

A CAMERA for RECORDING the DYNAMIC BLOOD CIRCULATION of the EYE

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Introduction

THE EYE, FROM AN ELEMENTARY POINT OF VIEW, consists of a lens system and a photo-sensitive receiver surface. The lens system, the combination of cornea and lens, has a focal length of about 15 mm and the receiver surface, the retina, is large enough so that a field of view of over 180° is possible. Figure 1 is a schematic view of the eye. Upon closer examination, the eye is found to be much more complex. The retina is composed of many layers. The rods and cones, which are the photoreceptors, are fastened to the choroid and the choroid to the outer scleral layer. In the outer anterior layer of the retina are the veins and arteries that nourish it. We are interested in obtaining information concerning the perfusion of the retina with blood through this vascular system. However, the limiting optical system through which this information must pass to be recorded is that of the eye. Our specific interest is in blood flow through the retinal veins and arteries, the capillary bed connecting these, and in some cases the blood flow in the choroidal vascular system.

The blood vessels in the retina usually can be observed by an ophthalmologist using standard ophthalmological instruments except for the vessels in the capillary bed, and those in the choroidal layer. Figure 2 is a picture taken of a normal eye and shows what can be seen in a routine exam-

For studying the vascular system of the eye, a method called fluorescence angiography has been developed. In this procedure fluorescein dye is injected into the patient's blood stream. Several seconds later it appears in the blood vessels of the retina of the eye and can be photographed. A camera has been designed for recording the rapid changes that occur with this procedure. The initial investigations, the design considerations, and a prototype camera are discussed.

ination. The nutrition of the retina depends on the correct function of the capillary bed in the retina and in the blood vessel system of the choroid. Therefore, evaluation of changes within the circulatory system of the retina, in flow capability or structure when a patient has diseases which affect these parts, is important for a complete understanding of these diseases and as a diagnostic procedure.

The structural changes can be studied in some cases by microscopic examination of histologic sections. This usually happens only in the very late stages of a disease where the eye is removed or upon the death of a patient. In a living human eye the retinal and choroidal circulation has been studied by a method called fluorescence angiog-

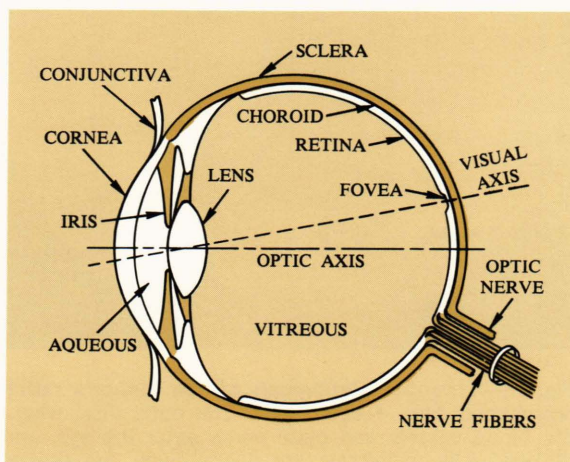


Fig. 1—Horizontal section of the eye.

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raphy developed by Novotny and Alvis¹ in 1961. In this method, a few cubic centimeters of concentrated fluorescein dye is injected into a vein in the arm, and it appears in the retinal vascular system seven to ten seconds later. The dye is excited by blue light; its fluorescent emission is green light which is filtered and photographed. If the media of the eye is clear, the fluorescein provides sufficient additional contrast so that capillaries in the retina are well visualized. Changes not visible by any other method can be documented for detailed study. Figure 3 is a photograph taken of a very clear eye during a fluorescence angiographic study. Investigations using this technique have added to the understanding of such important disorders as diabetic retinopathy, detachments of the central retina, occlusive diseases of the retinal vessels, and senile degenerative processes. Lately, this method has been applied for investigations of the choroidal circulation, which are difficult to study ophthalmoscopically. In the last five years fluorescence angiographic studies have become an important part of routine clinical studies in patients with disorders of the retinal vascular system.

¹ H. R. Novotny and D. L. Alvis, "A Method of Photographing Fluorescence in Circulating Blood in the Human Retina," *Circulation* 24, 1961, 82-86.

