two earlier reports from the Wilmer Institute dealt with choroidal angiography in subretinal neovascularization. Patz et al. (1976) studied 25 patients with the clinical suspicion of subretinal neovascularization, but they were able to resolve a neovascular membrane with ICG-angiography in only 2 of them. Later one case was reported, where the results of choroidal angiography determined the mode of treatment, while the main artery leading to the neovascular network could be distinguished by this method from the corresponding vein (Hyvärinen and Flower, 1980).

We reviewed 52 choroidal angiograms of 39 patients with SMD examined between 1972–1978 and 61 angiograms from 48 patients studied in 1982 and 1983. We found 4 types of pathologic choroidal vascular patterns:

a) *Delayed and/or irregular choroidal filling:* While the mean value of the

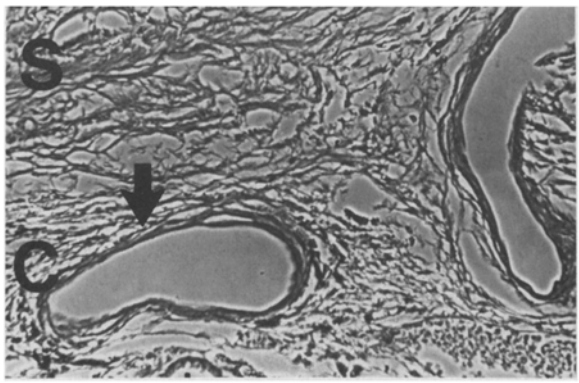

Figure 4.1. Dilated choroidal artery in a patient with disciform senile macular degeneration. (Histological section, H.E. × 25). Section through sclera (S) and choroid (C) of a 80 year old patient with SMD. The retina and the disciform lesion are detached (below the star, here not visible). Note the dilated choroidal artery in cross-section (arrow), probably a branch of the intrasclearally visible posterior ciliary artery (right). Courtesy of W.R. Green, Baltimore, Maryland. From 'Bischoff PM and Flower RW (1983) High Pressure in choroidal arteries as a possible pathogenetic mechanism in senile macular degeneration. Amer J Ophthal 96:398–399, AJO copyright'.

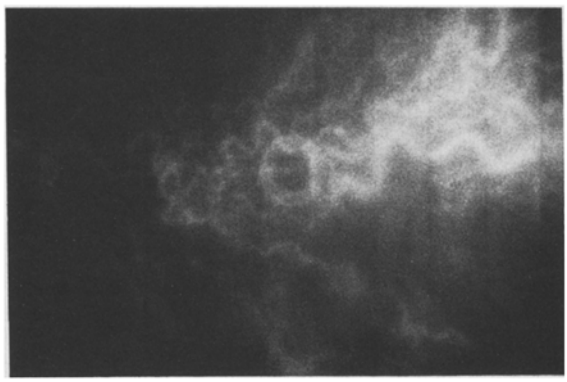

Figure 4.2. ICG angiogram in SMD: Meandering arteries. Sixty-nine year old patient, left eye, 2.2 sec. Meandering arteries and irregular choroidal filling may represent the signs of choroidal arteriosclerosis.

interval between first filling of choroidal arteries and choroidal veins was often in the normal range (2.0 seconds), in several patients these intervals were between 3.0 and 4.0 seconds long, suggesting a delayed choroidal circulation time. While in young normal volunteers the choroidal veins are entirely filled within about 1–2 seconds, in some patients this venous filling took up to 3.8 seconds. In the absence of enough data about the normal choroidal filling time in the older age groups, one has to be cautious with the diagnosis of 'delayed choroidal circulation time'. Easier to register are irregular filling

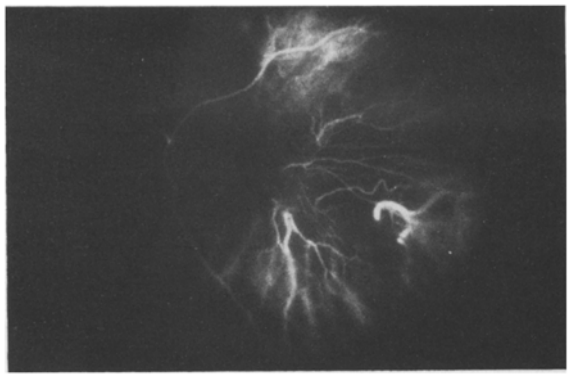

Figure 4.3. ICG angiogram in SMD: Dilated arterial loop. Fifty-eight old patients, left eye, 2.2 sec. Early filling of a dilated arterial loop in the submacular choroid. In the region of the dilated artery there is atrophy of the pigment epithelium and of the choriocapillaris.

patterns with an angiogram. In patients with SMD we found often the delayed filling of some areas of choriocapillaris (Figure 4.2). At this time such dynamic abnormalities cannot yet be correlated to the stenosis of a choroidal or ciliary artery. More clinical studies and the correlation to histopathologic findings would be necessary to allow such a diagnosis to be taken from an ICG-angiogram.

b) *Generalized arterial changes*: In some patients with SMD meandering arteries have been found (Figure 4.2), possibly a sign of arteriosclerosis. Here also, our numbers are too small to distinguish these pathological changes from normal age-related changes.

c) *Localized arterial changes (dilated vessel loops)*: In about 1/4 of our patients with SMD we found a marked dilation of one, seldom of 2–4 submaculat choroidal arteries. Typically those early filling vessels formed a small loop (Figure 4.3) sometimes they were more straight. The most striking feature was the anatomical relationship of these dilated vessels to pathologic macular changes (Bischoff and Flower, 1983). The vessel loops pointed then to a pigment epithelial detachment or to choroidal neovascular membranes (Figure 4.5). Occasionally these unusual choroidal vessels have also been seen underlying areas of pigment epithelial atrophy. We interpret these findings as a confirmation of the earlier discussed hypothesis explaining the predilection of the macula for degenerative diseases with the anatomical particularity of the submacular choroidal arteries.

d) *Subretinal neovascularization*: The results of choroidal angiography in this group of about 50 patients were disappointing and fascinating at the same time. It was disappointing because the resolution of a subretinal neovascular

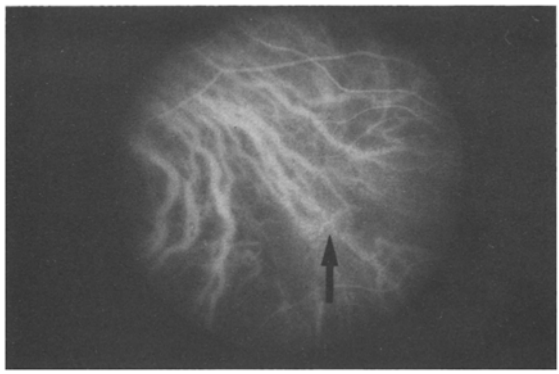

Figure 4.4A. ICG angiogram in SMD: choroidal neovascularization. Seventy-six year old patient, right eye, 7.7 sec. Almost perpendicularly to the choroidal veins a fan of new vessels is visible in the submacular choroid (arrow).

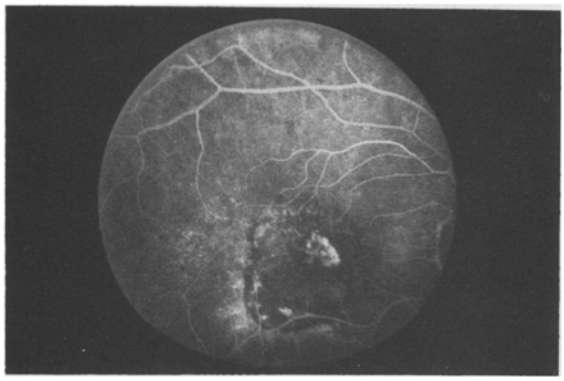

Figure 4.4B. Fluorescein angiogram (same patient) 8.4 sec. Central pigment epithelial defect, lacy fluorescence: suspected subretinal neovascularization.

