FLUORESCEIN ANGIOGRAPHY: ITS CONTRIBUTIONS TOWARDS UNDERSTANDING THE MECHANISMS OF VISUAL LOSS IN GLAUCOMA*

BY *George L. Spaeth,* MD

INTRODUCTION

THE PURPOSE OF THIS REPORT IS TO DOCUMENT THE CHARACTERISTICS OF GLAUCOMA as evidenced by fluorescein angiography and to analyze the data in terms of their possible contribution towards understanding the mechanisms of visual loss in glaucoma. Appropriate literature will be reviewed. The design and method of the study will be described. The results of a statistical analysis of the data will be summarized. Individual cases will document the statistical analyses and introduce new material.

The conclusion will be drawn that fluorescein angiography is of value in the study of glaucoma. A classification of glaucoma incorporating the new information and integrating older concepts will be offered.

HISTORICAL REVIEW

Causes for visual loss due to glaucoma will most likely be revealed by sequential study of the optic nerve and retina of humans with the disease. The definitive method of investigation, histopathological study of globes removed from individuals in all stages and with all varieties of glaucoma, is not readily accomplished; also it precludes repetitive studies in individual subjects. Consequently other methods, such as the meticulous and imaginative study of visual function, are of great importance and certainly have not yet reached the limits of their potential. Interpretation may be difficult however, because precise correlations between structure and function are still lacking; an understanding of causation can not always be determined from the nature of functional defects. Fluorescein angiography offers a method of studying living humans sequentially, and as such may provide information presently unobtainable.

*From the Glaucoma Service of the Wills Eye Hospital, Thomas Jefferson University, Philadelphia, Pennsylvania.

TR. AM. OPHTH. SOC., vol. LXXIII, 1975

Though the first report of successful clinical fluorescein angiography was in 1961, it was not until six years later that a report refining the technique for purpose of studying the optic disc appeared, and still another year before the first article on the fluorescein angiographic aspects of glaucoma.[1-3] One reason for this delay was the technical problem associated with pseudofluorescence of the optic nerve head.[4] Since the disc reflects light it will appear fluorescent on the angiogram even prior to injection of dye unless a barrier filter is employed that completely excludes wavelengths permitted to pass through the excitor filter. This pseudofluroescence makes interpretation of the angiogram difficult; the time at which dye first enters the disc cannot be accurately determined and details of the fluorescent pattern are obscured by the spurious fluorescence. Intensity of pseudofluorescence is largely a function of the degree of overlap of the transmission characteristics of the barrier and the excitor filter: the smaller the overlap the less the pseudofluorescence. The "ideal" barrier filter should block all wavelengths except those in the range of fluorescent light, that is between 485 and 600 nm. Thus the barrier filter should have a sharp cut off around 490 nm; in order to permit adequate exposure of the film it should transmit all shorter wavelengths. The ideal excitor filter transmits all light energy with wavelengths longer than 490 nm. The more completely the barrier filter excludes light allowed to pass through the excitor filter the less the pseudofluorescence.

The filter system that first minimized pseudofluorescence well was reported in 1966.[5] The use by Hodge and Clemett of an interference excitor filter (Baird-Atomic) was a major advance in technique; the absorption type barrier filter they continued to employ, however, allowed excessive overlap. This was largely corrected by utilizing two interference filters, such as the Baird-Atomic B4 and B5 filters.[6] A different technique employed by Machemer, Norton, Gass and Choromokos, used the B5 in conjunction with the Kodak Wratten 12, with good suppression of pseudofluorescence.[7] Probably the most important advance in the study of disc fluorescence is the utilization of high quality, matched interference filters which eliminate pseudofluorescence almost totally.[8,9] Variable coating of interference filters may introduce bands of transmission common to both filters. Therefore, when two interference filters are used together they should be specifically matched. These filters have the advantages that the transmission of excited fluorescent light up to a wavelength of 500 nm is great (about 90 percent), the cut off at the shorter wavelength of the barrier filter is extraordinarily steep at slightly above 500 nm, and the transmission of light of longer wavelengths is eliminated and yet the amount of light reaching the photographic film is great. (Figure 1)