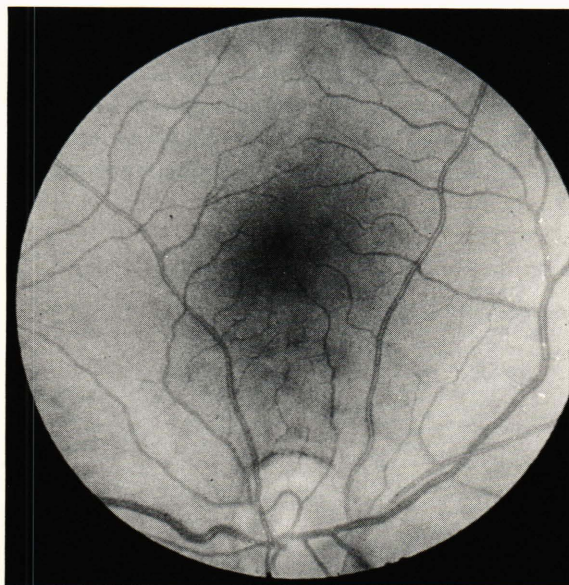


Fig. 2—A normal photograph of the author's retina reproduced from a color slide. The optic disc, where the blood vessels and optic nerve enter the eye, and the major blood vessels are clearly seen. The central small area devoid of blood vessels is the macula, the area of highest visual acuity.

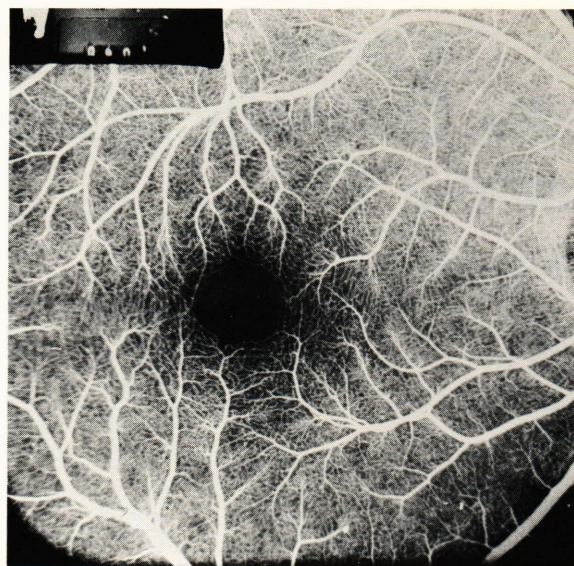


Fig. 3—A fluorescence angiograph of a patient demonstrating the marked increase in visibility of the blood vessels and the appearance of the capillary bed.

In early clinical studies a single photograph was taken when the entire retinal vascular system was perfused with fluorescein dye. If temporal data were required, repeated injections were made. This method is still used if more modern equipment is not available.

Currently, the most widely used equipment for this purpose is the Zeiss fundus* camera modified to take a picture sequence at a rate of about one picture per second. This picture sequence rate is suitable for studying ocular lesions where leakage of fluorescein is relatively slow, for studying gross features of the dynamics of retinal circulation such as capillary perfusion and mean retinal circulation time, and for studying different vascular tumors.

However, for studying the hemodynamics of the normal and abnormal retinal circulation, a higher sequence rate is necessary. Although high frame rate cinematography is not a widely used technique, enough experimental work has been done on animals and in clinical research with humans to demonstrate that its use brings out many striking features of the normal and abnormal retina that are commonly concealed. For example, studies have been made of normal retinal blood flow in humans and of capillary abnormalities

* The fundus is the area of a cavity opposite an opening. The fundus of the eye is therefore the retina.

found in diabetic retinopathy. Hyvärinen² has studied the effects of experimental hypercholesteremia on the circulation and retinal vessels in the rabbit eye. Flower, Patz, and Speiser³ have studied the effect of oxygen upon the immature retina by cinematography. It is apparent also that these techniques could be useful for studying the effects of drugs upon the dynamics of retinal circulation in, for example, hypertensive patients.