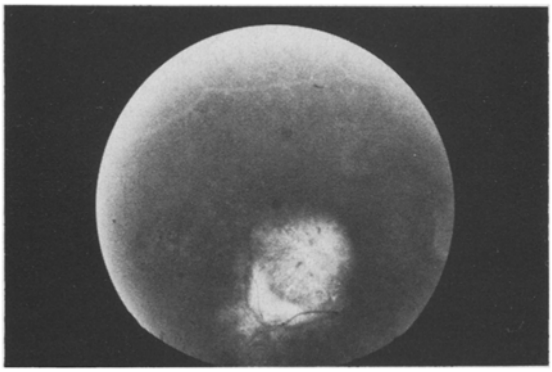

Figure 4.4C. Fluorescein angiogram (same patient) late picture. Diffuse fluorescein staining due to a pigment epithelial detachment and an elevation of the sensory retina.

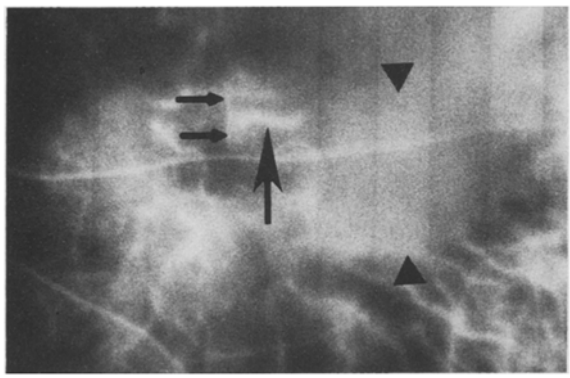

Figure 4.5. ICG angiogram in SMD: choroidal neovascularization and pigment epithelial detachment: Fifty-nine year old patient, left eye, 3.0 sec. A horizontal prominent choroidal vessel (*long arrow*) 'points' to the temporal pigment epithelial detachment (triangles) and to the vertical choroidal new vessel (*short arrows*).

membrane was possible only in one of ten patients before 1976 and in one of three patients at the present time (Figure 4.4, 4.5). Moreover, except in the already published case from Hyvärinen and Flower (1980), it was never possible to clearly distinguish between a feeding artery and the corresponding vein, a distinction necessary for focal treatment. The lack of resolution of these networks lies in their choriocapillaris-like structure, whereby the distances between two vessels are smaller than the vessels themselves. Also with fluorescein angiography it is often impossible to resolve these vessels, whereas the diagnosis of subretinal neovascularization is made by indirect criteria (Schatz et al., 1978).

Has choroidal angiography any value for patients with that type of SMD at all? With regard to the unknown etiology of the subretinal neovacularization careful studies of the choroidal vasculature may contribute important data that might resolve this problem. The topographical relationship we detected between the neovascularization and dilated choroidal vessel loops may be one such important bit of information. Moreover, studies of the influence of laser treatment of subretinal membranes to the choroidal circulation might help to understand better the importance and also the risks of the procedure.

4.2 Diabetic retinopathy

The terminology 'retinopathy' implies that diabetic changes in the ocular fundus mainly or solely are confined to the retina. To explain the potential value of choroidal angiography, three aspects will be discussed here first, namely the diabetic choroidopathy, the pathogenesis of the retinopathy and the influence of panretinal laser coagulation in proliferative retinopathies.

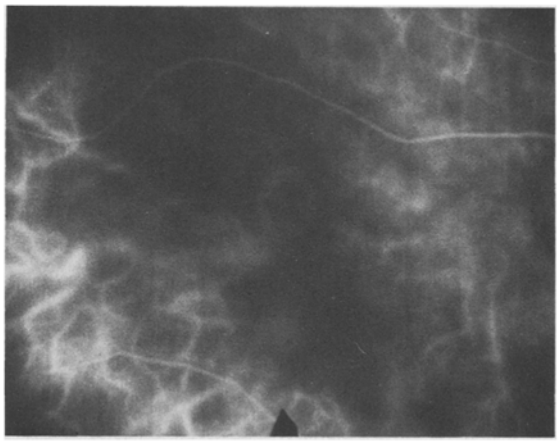

Figure 4.6A. 2.8 sec: Irregular and delayed filling of arteries in the submacular choroid.

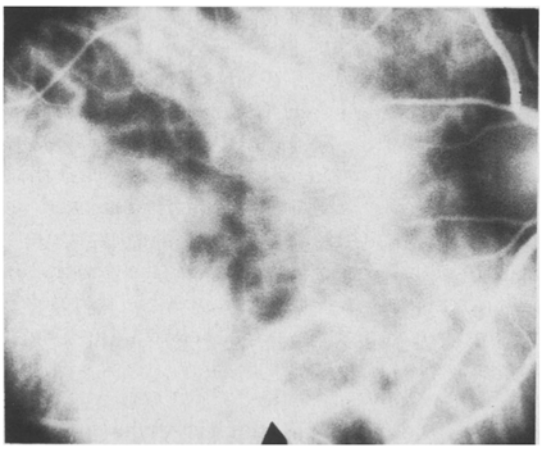

Figure 4.6B. 9.0 sec: The irregular fitting pattern is still visible.

Figure 4.6. ICG angiogram in diabetic retinopathy: irregular choroidal filling. Fifty-six year old patient with background retinopathy, right eye.

(1) Does a diabetic choroidopathy exist? Diabetic retinopathy begins as a microangiopathy. As in other parts of the body, also in the choroid subtle diabetic changes have been found in the vessel wall, for instance a thickening of the basal membrane in the choriocapillaris, in arterioles and also in Bruch's membrane (Naumann, 1980; Hidayat and Fine, 1983). Hypertensive changes also have been found frequently in choroidal arteries and arterioles of diabetic patients (Friedman et al., 1964). On the other hand, in the choroid an equivalent to the retinal neovascularization never has been described.

(2) May the diabetic choroidopathy influence the retinopathy? Several hypotheses have been tried to understand the etiology and pathogenesis of the diabetic changes in the retina. As primary lesion a hypoxic vasodilation has been postulated caused by the elevated oxygen affinity of Hb AIc that is increased in diabetics (Ditzel, 1976). Also the fluctuation of the glucose level in the blood proved to aggravate the disease in animal experiments (Engermann et al., 1977). Another hypothesis starts with the mentioned thickening in Bruch's membrane, leading to a reduced fluid transfer between retina and choroid with subsequent retinal edema and hypoxia (Colenbrander, 1975). The diabetic choroidopathy finally also could influence the retinopathy by reducing the supply of oxygen and fluid to the outer retinal segments (Hidayat and Tine, 1983).

(3) What happens in the choroid after panretinal photocoagulation? Panretinal laser treatment proved to be helpful for the majority of patients with mild to moderate proliferative retinopathy (*The Diabetic Retinopathy Study Group, 1978*). As the mechanism of this benefit, the destruction of hypoxic retina with subsequent reduction of the also hypothetical 'angiogenesis factor' (Patz, 1982) has been discussed. There is no question that laser photocoagulation also influences the choroid; at least scarring in the choriocapillaris can be expected. It is quite possible that the changes induced in the border retina and choroid influence the transfer of oxygen and fluids which may ultimately alter the diameter of retinal vessels (Colenbrander, 1975). It is currently not well known if there are also pressure changes between choroidal and retinal circulation induced by laser treatment. Changes in pressure gradient have been postulated to alter regression rate in one of two hydrostatically coupled vasculatures (Bischoff et al., 1983).

What now are the results of choroidal angiography in these patients? It has already been published that disc neovascularization either does not show up on the angiogram (Habozit, 1976) or is detectable, but fluid does not leak from it, as is the case with fluorescein (Orth et al., 1976). We reviewed 91 choroidal angiograms of 60 patients, mostly with the proliferative form of the disease. Our main findings are as follows:

Irregular and delayed choroidal filling occurred in the majority of patients with proliferative diabetic retinopathy and in about 1/2 of the patients with background retinopathy (Figure 4.7).

