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INDOCYANINE GREEN FLUORESCENCE ANGIOGRAPHY

BY

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Indocyanine green (ICG) fluorescence angiography has been further refined for use in both laboratory and clinical investigations. In the present modification of the Zeiss fundus camera all lenses except the aspherical objective lens have been specially antireflection coated to increase light transmission in the spectral region around 800 nm. A 300 watt indium iodide lamp continuous light source has replaced the conventional xenon flash lamp. This light source produces a retinal irradiance of 265 mw, and therefore restricts retinal exposure time to 11.9 seconds, but that time is more than adequate to record passage of dye through the choroid. Spatial resolution of the fundus on the film has been increased from 11.7 microns to 7.4 microns.
With these technical refinements the choroidal circulation can be studied at 20 frames per second, which is adequate to document the very rapid movement of blood through the vasculature. ICG angiography may change our interpretations of choroidal circulatory phenomena which are now based on fluorescein angiography, and it clearly is an effective tool in laboratory (experimental) investigations.

Key words: indocyanine green fluorescence – angiographic studies of the eye – choroidal circulation.

Sodium fluorescein angiography has been an important part of ophthalmology's armamemtarium for well over a decade now, and its clinical diagnostic value in retinal vascular diseases cannot be impugned. However, its usefulness in studying bloodflow dynamics is limited, especially in the choroid where transmission of visible light wavelengths is poor and extravasation of fluorescein dye readily occurs.

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There are even instances in which misinterpretation of fluorescein angiograms may have led to erroneous conclusions about choroidal bloodflow (Flower 1972, 1980).

Development of indocyanine green (ICG) fluorescence angiography was initially persued solely as a way to obviate the limitations imposed by fluorescein dye during experimental studies of choroidal bloodflow dynamics. It was serendipitous that early on in development of the technique it became evident that ICG angiography could be used safely and routinely on human subjects as well. Clinical ICG angiography has been performed since about late 1973, and the data obtained have been invaluable to refinement of the technique. The accumulated angiographic material is still insufficient to warrant interpretation of choroidal circulatory phenomena in pathological conditions. However, some observations can be reported.

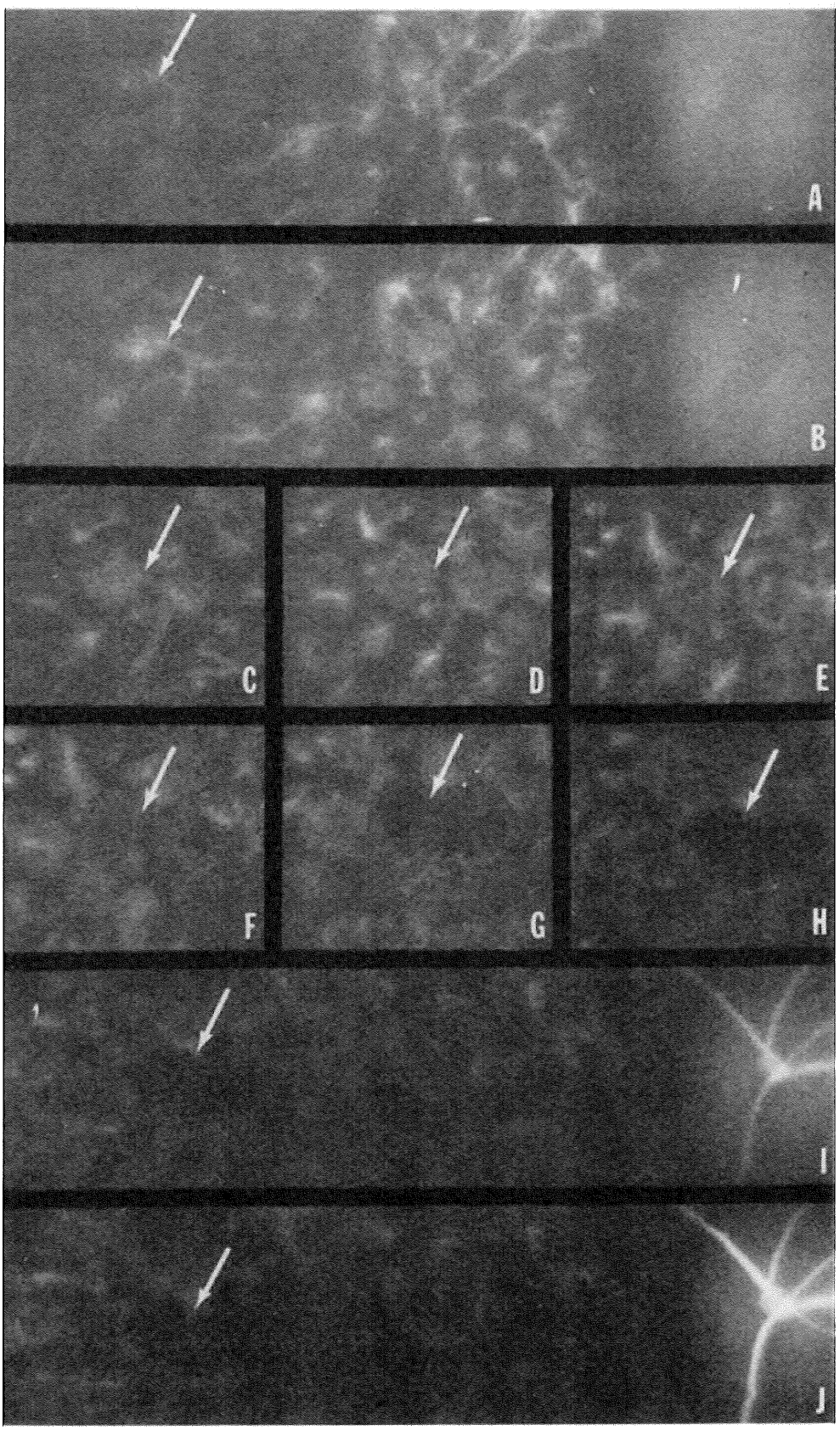
Both ICG absorption angiography and the early method of fluorescence choroidal angiography have been described in detail before (Flower 1972a,b; Flower & Hochheimer 1973, 1976; Flower 1976), therefore it is the refinements and resulting improvements in spatial and temporal resolution achieved since these which are described below.