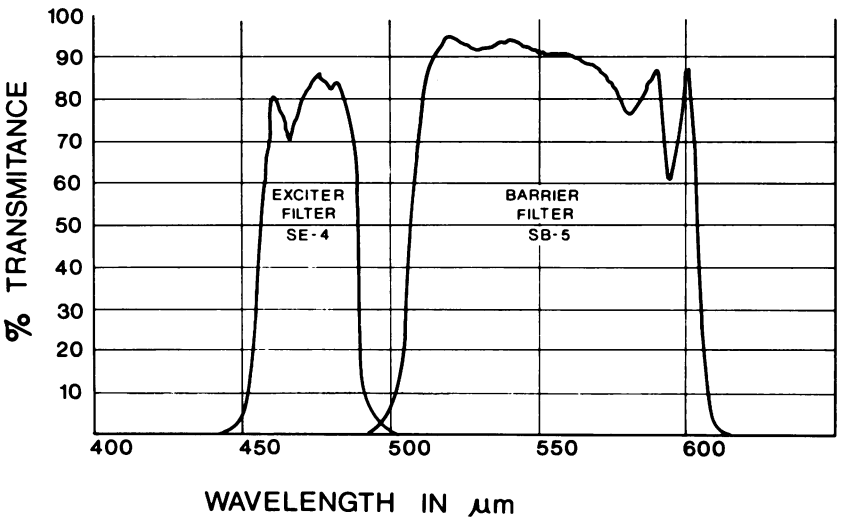


FIGURE 1
Spectral transmission characteristics of the Spectrotech SE4 and SB5 interference filters. Note almost complete absence of overlap, steep cutoffs, and high light transmission.

The development of filter systems has been considered in moderate detail because the visibility of dye in the optic disc depends on absence of pseudofluorence and good resolution, both of which demand proper light filtration.

Using one of these better systems, O'Day and co-workers described the normal fluorescence of the optic disc.[2] They observed that following intravenous injection of fluorescein the nerve started to glow synchronous with the onset of choroidal fluorescence and prior to filling of the cental retinal artery. Fluorescence, at first dull and unevenly distributed in the nerve head, became increasingly brilliant, and by the time dye started returning toward the disc in the larger retinal veins the disc head was glowing brightly; luminous intensity reached its peak about the same time and then faded quite rapidly. A second feature consisted of fine vessels outlined on the disc at the time dye first entered the major branches of the central retinal artery. These small vessels formed a radiating surface network extending peripherally past the disc margin. The small veins filled almost immediately and dye in these small vessels returned to the central retinal vein well before it was visible in the larger veins of the retina. In some individuals a circumpapillary areola of fluorescence developed simultaneous with choroidal filling; unlike the disc, here the intensity consistently increased and persisted well beyond the end-point of central

retinal venous return. Shimizu, using a technique described by Oosterhuis and Gortzak-Moorstein, divided disc fluorescence into four aspects: (1) a hazy fluorescence in the deeper layers of the disc above the level of the lamina cribrosa, (2) a racemose pattern of the prelaminar plexus, (3) superficial, radially arranged prepapillary capillaries, believed to be of choroidal origin since they frequently filled in a sectorial order closely corresponding to the choroidal filling, and radially arranged prepapillary or epipapillary capillaries which also showed a sectorial filling pattern, but appeared to be derived from the central retina artery system; these filled later than the prelaminar capillaries, were primarily venous and "overwhelmed" the visibility of the earlier filling vessels,[10,11] (4) the peripapillary halo, was present in approximately 50 percent of normal eyes and was best characterized by its late onset during the late venous phase, after the disc fluorescence had largely waned; it was usually still visible 60 seconds later. Shimizu postulated that this late halo was possibly an expression of pial vessel blood flow.

The availability of more concentrated solutions of fluorescein made feasible the injection of smaller amounts of dye; this resulted in better definition of vessels by permitting the wave front of the bolus to be defined more accurately.[12] Placement of dye directly into the superior vena cava results in even better resolution, but is considered by some to introduce an unwarranted risk to the patient. Similarly, though the intracarotid route of injection of fluorescein probably allows the best possible detail, it is not a feasible technique in studying patients with glaucoma.[13] Other technical developments have been of less importance, with the exception of the construction of capacitance systems to power the high intensity, rapid sequence illumination needed to capture the dynamics of flow.[14,15] In an attempt to visualize the choroidal flow more accurately indocyanine green, or a combination of indocyanine green with fluorescein has been used.[16,17] However, since the major concern in glaucoma is probably the nature of the optic disc and retina, where the pigment epithelium barrier is no problem, the additional knowledge to be gained from this technical advance is not likely to be great.