The utility of this technique could be greatly enhanced and extended if it could be placed into routine clinical use, thus providing fast cinematographic data on large numbers of patients. In all cases where experimental equipments have been developed, they have been modifications of existing ophthalmological instruments—by far the most used has been the modified Zeiss fundus camera. The main problem that is encountered in the use of the modified Zeiss fundus camera for cinematography is the need for high intensity light which in man is intolerably bright and, in fact, may be dangerous to the retina in some cases. One solution to this problem that has been employed by Dollery⁴ is to use an image intensifier. This solution has been used successfully although it increases the weight, complicates the operation, and limits the resolution to no more than that possessed by the image amplifier. This solution is not generally available to others since the image amplifier used by Dollery is an experimental device and those that are commercially available have lower resolution than that quoted for Dollery's device. Others have attempted to solve the problem by using a pulsed series of light flashes. Patient acceptance is marginal; the damage threshold for such short duration pulses is not well known, and in general the equipment becomes quite large.

The Zeiss fundus camera was designed for a specific purpose; that of taking human fundus pictures of very high quality in a routine manner in a clinical environment. It has been successfully modified for use in the clinic for low rate (approximately one per second) fluorescence

photography by substituting a pulsed light source and a motor-driven camera. The desire of the ophthalmologist to overcome the limitations of presently available equipment has motivated this study and has led to a new fundus camera design.

For high speed retinal fluorescence photography, our rationale is that a fundus camera specifically designed for this purpose will overcome many of the disadvantages inherent in the modification of a device that was specifically designed for other uses in which the conservation of light was not a primary design objective. A careful optical design with maximum attention to the conservation of light and careful selection of optical components, light sources, and detectors could result in a device which would accomplish its purpose and at the same time be relatively light, compact, and versatile, leading to acceptance for use in the clinic by the clinician, the technician, and the patient.

Initial Investigations

Our initial design objectives were to produce a prototype fundus camera that would cover an 8-mm-diameter field of view on the retina with a resolution of ten microns or better at a frame rate of 16 per second. Since the camera is to be used on human subjects, it is required that an absolutely safe and reasonably acceptable light level be used.

Some exploratory investigations were made aimed at an understanding of the problem, and pilot systems were made in order to define some parameters of a possible solution.

First, a simple optical system was set up in which the components could be easily interchanged. During this phase of the program, filters were evaluated in conjunction with several different light sources. Zirconium arcs, tungsten and tungsten iodide lamps, and the concentrated mercury arc lamp were tested and filter combinations selected. In particular, a small pulsed argon ion laser was tested to ascertain that the fluorescent emission was wideband even with monochromatic excitation. After these laboratory tests were performed, some animal tests were conducted. Rabbits and kittens were used as subjects. These experiments indicated that 16-mm motion pictures at frame rates up to 64 frames per second were possible and that television recordings on video tape could be made. In general, the results were such as to encourage further tests.

² L. Hyvärinen, "Fluorescence Cineangiographic and Histological Studies on the Rabbit Eye during Experimental Hypercholesteremia," *Acta Ophthalm.* 45, 1967, 1-22.

³ R. W. Flower, A. Patz, and P. Speiser, "New Method for Studying Immature Retinal Vessels in Vivo," *Invest. Ophthalm.* 7, 1968, 366-370.

⁴ C. T. Dollery, "Dynamic Aspects of the Retinal Microcirculation," *Arch. Ophthalm.* 79, 1968, 536-539.

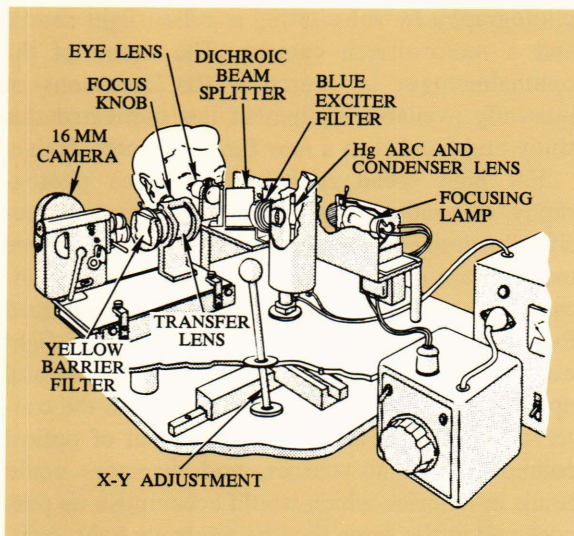


Fig. 4—Camera for testing basic optical designs.