Technique

During the development of the new camera for ICG angiography approximately 150 ICG human angiograms were made at the University of Oulu, Department of Ophthalmology and 480 in the Wilmer Ophthalmological Institute. ICG and fluorescein angiograms were done a few minutes apart. Injection of ICG dye was made via a 3-way cannula followed immediately by a saline flush (Flower 1973). No allergic or vasovagal reactions occured, and none of the patients were discomforted by the illumination used for ICG near-infrared photography.

220 ICG angiograms of rhesus monkeys were made at the Wilmer Ophthalmological Institute. The injection technique was identical with that in human studies except that smaller volumes were injected, and all animals were anesthetized with halothane.

Fluorescence ICG angiography is performed in much the same way as fluorescein angiography, the major difference being that ICG angiography utilizes near-infrared light wavelengths while fluorescein utilizes light wavelengths in the visible region of the spectrum. Descriptions of the absorption and emission ICG dye spectra as well as characteristics of the photographic film and excitation and barrier filters used in choroidal angiography have been previously published (Flower & Hochheimer 1973, 1976). Briefly, the advantages of ICG dye in choroidal angiography are that there is no extravasation from the choriocapillaris, that it absorbs



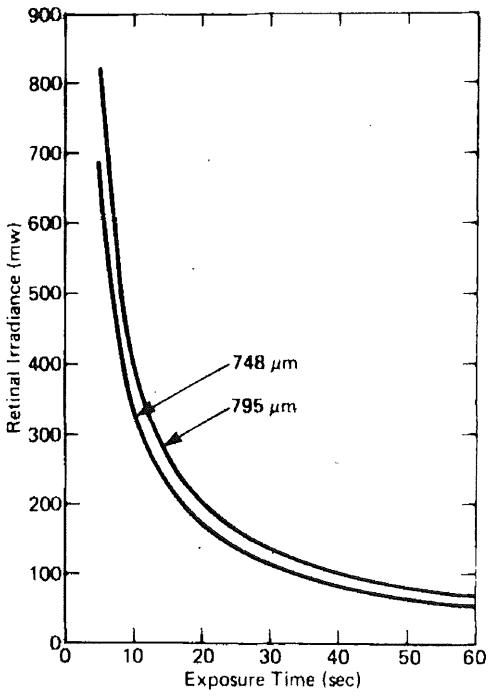


Fig. 1.
Graph indicating maximum level of safe retinal irradiance as a function of exposure time.