With this brief background of the technical considerations that have so greatly influenced the ability to use fluorescein angiography as a means to study glaucoma it now seems appropriate to recount the information that has gradually been accumulating.

The first published study, of Hayreh and Walker in 1967, noted a reduction of fluorescence of the optic disc in many of the patients with glaucoma.[3] The authors pointed out that the technical difficulties of angiography in patients with glaucoma and the small number of cases

studied limited the ability to draw meaningful conclusions. An element of permanent interference of blood supply to the optic disc was commented upon. This observation of reduced optic disc vascularity in patients with glaucoma whose pressures were normal at the time of angiography indicated to Hayreh and Walker that the reduced blood supply in such eyes was not simply a function of raised intraocular pressure. This was important evidence in living humans supporting one of the two theories that have totally dominated thinking regarding the pathogenesis of glaucomatous visual loss; namely, the vascular (von Jaeger) as opposed to the mechanical (Müller) pathogenesis of cupping. These two contending schools of thought will be considered in detail in the discussion section of this presentation, but their existence as the thesis and antithesis components of an evolving understanding of the cause for visual loss in glaucoma should be introduced here. Objections have been raised to Hayreh and Walker's suggestion that the observed decrease in vascularity was pathogenetically significant. For example, the vascular change may be merely a secondary ischemia following atrophy, the primary pathology being neuronal loss unrelated to vascular insufficiency. One patient with normal appearing discs and fields was found to have "practically no fluorescence of the optic disc during the arterial phase." Does this suggest that vascular changes preceded functional and anatomical alterations, or was this just normal variation?

A report of great importance for the subsequent development of concepts regarding the vascular pathogenesis of glaucoma was that by Hayreh, entitled "Blood supply of the optic nerve head and its role in optic atrophy, glaucoma, and oedema of the optic disc."[18] He reviewed the literature and presented new material regarding the blood supply to the optic nerve. Hayreh concluded that "in the normal optic disc in man, the blood supply to the lamina cribrosa and the prelaminar regions is derived from the ciliary circulation, and that to the surface nerve fibre layer is a part of the retinal circulation." Original research was cited to support Hayreh's contention that acute elevation of intraocular pressure (in monkeys) "selectively obliterates the vessels of choroidal origin in the optic disc and the peripapillary choroid but without any obliteration of the retinal vasculature." Hayreh disagreed with the report of Henkind showing an effect of increased ocular pressure on retinal circulation, explaining the observed retinal defects as an example of normal spatial variation in the filling of the retinal vasculature.[19] Hayreh concluded, "the fact that the choroidal contribution to the blood supply of the optic disc and the peripapillary choroid is most susceptible to obliteration by elevated intraocular pressure would go a long way towards explaining the pathogenesis of the nerve

fibre bundle defects, cupping of the optic disc, and cavernous degeneration of the optic nerve in glaucoma."[18] This report states in a definitive tone the case for choroidal ischemia as the major mechanism for visual loss in glaucoma. In a subsequent article Hayreh states "glaucoma may be defined as a disease wherein the normal balance between the intraocular pressure and the blood pressure in the choroidal vessels supplying the optic disc and retrolaminar part of the optic nerve is disturbed, resulting in vascular insufficiency in the optic disc and retrolaminar part of the optic nerve, and hence in visual field defects and pathological changes in the optic disc and optic nerve.[20]

Several reports dealing with the fluorescein angiographic changes caused by spontaneously elevated intraocular pressure were published in 1970. Rosen and Boyd described a method of assessing flow in the peripapillary choroid and the retina.[21] They observed that in normal eyes the peak of the intensity-time graph for choroidal fluorescence occurred simultaneously with that in the retinal artery; in thirty percent of cases the choroidal peak actually preceded the retinal, and in no case was it delayed beyond the retinal arterial peak. However, in all glaucomatous eyes studied the peak choroidal fluorescence was delayed beyond the retinal arterial peak. Rosen and Boyd also believed that the interval between the retinal and choroidal peaks increased with increasing intraocular pressure and vice versa. They concluded that the delay in choroidal filling was an expression of the fundamental pathology of glaucoma, and furthermore that the level of intraocular pressure at which the delay disappeared might be the "upper limit permissible for control of the glaucomatous ischemia . . . In ocular hypertension, the presence of circumpapillary choroidal perfusion delay may suggest that ischemic damage will ultimately occur." Similar findings were reported by Raitta and Sarmela who studied 12 cases of chronic open-angle glaucoma and concluded that diminished vascularity of the disc and circumpapillary choroid was present in all cases.[22]