Effects of panretinal laser coagulation were surprisingly evident in the choroid (Figure 4.8). Localized spots or relatively large regions of choriocapillaris were closed. Also, the speed of choroidal filling was sometimes markedly reduced. Interestingly enough, irregular filling was also observed in the non-coagulated submacular choroid of this patient (Figure 4.8A).

Our preliminary findings suggest the potential value of doing more extensive studies in diabetic patients. Such questions as the following could at least be

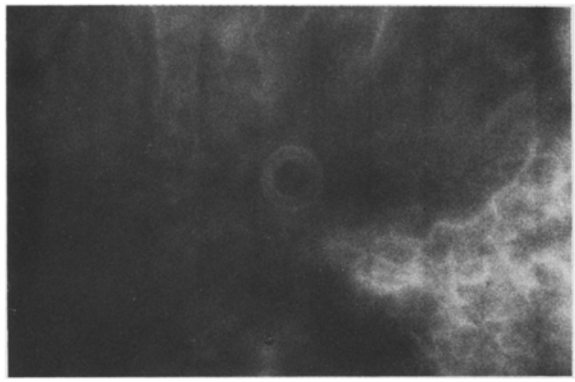

Figure 4.7A. 1.5 sec: Choriocapillaris filling only in a sector temporal to the macula.

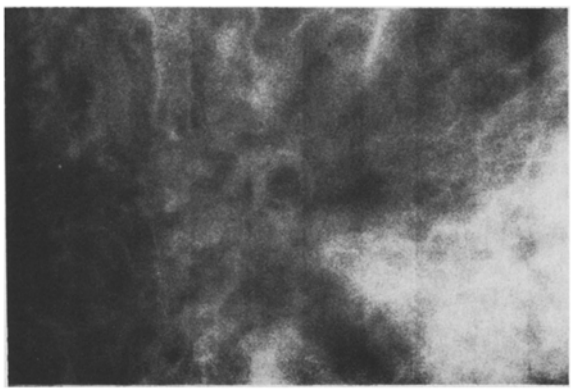

Figure 4.7B. 2.6 sec: Only sluggish filling of the choriocapillaris in some sectors of the central choroid.

Figure 4.7. ICG angiogram in diabetic retinopathy: irregular choroidal filling. Twenty year old patient with early proliferative diabetic retinopathy, left eye.

partly answered by such studies: It is the efficiency of the panretinal laser treatment correlated with the destruction of small or medium choroidal vessels? What are the immediate and late changes in the choroid observed after laser treatment? Does macular edema occur as a complication of laser treatment due to the coagulation of deeper choroidal vessels?

4.3 Choroidal tumors

The value of choroidal angiography for differential diagnosis of choroidal tumors has been confirmed by several authors (Patz et al., 1976; Habozit, 1976; François et al., 1977; Chopdar et al., 1978; Bacin et al., 1981). Infrared photography has been recommended earlier to allow the differentiation between pigmented and non-pigmented lesions (Sautter et al., 1974) because infrared light is much more efficiently absorbed by melanin than in blood.

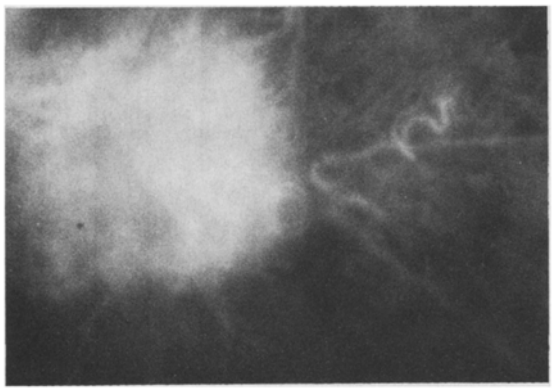

Figure 4.8A. 2.5 sec: Slow and irregular filling of the submacular choriocapillaris, only single choroidal vessels are visible in the peripheral region. (The disc is not visible here, it lies on the left side of the picture).

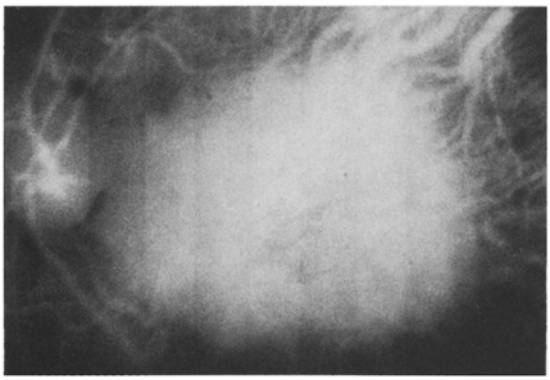

Figure 4.8B. About 15 sec: Only the submacular choroid choriocapillaris has been filled. The venous drainage is directed entirely toward a superior temporal vortex vein.

Figure 4.8. ICG angiogram in diabetic retinopathy after panretinal laser coagulation: Twenty-six year old patient with proliferative diabetic retinopathy one year after panretinal photocoagulation, left eye.

The additional information derived by using ICG dye is twofold. First, the vascularization of non-pigmented tumors can be studied. This is most important for the diagnosis of choroidal hemangioma. Secondly, defects in the choroidal vasculature are a topographic parameter useful in delineating the size and the growth of choroidal tumors. This could prove to be helpful in evaluation and treatment of nevi or small melanomas.

(1) Choroidal nevi: These occur frequently, having been found in up to 11% of all eyes at autopsy (Naumann, 1980). While it is easy to diagnose a small nevus, differentiation between a medium sized nevus and a small melanoma is

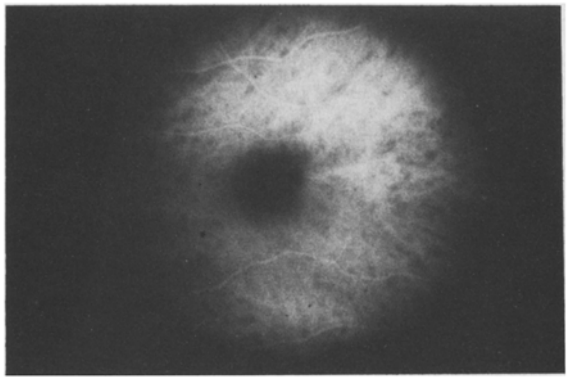

Figure 4.9. ICG angiogram in choroidal tumors: Small nevus. Thirty-nine year old patient, left eye, 7.0 sec. A small nevus in the central macula results in a 'black macula' normally not found in ICG angiograms.

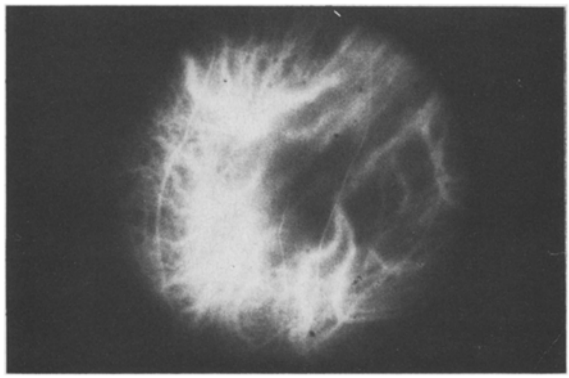

Figure 4.10A. Dec. 1975.

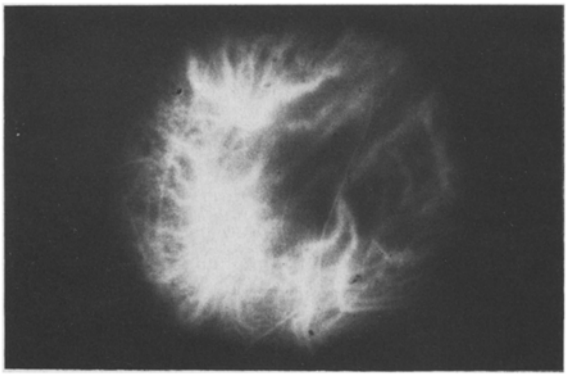

Figure 4.10B. April 1976.