A second optical system was set up with provision for crude X-Y translation of the instrument and an additional white light source for focusing. Tests on human volunteers indicated that retinal vessels of the order of 10 microns in diameter were visible over a 5-mm-diameter field. This was confirmed with additional animal tests. Figure 4 shows this second test instrument. The mercury arc is enclosed within a cylindrical housing, and blue light from this lamp is projected into the patient's eye through the beam splitter and eye lens. Fluorescent emission from the retina is directed by the beam splitter to the camera. Focusing light from the tungsten lamp is directed into the eye by a mirror and an additional beam splitter.

Although only a 5-mm-diameter field of view was covered, the other initial objectives were met. The best results on human subjects from this test instrument are shown in Fig. 5, where every twentieth frame from the first several seconds of a test is shown.

It should be emphasized that these initial optical systems were constructed from available components in order to evaluate the basic system design, and in many cases optimum component performance was not achieved. With proper components the resolution and field of view of the instrument will be improved.

Design Parameters

The Eye—For the design of a fundus camera the eye itself must be studied, since it will be the ultimate limiting part of the complete system.

The variations of spherical aberration of the eye are so great that to make an average correction for this seems somewhat meaningless. The values usually stated for this take into account the optics of the eye and the characteristics of the retina. Campbell and Green⁵ have made a separate evaluation of the resolution of the retina and the complete optical system of one individual. This enables some estimation of the resolving power attributable to the optical system of the eye alone. For a 6-mm pupil the measured system resolution is 6.3 microns and the retinal resolution is 4 microns, which leaves about 2.3 microns for the optical system resolution. This is small enough to leave uncorrected in a fundus camera design.

For high contrast targets the limit of resolution of the eye is almost constant over an extremely wide range of pupil diameters. Therefore, for high resolution, it is not necessary to use small eye pupils, which would unnecessarily limit the light-gathering power of the system.

The chromatic aberration of the eye is rather constant among different subjects in the spectral region from 5000 to 6000 Å. The average amounts to about 50 microns for a large pupil. This aberration can be corrected, if necessary, by a specially designed eye lens. The other aberrations, for example, coma and astigmatism, have not yet to our knowledge been investigated.

The remaining primary eye defect is axial astigmatism. A retinal camera should correct this, as

⁵ F. W. Campbell and D. G. Green, "Optical and Retinal Factors Affecting Visual Resolution," *J. Physiol.* **181**, 1965, 576-593.

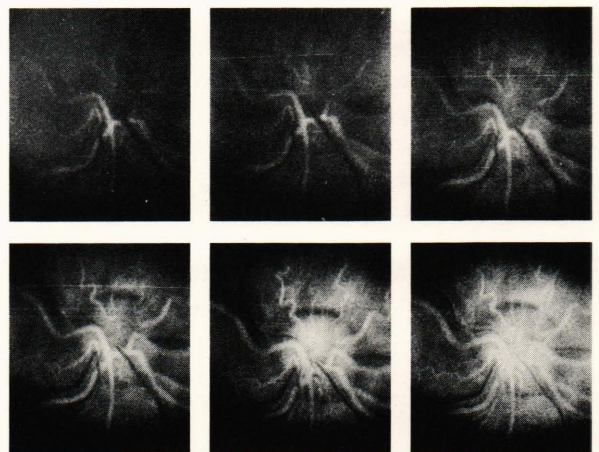


Fig. 5—Photographic results from test camera. Every 20th frame from a 16-frame-per-second record is shown.