The circulation times of patients with various conditions including nonglaucomatous optic atrophy, chronic open-angle glaucoma, questionable chronic open-angle glaucoma, low-tension glaucoma and secondary glaucoma were investigated by Spaeth.[23] He concluded that patients with open-angle glaucoma showed an increase in the arm to retinal circulation time, an increase in the time required for blood to pass through the retinal circulation, a greater involvement of the choroidal than the retinal circulations, and in some cases an abnormal peripapillary flush that could not be expected from the ophthalmoscopic appearance. These conclusions were open to criticism because of the technical inadequacy of the angio-

grams, the limited number of cases and the absence of normal controls. Consequently his conceptual conclusion was also unproven, specifically that neither elevated intraocular pressure nor glaucomatous pathological change in the optic nerve alone was causally responsible for the characteristic abnormality of blood flow seen in patients with chronic open-angle glaucoma, but rather that the abnormality was most often present when elevated intraocular pressure occurred in an eye predisposed to the pathological changes of glaucoma. An exception was low-tension glaucoma in which an abnormal blood supply was postulated to be the primary pathologic feature.

These initial studies directed attention primarily to the nature of the peripapillary choroid. Reasons for this were the prominent visibility of these changes, the lack of completely satisfactory filter systems with consequent inadequate definition of disc detail, and the lack of differentiation between normal variations and actual pathology. However, in the same year Oosterhuis and Gortzak-Moorstein described changes in the appearance of the nerve head itself.[10] Their angiographic technique was adequate to permit meaningful analysis. They noted a rough correlation between ischemic areas on the disc and the location of visual field defects and concluded that the fluorographic evidence confirmed previous histological and experimental evidence that optic disc changes in glaucoma were the result of circulatory insufficiency of the nerve head.[24,25] In this they aligned themselves directly with the "vascular (von Jaeger) school." However, it is important to note that they seemed to ignore their reported observation that some patients with glaucoma and visual field defects did not have apparent ischemia, a finding supporting the mechanical (Müller) hypothesis of cupping and visual loss. An additional observation was the poor correlation between ophthalmoscopic appearance of the optic rim and vascularity as revealed by fluorescein.

At the time these studies were being conducted a different investigative trend was developing: angiography was performed during a period of "induced ocular hypertension." Dollery, Henkind, Kohner and Paterson demonstrated that elevated intraocular pressure reduced flow in both the choroid and retinal vessels of the pig.[26] No selective changes were noted that allowed speculation regarding the possible vascular defect in glaucoma. The authors stated, "It is important to point our that our results relate to acute elevations of intraocular pressure in the young anesthetized pig and not to a human afflicted with glaucoma," a qualification apparently sometimes overlooked by others. Hayreh and Perkins studied the effect of intraocular pressures of 30, 50, and 75 mm Hg on the angiographic appearance of the fundus in rhesus monkeys by means of intracarotid injec-

tions of 5% fluorescein.[27] The angiographic pattern at normal intraocular pressure was similar to that seen in man, as already described. Specifically, filling of the temporal capillaries of the disc preceded the filling of the central retinal artery. Spatial and temporal variations in filling were observed and the point made that were the normalcy of these variations not recognized erroneous conclusions would be reached. They noted that elevation of intraocular pressure did not obliterate the capillaries of the retina or those on the surface of the disc until the pressure was raised to such a height that retinal artery pulsations were present. However, disc capillaries considered by the authors to be of choroidal origin became less prominent when intraocular pressure was raised. The authors noted that the normal ophthalmoscopic pallor of the temporal portion of the disc was not confirmed by angiography, which showed a greater vascularity of the temporal portion of the nerve head. Increased intraocular pressure decreased the fluorescence of both disc and choroid. Lastly, the time required for fluorescein to pass through the retina was definitely prolonged by elevation of intraocular pressure; this prolongation did not appear to be due to filling of the retinal arteries but rather to delay in the venous phase of the transit (with the exception of the highest pressures when there was an additional delay in the arterial filling as well). At pressures above 55 mm Hg the carotid artery-to-retina circulation time was also prolonged. Hayreh and Perkins concluded that "a significant part of the blood supply to the disc is derived from the ciliary circulation, and that in glaucoma there is a reduction in blood flow in both the choroid and disc, with marked absence of capillaries in the disc and retina. . . . Acute rises of intraocular pressure in experimental animals do not lead to obliteration of retinal capillaries but to venous stasis in the retina. The choroidal circulation is, however, reduced, and the vessels of choroidal origin which supply the discs become less prominent or even obliterated. It is postulated that the primary factor responsible for the field defects and optic atrophy in glaucoma is most probably interference with the choroidal contribution to the blood supply of the optic disc." One wonders if this last conclusion follows from the experimental data. Nowhere was there actual proof that the capillaries believed to be of "choroidal origin" were in fact springing from such a source; they could have been direct branches of the short posterior ciliary arteries or perhaps come from the pial vessels. The observation of decreased choroidal fluorescence associated with increasing intraocular pressure was probably the finding leading the authors to conclude that the obliteration of disc capillaries was secondary to choroidal insufficiency caused by elevated pressure. However, as will be discussed later, the time-intensity curve of choroidal fluo-