Figure 4.10. ICG angiogram in choroidal tumors: Control of growth. Patient with a stationary choroidal nevus in the left eye.

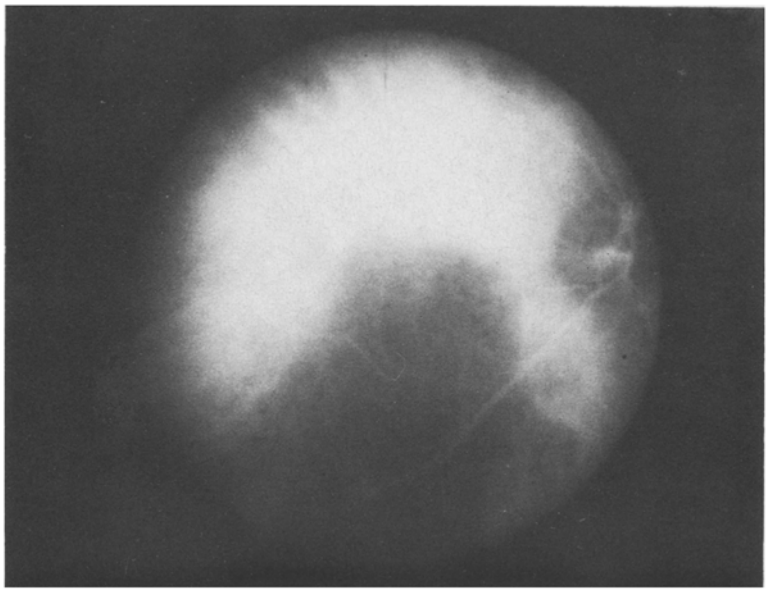

Figure 4.11. ICG angiogram in choroidal tumors: Melanoma. Seventy-three year old patient, right eye, 7.2 sec. The melanin in the tumor masks the underlying choroidal vessels. There is no significant difference between this and a large choroidal nevus but there is a clear difference with respect to an hemangioma.

sometimes very difficult (Gass, 1977). Due to the absorption of infrared light by the melanin, and possibly also due to the compression of choroidal vessels by the tumor, a choroidal nevus remains 'white' on the photographic negative while the surrounding region figures the fluorescent choroidal vessels, therefore, on the positive print, the nevus appears to be black and the choroidal vessels white (Figure 4.9). If pigmentation in the nevus is not too dense, some big choroidal vessels will remain visible (Figure 4.10). These vessels must not be confounded with 'vascularization of the tumor'. The stable appearance in terms of size of a choroidal nevus in angiograms is demonstrated in Figure 4.10A & B.

(2) Choroidal melanoma: Our experience with choroidal melanoma is rather small, 10 patients. While the diagnosis was rather easy to make in the case of some big and elevated melanomas, choroidal angiography proved to be helpful in the case of small and medium melanomas where differential diagnosis suggesting benign hemangioma is a possibility. Similar to the findings in nevi, the melanin in the tumor absorbs the infrared light leading to the 'shadow' in the angiogram (Figure 4.11). Sometimes we also found faintly visible vessels in the tumor, but at present we are not able to clearly distinguish between choroidal nevus and choroidal melanoma.

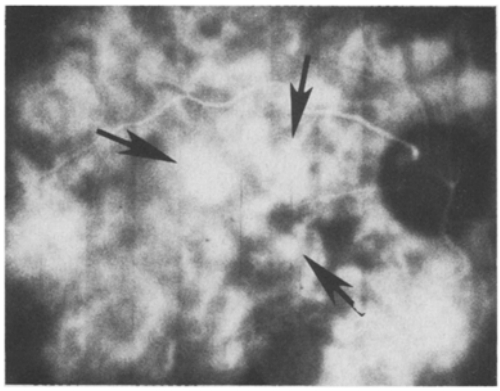

Figure 4.12A. 1.7 sec: Early filling of wide vessels (arrows) within the hemangioma between the disc and the macula.

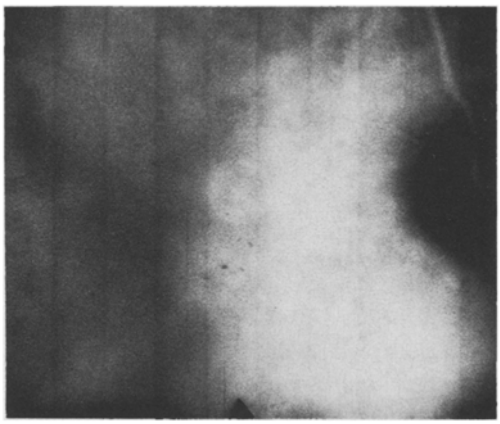

Figure 4.12B. 15 sec: The diffuse staining in the late phase is characteristic for the hemangioma.

Figure 4.12. ICG angiogram in choroidal tumors: Hemangioma. 21 year old patient, right eye.

(3) Choroidal hemangioma: In relation to the cystic vascular spaces, a hemangioma appears highly fluorescent in the choroidal angiogram (Figure 4.12). It is mentioned in the literature that this fluorescence persists for several minutes (Habozit, 1976) and that often separate vessels in the hemangioma can be distinguished, while fluorescein angiography shows only a diffuse leakage of the dye (Chopdar et al., 1978). While 70% of all solitary hemangiomas are located at the temporal posterior pole (Witschel and Font, 1976) a suspicious lesion should not be mistaken for a melanoma, and the eye should not be enucleated. Habozit, in 1976, for example, records that enucleation was performed after a choroidal angiogram but before the development of the infrared film; histology and choroidal angiograms showed too late the benign nature of the tumor.

(4) Choroidal metastases: Bacin et al., in 1981 recorded one case where the metastasis was extensively vascularized and appeared on the choroidal angiogram as a choroidal hemangioma. Although we have had no experience with such patients, this example indicates that at the moment choroidal angiography can be helpful in differential diagnosis, but it must be combined with other techniques such as fluorescein angiography and ultrasonography to arrive at the correct diagnosis.

4.4 Preliminary results in various other fundus diseases

In this section we can report only about a few examples because the number of choroid angiographic studies performed in each group ranges between one and twenty. These results may, however, suggest those cases in which choroidal angiography could be clinically useful. No significance should be attached to the sequence in which the following diseases are discussed. Moreover, there are certainly still fundus diseases, not discussed here, in which choroidal angiography might provide important information, including for example glaucoma or hypertensive and hypotensive vascular disorders. The value of choroidal angiography in cases of atypical central serous chorioretinopathy has been described earlier (Speiser and Bischoff, 1984).

(1) Presumed histoplasmosis syndrome: Angiographic studies in 6 juvenile patients with hemorrhagic maculopathies demonstrated lesions located within a vascular segment associated with a specific short ciliary artery (Saari, 1977), and it was postulated that intravascular thrombosis occurs in the central choriocapillaris. We reviewed 15 choroidal angiograms from 11 patients. In those patients who underwent earlier laser treatment, we could find no abnormalities in addition to the choroidal scars. In two patients we found marked regional delays in choroidal filling (Figure 4.13) suggesting the involvement of the choroid in this disease entity.

(2) Best's macular degeneration: This autosomal-dominant inherited disease involving early electro-oculographic changes has been associated with an enzymal defect of the pigment epithelium. Fluorescein angiograms indicate late choriocapillaris filling (Archer et al., 1972). We reviewed 20 ICG angiograms of such patients with different stages of the disease. The main finding was the poor quality of all angiograms in which the vessels could not be clearly distinguished from background fluorescence. While the possibility of poor techniques in producing these early angiograms cannot be excluded with certainty, it is still possible that changes in the pigment epithelium altered the infrared light transmission characteristics of the tissue, accounting for the appearance of the angiograms.