light and fluoresces in a spectral region where retinal and choroidal pigments are fairly transparent, and that its long wavelengths of emitted light are more than six times less scattered by the ocular media than the shorter visible light wavelengths emitted by fluorescein. Its principal disadvantage is that it does not fluoresce efficiently. Whereas the quantam efficiency of fluorescein dye in blood is nearly 1, that of ICG dye is only 0.13, and if the relative fluorescence intensity of fluorescein is arbitrarily set at 1, that of ICG is 25 times less. Therefore, developing the instrumentation for choroidal angiography essentially has been an exercise in optimizing ability to record the fluorescent light energy emitted by ICG dye in the ocular blood vessels.

Fig. 2.
Ten consecutive frames of a 20 frame per second ICG fluorescence angiogram made of an adult rhesus monkey. Arrows indicate the location of the same individual choroicapillaris lobule throughout the sequence. In frames A-D, the arterial feeder of the lobule can be identified. In frames D-F, to the left of the arrow, the drainage venules into which the lobule empties can be seen. Note that in frame A-F the lobule appears white as it fills with dye and then appears black in frames G-J where it has essentially emptied. Maximum filling of the lobule occurred by frame D, indicating a filling time of only 0.2 seconds.

The lenses of the fundus camera are normally antireflection coated to efficiently transmit light throughout the visible spectrum with maximum transmission occurring at about 530 nm wavelength. However, near 800 nm wavelength where ICG fluorescence occurs, the measured loss of light energy at each lens surface is about 4% (the loss nominally occuring at most wavelengths when uncoated lens elements are used). By antireflection coating lens elements specifically for 800 nm wavelength, this loss can be reduced to as little as 0.3% per lens surface. This was done to all lenses in the Zeiss fundus camera imaging optics except the aspherical objective lens which is normally uncoated. Providing one of the auxillary accomodation lenses is not used, there are 14 lens surfaces in the fundus camera imaging optics. At 800 nm wavelength, with the original lens coatings, total light transmission was $0.960^{14}=0.560$ or 56%; with proper antireflection coatings, total transmission became $0.997^{14}=0.959$ or 96% which amounts to 40% more light available to make film exposures.

The effective aperture stop in the Zeiss camera is the hole drilled through the diagonal mirror located between the aspherical objective lens and the auxillary lens wheel. Normally this hole is 5 mm in diameter, but by enlarging it to 1 cm, 4 times as much light can pass through the imaging optics to the photographic film. Reduction of this diagonal mirror surface which reflects light into the eye only results in an 11% decrease of 800 nm wavelength excitation light energy, and that is regained by replacing the aluminum coatings on both diagonal mirrors in the illumination optics with quartz-clad silver. Added to the gain in transmission achived by using better lens coatings, a total gain of 5.7 times in light energy transmission at 800 nm wavelength makes it possible to photograph the choroid at the 2.5 times magnification of the standard Zeiss fundus camera.

Of equal importance is improving temporal resolution of the rapid choroidal dye-filling sequence of events. Since no flash lamp light source is available which can be re-cycled at a sufficiently high rate and yet deliver enough light energy on each flash to perform ICG angiography, a continuous light source was installed. Initially, a 150 watt quartz halogen lamp was used, and in order to increase the available light intensity, an adjustable mirror was also installed behind the lamp. More recently we used a 300 watt indium iodide lamp which has a much larger in light energy component at 800 nm wavelength. Caution must be exercised in using such a continuous light source to insure that retinal irradiance does not exceed a safe level. For the approximate 35 degree fundus area illuminated by the Zeiss fundus camera and for the light wavelengths required to excite ICG dye to fluorescence, the maximum permissible exposure of the retina is 3160 mw-seconds (American National Standard for the safe use of lasers 1973). Retinal irradiance is shown as a function of continuous exposure time in Fig. 1. The indium iodide light source produces a retinal irradiance of 265 mw, consequently, an exposure time of no

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