rescence is difficult to assess correctly in view of the filtering effect of the retinal pigment epithelium.[28] A second criticism relates to the authors' generalization from their experimental findings to "glaucoma." Their study of "induced ocular hypertension" can serve as an accurate model only for that type of glaucoma in which there is an acute rise of intraocular pressure unassociated with other disease.

Blumenthal, Gitter, Best and Galin, using a suction cup to elevate intraocular pressure in normal humans, noted that choroidal vasculature appeared to collapse at lower intraocular pressure than the retinal circulation, and concluded that the peripapillary arterial supply to the optic nerve and the optic vessels was most vulnerable to increases in pressure.[29] In contrast, Archer, Ernest and Krill noted that the choroidal and retinal vasculature filled simultaneously.[30] They used induced ocular hypertension angiography to study individuals with albinotic or lightly pigmented fundi. In these the choriocapillaris generally seemed able to withstand a higher intraocular pressure than the retinal capillaries. This finding, at odds with previous opinions, was explained in terms of the better visibility of choroidal circulation in these specially selected patients. The previously noted increased sensitivity of the choroid was thus considered to be a technical artifact. However, while such may be the case, especially in view of Ben-Sira and Riva's report, such reasoning could not logically be applied to the observation that vessels on the disc also appeared to collapse at lower pressures than did the retinal vasculature.[29] Ernest and Archer reported other work not in complete agreement with previous studies. Using induced ocular hypertension they concluded that the peripapillary choroid did not make a significant contribution to the vasculature of the optic disc in man.[31] They commented that the fluorescence of the optic disc was a function of four components, transillumination from retrobulbar vessels, primary vasculature of the nerve head as branches of the short posterior ciliary arteries, venous drainage from the peripapillary retina, and leakage of fluorescein into the nerve head from the peripapillary choroid.

Swietliazko and David observed that the interval between the time of dye injection and its first appearance in the choroid was shorter than the retinal artery appearance time in most eyes of owl monkeys when the intraocular pressure was normal.[32] Elevation of intraocular pressure caused a delay in both appearance times. Glaucoma patients studied by Blumenthal and associates with induced ocular hypertension angiography showed two major findings: (1) when the intraocular pressure was normal there was a delay in choroidal fluorescence that involved the entire choroid or, more frequently, a sharply outlined area near the disc

margin; (2) when the pressure was markedly elevated, defects in peripapillary choroidal fluorescence were noted.[33] Since such "filling defects" occur in normal individuals the significance of the "defects" must be questioned.

The use of experimentally-induced ocular hypertension has probably not provided major information regarding the cause of visual loss in patients with chronic open-angle glaucoma. There is little similarity between the situation in which an apparently normal eye is subjected to a sudden, short-term elevation of pressure and that in which an eye possibly already morbid sustains an intraocular pressure which slowly rises above normal over a period of many years. The acute experiments may be accurate models of acute angle-closure glaucoma, but neither the histopathological nor the angiographic results of studies of acute ocular hypertension can reasonably be expected to reflect correctly the changes of primary open-angle glaucoma.