(3) Vasoocclusive disorders: Experimental occlusion of posterior ciliary arteries has been performed in the past (Leber, 1903) and in recent years as

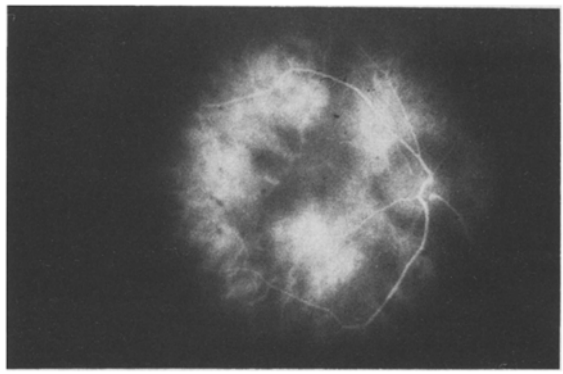

Figure 4.13A. 2.6 sec: Marked filling defect in the submacular choroid.

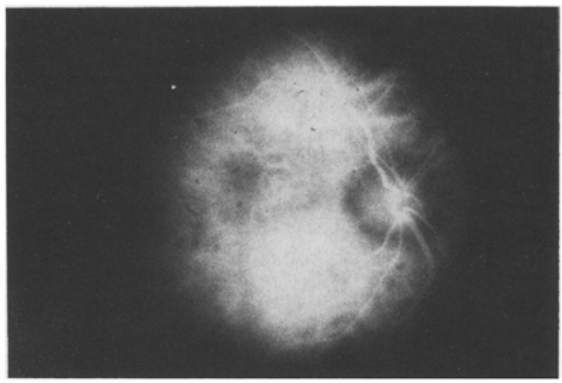

Figure 4.13B. 7.6 sec: Some late filling occurred in the submacular choroid too, providing a real filling defect instead of the masking of underlying choroid as might be produced by a scar.

Figure 4.13. ICG angiogram in presumed histoplasmosis syndrome. Fifty year old patient, right eye.

well (Hayreh, 1975; De Venecia et al., 1980; Nyama et al., 1980). These animal studies, together with clinical and histopathological studies in humans (Klien, 1968; Amalric, 1973; Naumann, 1980), have shown that the occlusion of a short posterior ciliary artery leads to a triangular choroidal filling defect and choroidal scar, the base of the triangle lying toward the periphery. Ischemic infarcts due to occlusion of a choroidal arteriole have areas of about 1/4 that of the disc, similar to the Elschnig spots in systemic hypertension. Serial histological sections of autopsy eyes have shown that the walls of the posterior ciliary arteries are often thickened and in older eyes are sometimes infilitrated by inflammation cells. Therefore, occlusions of such vessels may occur more often than they are diagnosed. In 3 of our 8 patients we found an interesting relationship between retinal and choroidal vaso-occlusion. One

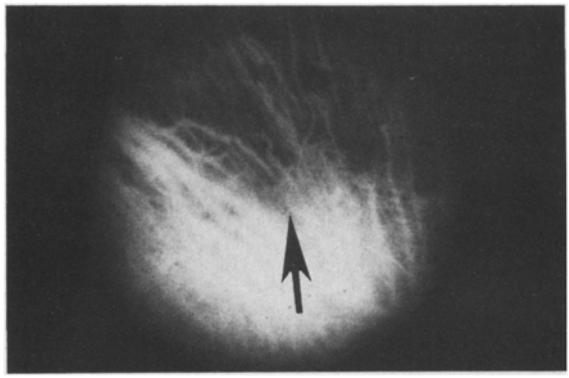

Figure 4.14A. ICG angiogram in choroidal and retinal thrombosis. Forty-two year old diabetic patient, right eye, 7.0 sec. Localized filling defect in the temporal superior choroid. The arrow points to the thrombosed retinal vein.

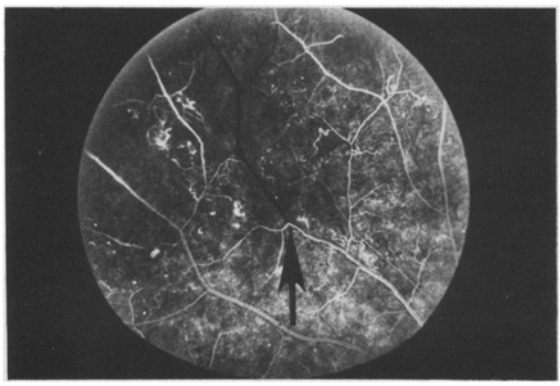

Figure 4.14B. Fluorescein angiogram (same patient): Old branch vein thrombosis in the temporal upper quadrant, exactly corresponding to the choroidal filling defect (same arrow).

patient with a central retinal artery occlusion later presented with delayed filling of the choroid (Flower et al., 1977). Two patients presented with a branch vein occlusion ophthalmoscopically. The ICG, and to a certain extent the fluorescein angiograms also, (Figure 4.14A & B) demonstrated exactly in the region affected by the occluded vein, showing a marked filling defect in the choroid.

(4) Retinitis pigmentosa: The etiology of this degenerative hereditary disease is not yet known with certainty. While both the photoreceptors and the pigment epithelium are supplied by the choroid, the question as to the vascular genesis of this disease has been extensively discussed (reviewed by Weinstein et al., 1971). Fluorescein angiography is negative in earlier stages

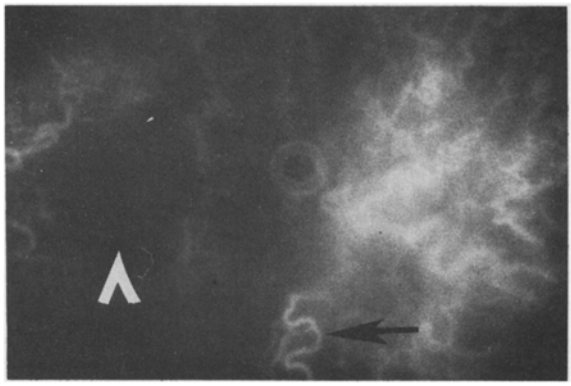

Figure 4.15. ICG angiogram in retinitis pigmentosa. Thirty-one year old patient, left eye, 1.3 sec. Uncommon meandering artery (black arrow) and delayed filling of the retinal circulation, 'black disc' (white arrow).

(Geltzer and Berson, 1969; Archer et al., 1972), sometimes however, delayed filling of single choriocapillaris units has been noted (Hyvärinen et al., 1971). In later stages of the disease, fluorescein angiography shows marked loss of choriocapillaris, where mostly isolated choroidal "islands" keep filling (Hyvärinen et al., 1969). We reviewed 16 choroidal angiograms of these patients. Most often we also found delayed and reduced filling of the choriocapillaris. The choroidal veins were always normal, but in two cases we found some uncommon meandering arteries (Figure 4.15); these arteries may, however, represent a normal variant. We measured in these patients a 1.6 second mean interval between first filling of choroidal arteries and choroidal veins; that is normal. However, we found a delay of about 1.9 seconds between first filling of choroid and retinal vessels; normally this should be 0.7 seconds. This delay may be the consequence of vasoconstriction in the retinal circulation. In summary, presently choroidal angiography does not appear to add valuable information about this retinal disease.

(5) Vitreous hemorrhage: Since absorption of infrared light by blood is less than that of visible light, angiography of fundus vessels may be possible using ICG in some situations where scattering and absorption of blue light is too great to perform fluorescein angiography. Our limited experience to date, however, indicates that the fundus should at least be visible ophthalmoscopically to obtain good quality choroidal angiograms.

(6) Papilledema: As in the case of disc neovasculatization, papilledema usually shows no leakage of ICG (Orth et al., 1976).