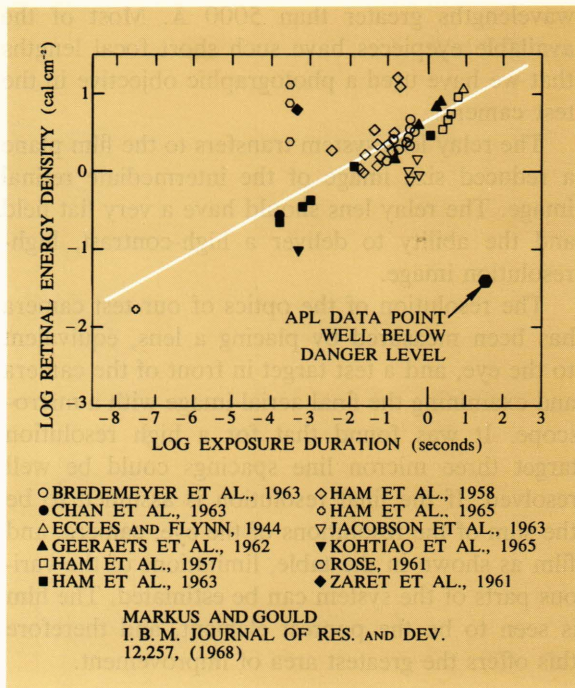


Fig. 6—The energy and exposure duration needed to produce visible eye damage. The energy and duration for the test camera is shown and is clearly below eye damage level.

it is sometimes large and very often found in human eyes.

Light Source—The effects of high intensity light on the eye were studied in detail to avoid injury or discomfort to patients. A summary of work on eye damage by light is shown in Fig. 6. Our exposure level is also shown. This intensity level is not uncomfortable to any of the subjects tested, but a factor of two higher causes some discomfort and causes some subjects to blink at a fairly fast rate. As shown in the figure, our input level is well below any danger level.

Our light source is continuous rather than pulsed. It has been reported that pulsed light sources are necessary to stop eye motion. However, the fine retinal motion is 30 to 70 Hz, with an amplitude of 20 seconds of arc; this is only 1½ microns on the retina. The use of a pulsed light source was not considered necessary and because of marginal patient acceptance was not considered desirable.

The light source we used is a 100-watt concentrated mercury arc. Its emission spectrum is shown in Fig. 7. Also shown are the absorption and emission curves of fluorescein. We experimented with several sources, zirconium arcs,

tungsten halogen lamps, xenon arcs, and argon ion lasers. The mercury arc is as efficient as any of these; it is compact, requires no special cooling, utilizes a reasonably sized power supply, and in the 100-watt size has more than adequate energy in an easily utilized source configuration. Fluorescein is usually excited by energy in the spectral region from 4000 to 5000 Å for retinal investigations since the other parts of the eye are transparent at these wavelengths. Peak excitation efficiency is at 4880 Å. We used the 4358 Å mercury line for excitation, and although this means a loss in efficiency by a factor of about 3, this defect is more than offset by the decrease in visual sensitivity of the eye which is about one-twentieth of what it is at 4880 Å.

Filters—Filters are needed that enable the maximum amount of fluorescent energy to reach the detector and at the same time exclude all excitation energy. The 4358 Å mercury line is sufficiently far from the fluorescein emission that a simple filter system could be used. With a barrier filter having a cut-off at about 5000 Å, there is no crossover between emission and excitation energy and, consequently, no specular reflection problem, and a very efficient camera system can be designed.

Detectors—Several detectors were considered—film, television, and image intensifiers. The last was ruled out because of cost, complexity, and the nonavailability of high-resolution tubes. Television was used in some early animal trials and has some merit. It was not used initially because of inherently low resolution, high cost, and

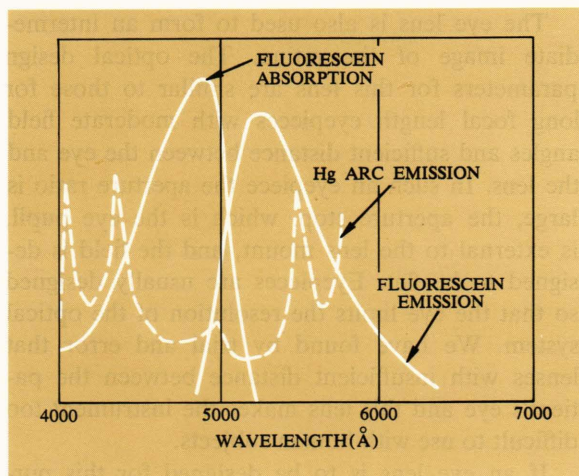


Fig. 7—Mercury lamp emission, and absorption and emission of fluorescein.

complexity. The final choice was film. Of the available film sizes, 16-mm seemed the logical choice. Cameras, lenses, processing and projection equipment are available nearly everywhere.