(7) Retrolental fibroplasia: The only example present in our archive is a 23 year old patient with a scar in the temporal periphery and traction of retinal

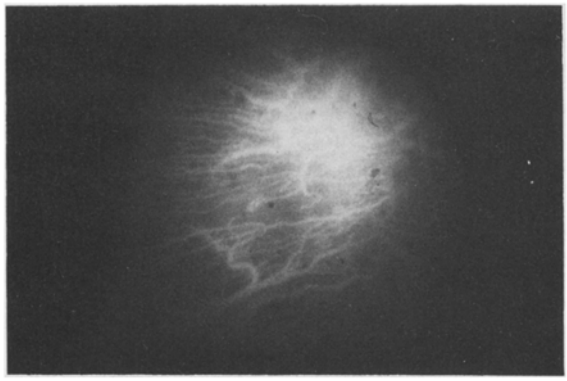

Figure 4.16. ICG angiogram in retrolental fibroplasia. Twenty-three year old patient, right eye, 5.8 sec. Not only the retinal but also the choroidal vessels 'point' directly toward the scar in the temporal periphery not visible here.

vessels toward that scar. The interesting finding here was that the choroidal vessels lead in a straight direction toward the temporal periphery (Figure 4.16) suggesting a traction of these vessels, also.

(8) Myopia: In high myopic eyes there is thinning and atrophy of some regions in the choroid (Apple and Naumann, 1980). In all 5 patients we noted reduced choriocapillaris filling (Figure 3.1). Two patients showed chorio-vaginal veins. Instead of leading toward the vortex veins, these vessles led toward the disc and left the globe adjacent to it. A possible explanation could lie in the posterior staphyloma that produced greater resistance in the path toward the vortex veins.

5. What is the future of choroidal angiography?

On the basis of the generally slow propagation of choroidal angiography since its introduction for clinical use in 1972, one might judge the future of this method rather pessimistically. Only a few ophthalmological institutes, mainly in Europe and in Japan, use this examination technique at the present time. Which is the reason for that seeming lack of interest by investigators?

(1) Is the choroid normally not involved in diseases of the fundus, and therefore any study of the choroidal circulation superfluous? Or, is sufficient information about the choroid available with the current routine methods such as ophthalmoscopy and fluorescein angiography?

The anatomy and the physiology of the choroid (chapter 1) clearly show the choroid to be the major supplier of blood to the normal eye. Moreover, there is no evidence to suggest that the choroid could not play any role in many diseases of the eye. The limitations of the routine methods for studies of the choroidal circulation are generally acknowledged (Hyvärinen et al.,

1969; Archer et al., 1972). and there seems to be no lack of interest on the part of investigators in the choroidal circulation which would account for slow propagation of the method.

(2) Is the equipment available today for choroidal angiography insufficient? Does any valuable information come from use of this technique?

When comparing a choroidal angiogram with a fluorescein angiogram, the ophthalmologist may initially be put off by the somewhat less striking appearance of the infrared photographs. However, one must not be tempted to ignor this method until it produces pictures as 'pretty' as fluorescein angiography. It is important to remember that most of the complications associated with interpreting this type of angiogram (part 2.3) are inherent in the three-dimensional structure of the choroidal vasculature itself; these cannot not be instantly overcome by technological miracles. In the future however, many improvements may develop, as for instance use of the TV-camera with its excellent temporal, but at the moment, too poor spatial resolution (Haining, 1981). Computerized image processing may add some further information. Also, laser technology could become involved in both fluorescein as ICG-angiography if development of the 'Scanning-Laser-Ophthalmoscope' (Webb et al., 1983) is successful.

All these developments will take time and money and be limited at the beginning to research centers. The question that must be answered today is whether or not the results obtained with the currently available equipment are at least promising enough to be used to increase our knowledge about the choroid in both the normal and diseased eye. Our own experience with over 500 choroidal angiograms indicate an affirmative answer.

(3) Is it perhaps only lack of knowledge about the possibilities of this method or the presently complicated equipment which prevents other clinics from using choroidal angiography? Or is the examination too bothersome or even dangerous for the patient?

The main reason for the slow propagation of this technique may be caused simply by the fact that it is impossible at present to buy the necessary equipment commercially. Until enough investigators become interested and use the methods, its actual clinical potential will never be known. The so-called 'compromise solution' described earlier for adopting the Zeiss fundus camera for choroidal angiography does not seem too complicated or expensive to prevent any interested ophthalmologist from using this methodology. The question of side effects of this angiographic technique has also been addressed (part 2.3); compared to fluorescein angiography, it seems less a risk.

As A. von Graefe (1854) pointed out with regard to the newly developed ophthalmoscope, there are multiple sources of errors to avoid in introducing a new type of examination. Besides the initial technical problems, the interpretation of the angiograms will lead to other difficulties since one cannot readily consult textbooks on this subject. Investigators must also avoid

dramatization of normal variants and yet not overlook discrete pathologic changes. There is, of course, the challenge of finding new and important data in a field which is relatively still unexplored today. The decision about the ultimate value of this method will finally be made with regard to its contribution for the diagnosis and treatment of eye diseases. This decision, however, can only be made after sufficient numbers of studies have been performed by different investigators. Without such studies choroidal angiography will never have a future. If one begins to undertake this work however, possibly important information about the poorly understood choroid will result, and we might join A. von Graefe (1854) who described the first results with ophthalmoscopy thereby: 'Under our eyes we see the fog disappear'.

Acknowledgements

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References

Alm A (1983) Microcirculation of the eye. In: Mortillaro NA (ed): The physiology and pharmacology of the microcirculation. New York, Academic Press

Amalric PM (1973) Choroidal vessel occlusive syndromes – clinical aspects. Trans Amer Acad Ophthal Otolaryng 77:291–299

Amalric P (1974) Veines choroidiennes, état normal et pathologique. Ann Oculist (Paris) 207:161–183

American National Standards Institute (ANSI) (1976) Safe Use of Lasers, Standard Z-136.1. New York, ANSI

Ansari A, Lambrecht RM, Packer S, Atkins HL, Redvanly CS and Wolf AP (1975) Note on the distribution of Iodine-123-labeled Indocyanine Green in the Eye. Invest Ophthal 14:780–782

Apple DJ and Naumann GO H (1980) Missbildungen und Anomalien des ganzen Auges. In: Naumann GOH (ed): Pathologie des Auges. Berlin, Springer-Verlag, pp 57–87

Araki M (1976) Observations on the corrosion casts of the choriocapillaris. Acta Soc Ophthal Jpn 80:315–326

Archer D, Krill AF and Newell FW (1970) Fluorescein studies of normal choroidal circulation, Amer J Ophthal 69:543–554

Archer DB, Krill AE and Ernest JT (1972) Choroidal vascular aspects of degenerations of the retinal pigment epithelium. Trans Ophthal Soc UK 92:187–207

Bacin F, Buffet JM and Mutel N (1981) Angiographie par absorption, en infrarouge, au Vert Indocyanine. Aspects chez le sujet normal et dans les tumeurs choroidiennes. Bull Soc Ophtal Fr 81:315–319

Behrendt T and Wilson LA (1965) Spectral reflectance photography of the retina. Amer J Ophthal 59:1079–1088

Benson RC and Kues HA (1978) Fluorescence properties of indocyanine green as related to angiography. Phys Med Biol 23:159–163

Bill A (1981) Ocular Circulation. In: Moses RA (ed): Adler's Physiology of the Eye, 7th ed. St. Louis, Mosby, pp 184–203

Bischoff PM and Flower RW (1983) High pressure in choroidal arteries as a possible pathogenetic mechanism in senile macular degeneration. Amer J Ophthal 96:398–399

Bischoff PM, Wajer SD and Flower RW (1983) Scanning electron microscopic study of the hyaloid vascular system in newborn mice exposed to 02 and C02. Graefe's Arch Clin Exp Ophthal 220:257–263