Tri-X is the most commonly used black and white film because of its high speed and wide exposure latitude. It has a speed of about 200, 80 lines/mm resolution, and moderate low sharpness. Low sharpness means that boundaries will not be well defined. Other emulsions such as Linagraph Shellburst or 2479 RAR may give better results although closer exposure control will be required. Shellburst has the same speed as Tri-X, resolution of 135 lines/mm and extremely high sharpness. This is the film that we have used for most of our tests.

Optical System—The optical system can be divided into several separate components. First, consider the illumination of the retina. The mercury arc energy is collected by the condenser focused on the eye pupil. From there it spreads over the retina (see Fig. 4). The mercury arc image at the cornea is 2 mm in diameter and does not need to be centered in the pupil, only reasonably close to it. The condenser must be large enough in diameter to fill the eye lens and with short enough focal length to collect sufficient energy. The eye lens and condenser combination must be free from excessive spherical aberration so that the light actually enters the eye and uniformly illuminates the retina. The area illuminated on the retina is determined by the aperture ratio of the eye lens. An $f/2$ lens will illuminate a circle 8 mm in diameter.

The eye lens is also used to form an intermediate image of the retina. The optical design parameters for this lens are similar to those for long focal length eyepieces with moderate field angles and sufficient distance between the eye and the lens. In such an eyepiece the aperture ratio is large, the aperture stop, which is the eye pupil, is external to the lens mount, and the field is designed to be flat. Eyepieces are usually designed so that the eye limits the resolution of the optical system. We have found by trial and error that lenses with insufficient distance between the patient's eye and this lens makes the instrument too difficult to use with human subjects.

If an eye lens is to be designed for this purpose, it should correct the chromatic aberration of the eye and be free from glasses that fluoresce at

wavelengths greater than 5000 Å. Most of the available eyepieces have such short focal lengths that we have used a photographic objective in the test camera.

The relay lens system transfers to the film plane a reduced size image of the intermediate retinal image. The relay lens should have a very flat field and the ability to deliver a high-contrast, high-resolution image.

The resolution of the optics of our test camera has been measured by placing a lens, equivalent to the eye, and a test target in front of the camera and examining the final aerial image with a microscope. It was found that for a high resolution target three micron line spacings could be well resolved. If the final resolution is assumed to be the sum of the resolutions of the eye, camera, and film as shown in the table, limitations of the various parts of the system can be estimated. The film is seen to be the poorest element, and therefore this offers the greatest area of improvement.

ESTIMATION OF RESOLUTION OF VARIOUS ELEMENTS

Eye (Campbell and Green)	2 μ
Camera (Measured)	3 μ
Film (Kodak Data)	7 μ
Assume	
Eye + Camera + Film = Final Resolution	
Final Resolution	
Estimated from Above	12 μ
Best Measured Value	10 μ

Since one of our main concerns is conservation of the fluorescent energy from the eye, special consideration has been given to the aperture and field stop positions and sizes. The full dilated pupil of the eye is the aperture stop, and no other stop limits the light throughput. The relay lenses are oversized so that a slight misalignment of the patient's eye and the camera optical system will not affect the energy at the film plane.

Focusing in the test camera is rather simple; the film and relay lens system is moved for coarse focusing, and the first of the relay lenses is moved for fine focusing.

Prototype Clinical Fundus Camera

After working with the test camera for a short time, some of the needed improvements became quite obvious. The field of view was too small; the design objective of an 8-mm-diameter field on the retina was not met. In addition to this, the resolution and contrast should be better, the field more evenly illuminated, and the camera should

be simple and convenient for the operator to use. With these improvements in mind, a prototype camera for use in the clinic at Wilmer Institute was designed and is presently being constructed. This camera is shown in Fig. 8.