Bloome MA (1980) Fluorescein angiography: Risks. Vision Res 20:1083–1097

Buffet JM, Bacin F and Audouin MC (1979) Une téchnique simple de-angiographie en infra-rouge au Vert d'Indocyanine. Bull Soc Ophtal Fr 79:209–211

Carski TR, Staller BJ, Hepner G, Banka V and Finney RA (1978) Adverse reactions after administration of indocyanine gree. J Amer Med Ass 240:635

Cherrick GR, Stein SW, Leevy CM and Davidson CS (1960) Indocyanine Green: observations on its physical properties, plasma decay, and hepatic extraction. J Clin Invest 39:592–600

Chopdar A, Turk AM and Hill DW (1978) Fluorescent infra-red angiography of the fundus oculi using indocyanine green dye. Trans Ophthal Soc UK 98:142–146

Colenbrander MC (1975) Hydrostatische Druckverhältinisse im Auge. Fluorescein erscheint erst in der Aderhaut und dann in der Netzhaut. Wie kann man das erklären? Klin Mbl Augenheilk 167:94–97

Craandijk A and Van Beek CA (1976) Indocyanine green fluorescence angiography of the choroid. Brit J Ophthal 60:377–385

David NJ (1971) Infra-red absorption fundus angiography. In: Proc. Int. Symp. Fluorescein Angiography Albi, 1969. Basel, Karger, pp 189–192

De Venecia G, Wallow I, Houser D and Wahlstrom M (1980) The eye in accelerated hypertension. I. Elschnig's spots in nonhuman primates. Arch Ophthal 98:913–918

Ditzel J (1976) Oxygen transport impairment in diabetes. Diabetes 25:832–838

Donders FC (1855) Beiträge zur pathologischen Anatomie des Auges. Graefes Arch Ophthal I (2):106–118

Engerman R, Bloodworth JMB and Nelson S (1977) Relationship of microvascular disease in diabetes to metabolic control. Diabetes 26:760–769

Enzmann V and Ruprecht KW (1982) Zwischenfälle bei der Fluoreszenzangiographie der Retina. Klin Mbl Augenheilk 181:235–239

Ernest JT (1977) The effect of systolic hypertension on Rhesus monkey eyes after ocular sumpathectomy. Amer J Ophthal 84:341–344

Flower RW (1972) Infrared absorption angiography of the choroid and some observations on the effects of high intraocular pressures. Amer J Ophthal 74:600–614

Flower RW (1973) Injection technique for indocyanine green and sodium fluorescein dye angiography of the eye. Invest. Ophthal 12:881–895

Flower RW (1974) Choroidal angiography using indocyanine green dye: A review and progress report. Ophthal Digest 36:18–27

Flower RW (1976) High speed human choroidal angiography using indocyanine green dye and a continuous light source. Docum Ophthal Proc Ser 9:59–66

Flower RW (1977) Simple adaptors for fast conversion of a fundus camera for rapid-sequence ICG fluorescence choroidal angiography. J Biol Photogr 45:43–47

Flower RW (1980) Choroidal fluorescent dye filling patterns. A comparison of high speed indocyanine green and fluorescein angiograms. Int Ophthal 2:143–149

Flower RW and Hochheimer BF (1972) Clinical infrared absorption angiography of the choroid. Amer J Ophthal 73:458–459

Flower RW and Hochheimer BF (1973) A clinical technique and apparatus for simultaneous angiography of the separate retinal and choroidal circulations. Invest Ophthal 12:248–261

Flower RW and Hochheimer BF (1976) Indocyanine green dye fluorescence and infrared absorption choroidal angiography performed simultaneously with fluorescein angiography. Johns Hopkins Med J 138:33–42

Flower RW, Speros P and Kenyon LR (1977) Electroretinographic changes and choroidal defects in a case of central retinal artery occlusion. Amer J Ophthal 83: 451–459

Fox IJ and Wood EH (1960) Indocyanine green: Physical and physiologic properties. Mayo Clin Proc 35:732–744

François P, Turut P and Delannoy C (1977) L'angiogluorographie choroidienne à l'indocyanine. Bull Soc Ophtal Fr 77:971–972

Friedman E, Smith TR, Kuwabara T and Beyer CK (1964) Choroidal vascular patterns in hypertension. Arch Ophthal 71:842–850
Garner A (1982) Vascular disorders. In: Garner A and Klintworth GK (eds): Pathobiology of Ocular Disease, part B. New York, Marcel Dekker, pp 1479–1575
Gass JDM (1977) Problems in the differential diagnosis of choroidal nevi and malignant melanomas (33rd Edward Jackson Memorial Lecture). Amer J Ophthal 83:299–323
Geeraets WJ, Williams RC, Chan G, Ham WT, Guerry D and Schmidt FH (1960) The loss of light energy in retina and choroid. Arch Ophthal 64:606–615
Geltzer AI and Berson EL (1969) Fluorescein angiography of hereditary retinal degeneration. Arch Ophthal 81:776–782
Goldmann H (1932) Experimentelle Untersuchungen über die Genese des Feuerstares: I. Mitteilung. Graefes Arch Ophthal 128:413–446
von Graefe A (1954) Vorwort. Graefes Arch Ophthal I:III-X
Green WR (1980) Clinicopathologic studies of senile macular degeneration. In: Nicholson DH (ed): Ocular Pathology Update. New York, Masson, pp 115–144
Habozit F (1976) Angiographie choroidienne au vert d'indocyanine. Thèse Lyon Méd
Haining WM (1981) Video fundoscopy and fluoroscopy. Brit J Ophthal 65:702–706
Hayashi K, Nakase Y, Nishiyama A, Tokoro T and Yoshida T (1982) Indocyanine Green Fluorescence Angiography, Report 2. Studies on New Interference Filters. Acta Soc Ophthal Jpn 86:1532–1539
Hayreh SS (1975) Segmental nature of the choroidal vasculature. Brit J Ophthal 59: 631–648
Hayreh SS and Baines JAB (1973) Occlusion of the vortex veins. Brit J Ophthal 57: 217–238
Hepburn ML (1912) Inflammatory and vascular diseases of the choroid. Trans Ophthal Soc UK 32:361–386
Hidayat AA and Fine BS (1983) Diabetic choroidopathy. Invest Ophthal Vis Sci 24 (suppl):247
Hochheimer BF (1971) Angiography of the retina with Indocyanine Green. Arch Ophthal 86:564–565
Hochheimer BF (1979) A dye for experimental choroidal angiography. Exp Eye Res 29:141–143
Hogan MJ (1961) Electron microscopy of the human choroid. III. The blood vessels. Amer J. Ophthal 51:1084–1097
Hyvärinen L and Flower RW (1980) Indocyanine Green fluorescence angiography. Acta Ophthal 58:528–538
Hyvärinen L, Maumenee AE, George T and Weinstein GW (1969) Fluorescein angiography of the choriocapillaris. Amer J Ophthal 67:653–666
Hyvärinen L, Maumenee AE, Kelley J and Cantollino S (1971) Fluorescein angiographic findings in retinitis pigmentosa. Amer J Ophthal 71:17–26
Iseki K, Onoyama K, Fujimi S and Omae T (1980) Shock caused by Indocyanine Green dye in chronic hemodialysis patients (letter). Clin Nephrol 14:210
Ketterer SG, Wiegard BD and Rapaport E (1960) Hepatic uptake and biliary excretion of Indocyanine Green and its use in estimation of hepatic blood flow in dogs. Amer J Physiol 199:481–484
Klien BA (1968) Ischemic infarcts of the choroid (Elschnig spots). Amer J Ophthal 66: 1069–1074
Kogure K and Choromokos E (1969) Infrared absorption angiography. J Appl Physiol 26: 154–157
Kogure K, David NJ, Yamanouchi V and Choromokos E (1970) Infrared absorption angiography of the fundus circulation. Arch Ophthal 83: 209–214
Krey HF (1975) Segmental vascular patterns of the choriocapillaris. Amer J Ophthal 80:198–202
Leber T (1903) Die Circulations- und Ernährungsverhältnisse des Auges. In: Graefe-Saemisch: Handbuch der gesamten Augenheilkunde, 2. Aufl., Bd. 2/2. Leipzig, Verlag W. Engelmann, pp 1–534
Leevy CM, Smith F and Kierman T (1976) Liver function tests. In: Bochus, HL (ed): Gastroenterology, 3rd ed., vol. 3. Philadelphia, Saunders, pp 68–82