The field of view will be about 1 cm in diameter. A widefield eyepiece of long focal length has been obtained and will be tried. Several photographic objectives of large aperture also appear suitable. With any of these lenses the design objectives should be met.

In our initial tests we seemed to be limited in resolution more by the film than anything else. An enlarged retinal image may be the easiest way to overcome this. Therefore, the relay lens system is designed to give a variable sized image of the retina on the film plane. However, if the linear size of the image is doubled, the available energy is spread over four times the film area. This will necessitate higher utilization of the fluorescent

light by decreasing losses. This can be done with higher transmission lenses and more efficient dichroic beam splitters.

The field of view will be evenly illuminated by decreasing the spherical aberration of the mercury arc optical system.

One problem that became noticeable in human trials, which did not appear in our earlier rabbit experiments, is the slight fluorescence of the cornea and lens which causes a loss in contrast in the pictures. This fluorescence will be removed with a small stop at the corneal image. This image is at the position of the barrier filters.

The greatest overall improvement will come in making the instrument easier for the operator to use. The base for a standard Zeiss camera with the headrest attached will be used. The patient will be more comfortable and his head will be more stable. The camera will be easily used since the operator adjustments are in almost identical positions as those of the Zeiss camera which is presently used. The movie camera body to be used is the type with through-the-lens focusing by moving a mirror into the film gate between exposures. This will provide the maximum amount of light for focusing and viewing. Provision is also made for simultaneously recording with film and television if this seems desirable.

The problem of data handling is still critical, however, even if short strips of film, five to ten seconds in duration, are used for each patient. The number of frames to be studied becomes quite high. The interpretation of cineangiograms will be, at least in the beginning, time-consuming and expensive. It will also require considerable skill and experience on the interpreter's part. In the beginning the cineangiographic studies will be considered as research work, but it is quite possible that they will soon have clinical importance, especially in the study of glaucoma patients and for the evaluation of circulatory changes induced by different drugs.

Acknowledgment

This project is part of a collaborative program in ophthalmology with the Wilmer Institute of The Johns Hopkins Medical School. Dr. Lea Hyvarinen and Mr. Terry George of Wilmer have participated in various phases of the design and evaluation of the prototype. Mr. C. F. Bradley of APL has assisted in the engineering of the test and prototype cameras.

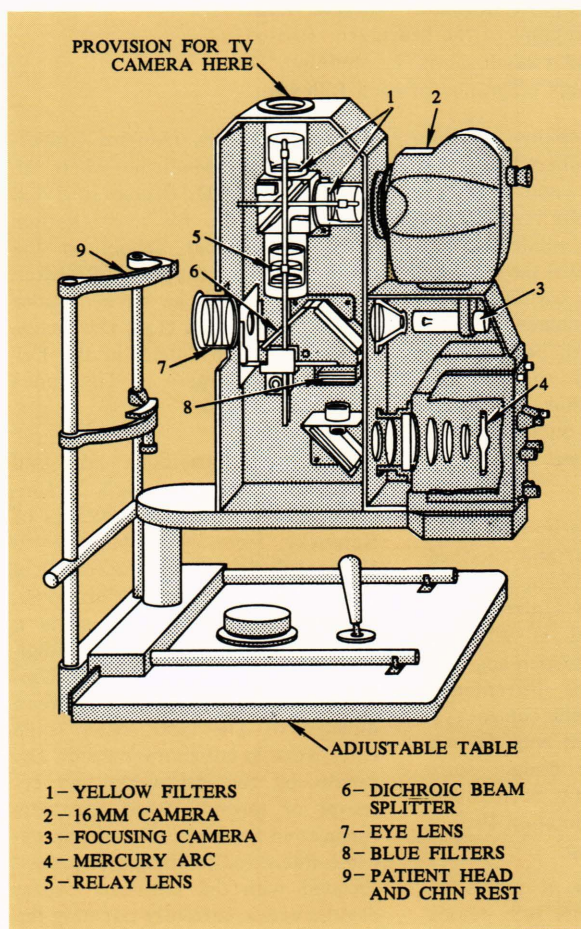


Fig. 8—Prototype camera.