Leibowitz HM, Krueger DE and Maunder LR et al. (1980) The Framingham Eye Study Monograph. Surv Ophthal 24 (Suppl):334–610

Lutty GA (1978) The acute intravenous toxicity of biological stains, dyes, and other fluorescent substances. Toxicol Appl Pharmacol 44:225–249

Lutty GA (1979) An intraperitoneal survey of biological stains, dyes, and other fluorescent substances. Bull Nippon Kanhoh-Shihiso Kenkyusho 50:25–50

Macular Photocoagulation Study Group (1982) Argon laser photocoagulation for senile macular degeneration, Results of a randomized clinical trial. Arch Ophthal 100:912–918

Müller H (1856) Anatomische Beiträge zur Ophthalmologie. Graefes Arch Ophthal II (2):1–69

Naumann GOH (1980) Uvea. In: Naumann GOH (ed): Pathologie des Auges. Berlin, Springer-Verlag, pp 408–500

Novotny HR and Alvis DL (1961) A method of photographic fluorescence in circulating blood in the human retina. Circulation 24:82–86

Nyama M, Ohkuma H, Itotagawa S, Koshibu A, Uraguchi K and Miki K (1980) Pathology of choroidal circulatory disturbance. I. Angioarchitecture of the choroid, observation on plastic cast preparation. Acta Soc Ophthal Jpn 84:1893–1909

Orth DH, Patz A and Flower RW (1976) Potential clinical applications of Indocyanine Green choroidal angiography – Preliminary report. Eye Ear Nose Throat Mon 55: 4–11

Par JC, Hodge JV, Clemett RS and Knight FH (1968) Fluorescence appearance time in retinal and choroidal vessels. Trans Ophthal Soc New Zealand 20:88–101

Patz A, Flower RW, Klein ML, Orth DH, Fleischman JA and McLeod S (1976) Clinical application of Indocyanine Green angiography. Docum Ophthal Proc Ser 9:245–251

Patz A (1982) Clinical and experimental studies on retinal neovascularization (XXXIX Edward Jackson Memorial Lecture). Amer J Ophthal 94:715–743

Pitts DG, Cullen AP and Dayhaw-Barker P (1980) Determination of ocular threshold levels for infrared radiation cataractogenesis, DHHS (NIOSH) publ 80–121. Washington, U.S. Government Printing Office, pp 1–55

Potts AM (1966) An hypothesis on macular disease. Trans Amer Acad Ophthal Otolaryng 70:1058–1062

Ring HG and Fujino T (1967) Observations on the anatomy and pathology of the choroidal vasculature. Arch Ophthal 78:431–444

Risco JM, Grimson BS and Johnson PT (1981) Angioarchitecture of the ciliary artery circulation of the posterior pole. Arch Ophthal 99:864–868

Saari M (1977) Disciform detachment of the macula. II. Fluorescein and Indocyanine Green fluorescence angiographic findings in juvenile hemorrhagic macular choroidopathy.Acta Ophthal 55:530–538

Sattler H (1976) Ueber den feineren Bau der Chorioidea des Menschen nebst Beiträgen zur pathologischen und vergleichenden Anatomie der Aderhaut. Graefes Arch Ophthal 22(2):1–100

Sautter H, Lüttewitz W and Naumann GOH (1974) Die Infrarot-Photographie in der Differentialdiagnose pigmentierter tumorverdächtiger Fundusveränderungen. Klin Mbl Augenheilk 164:597–602

Schatz H, Burton TC, Yannuzzi LA and Rabb MF (1978) Subretinal Neovascularization. In: Interpretation of Fundus Fluorescein Angiography. St. Louis, Mosby, pp 440–452

Shabetai R and Adolph RJ (1980) Principles of cardiac catheterization. In: Fowler NO (ed): Cardiac diagnosis and treatment, 3rd ed. Hagerstown, Haper & Row, pp 117–119

Shimizu K and Ujiie K (1978) The choroid. In: Structure of Ocular Vessels. Tokyo, Igaku-Shoin Med. Pub., pp 50–92

Sliney DH (1982) Optical radiation safety. Lighting Res Technol 14:142–150

Sliney DH and Wolbarsht ML (1980) Safety standards and measurement techniques for high intensity light sources. Vision Res 20:1133–1141

Speiser P and Bischoff P (1984) Die sogenannte Chorioretinopathia centralis serosa im Lichte der Aderhautangiographie. Klin. Mbl Augenheilk 185:378–380

Spitznas M (1974) The fine structure of the chorioretinal border tissues of the adult human eye. Adv Ophthal 28:78–174

The Diabetic Retinopathy Study Research Group (1978) Photocoagulation treatment of proliferative diabetic retinopathy: The second report of Diabetic Retinopathy Study findings. Ophthalmology 85:82–105

Tokoro T, Hayashi K, Muto M, Asahara N, Sato K and Yoshida T (1976) Studies on choroidal circulation, Report I: Fundamental studies on the infrared absorption angiography. Jpn J Ophthal 30:173–179

Torczynski E (1982) Choroid and Suprachoroid. In: Duane TD and Jaeger EA (eds): Biomedical Foundations of Ophthalmology, Vol. 1, chap. 22. Philadelphia, Harper & Row, pp 1–33

Tripathi RC (1974) Fine structure of mesodermal tissues of the human eye. Trans Ophthal Soc UK 94:663–695

U.S. Pharmacopeia (1980) Indocyanine Green. In: Nat. Formulary, 15th ed., Rockville, Md., United States Pharmacopeial Convention, p 399

Vogt A (1919) Experimentelle Erzeugung von Katarakt durch isoliertes kurzwelliges Ultrarot, dem Rot beigemischt ist. Klin Mbl Augenheilk 63:230–231

Wagner H. (1938) Pathologische und therapeutische Wirkungen des penetrierenden Ultrarot auf das Auge. Graefes Arch Ophthal 138:486–514

Wald G (1949) The photochemistry of vision. Docum Ophthal 3:94–134

Webb RH, Hughes GW, Timberlake GT and Mainster MA (1983) The scanning laser ophthalmoscope – summary of the first generation instrument. Invest Ophthal Vis Sci 24(suppl): 122

Weinstein GW, Maumenee AE and Hyvärinen L (1971) On the pathogenesis of retinitis pigmentosa. Ophthalmologica 162:82–97

Wenzel M (1786) Traité de la cataracte. Paris

Wheeler HO, Cranston WI and Mettzer JI (1958) Hepatic uptake and biliary excretion of Indocyanine Green in the dog. Proc Soc Exp Biol Med 99:11–14

Wise GN, Dollery CT and Henkind P (1971) Retinal neovascularization. In: The Retinal Circulation. New York, Harper & Row, pp 265–278

Witschel H and Font RL (1976) Hemangioma of the choroid. A clinicopathologic study of 71 cases and a review of the literature. Surv Ophthal 20: 415–431

Wolbarsht ML (1980) Damage to the lens from infrared. In: Wolbarsht ML and Sliney DH (eds); Ocular effects of non-ionizing radiation. Washington. The Society of Photo-Optical Instrumentation Engineers Publ., pp 121–142

Wolff E (1976) Eyeball. In: Warwick R (ed): Eugene Wolff's Anatomy of the Eye and Orbit, 7th ed. London, HK Lewis & Comp, pp 30–180

Wybar KC (1954) Vascular anatomy of the choroid in relation to selective localization of ocular disease. Brit J Ophthal 38:513–527