In an attempt to introduce a more physiological model of induced ocular hypertension a test was described in which the intraocular pressure was allowed to rise by withholding glaucoma therapy and performing a water-drinking test; the pupils were dilated with a pressure-increasing agent such as cyclopentolate, and fluorescein angiography performed; angiography was repeated when pressure was lower, the pupils being dilated with phenylephrine, and the two angiograms compared to see if the change in pressure had been associated with observable change in the blood flow patterns. The reported results were too preliminary to permit valid conclusions; furthermore, the distinction between normal variation and actual pathological change was not defined.

While some investigators were studying induced ocular hypertension others tried to find abnormalities in patients with glaucoma. Begg, Drance and Goldman studied 10 cases of primary open-angle glaucoma.[35] All of the eyes had "notches" of the optic disc except one with a "hole" in the floor of the cup adjacent to the rim; visual field loss, usually in the form of arcuate scotoma, was present in all. Eight of the nine eyes with satisfactory angiograms showed local avascularity of the anterior lamina cribrosa corresponding to the notched area of the disc. The area of complete or relative avascularity was larger than would be expected from the opthalmoscopic appearance of the disc or the extent of the field loss. A sector-shaped peripapillary zone of choroidal hypofluorescence was observed in two eyes. This study more clearly than any before documented a close correlation between glaucomatous pathology of the disc and ischemia, showing a strict relationship between the damaged sector of the disc and local changes in capillary vascularity. Though the authors did not so sug-

gest, the observation that the avascular area exceeded the definitely pathological area could be taken as an indication that ischemia precedes rather than follows tissue loss. A speculation was made regarding the nature of the choroidal filling delay in the damaged segment and the presence of hemorrhages on the neuroretinal rim were very suggestive of the former. This investigation, then, appeared to support the "ischemic hypothesis" of optic nerve damage in glaucoma. However, two of the nine eyes had disc hemorrhages, a proportion vastly greater than the number expected to show such hemorrhages in an unselected glaucoma population. This suggests that a bias in favor of eyes with hypoperfusion may have been introduced. Furthermore, the presence of a filling delay is not necessarily proof of actual ischemia, as the authors themselves point out. The earlier studies of Hayreh and the later investigations of Evans and co-workers demonstrated that peripapillary delays in choroidal filling indistinguishable from those considered by some to be characteristic of glaucoma were regularly seen in the angiograms of apparently normal eyes.[20,36]

Halasa studied 10 subjects with intraocular pressures between 27 and 36 mm Hg, but without visual field defects or pathological cupping of the optic discs.[37] No definite alterations were noted in eight of the ten subjects, but in two a "marked increase in the fluorescence of the disc and peripapillary choroid" was observed when the intraocular pressure was reduced by administration of glycerol; this latter observation had previously been noted in patients with glaucoma.[23]

It should be apparent to the reader of this chronologically organized narration regarding the use of fluorescein angiography to study glaucoma that investigators differ in their concept of the role of the peripapillary choroid. Oosterhuis and Boen-Tan seemed to express a widely accepted opinion when they stated that in normal humans fluorescein flowing to the eye becomes visible in the choroidal prior to the retinal vasculature.[39] The choroidal filling is patchy and irregular but definitely visible even though partly hidden by the retinal pigment epithelium. In glaucoma, or in eyes with induced ocular hypertension, however, the peripapillary circulation appeared to some to be insufficient.[21,22,23,29,33,37] Others did not find peripapillary hypoperfusion.[31,35,36] An explanation for the discrepancy was provided by Ben-Sira and Riva who pointed out the difference in the fluorescein angiographic filling patterns of albino as opposed to pigmented rabbits, attributing the observation to the retinal pigment epithelium's masking effect on visible fluorescence of the choroid in contrast to the unobstructed fluorescence of the retina.[28,39] Apparent delay of dye in the choroidal circulation in normal rabbits and presumably

humans is at least partly a technical artifact caused by this masking. For fluorescence of the choroid to be visible, the concentration of dye in the choroidal vessels must be higher than that needed to cause detectable fluorescence of the retina or optic nerve head. The shape of the fluorophotometric curve compounds the problem in "induced ocular hypertension," for as the total amount of dye entering both the retinal and choroidal systems decreases, the blocking effect of the pigment epithelium will appear to cause a greater decrease in choroidal than in retinal fluorescence. Thus, in eyes studied by inducing ocular hypertension, neither change in intensity of fluorescence nor sequence of dye entry can be taken as a valid indicator of the actual hemodynamics of the choroid. The same principle applies to eyes in which the intraocular pressure changes spontaneously or in response to treatment.

This finding of the variable artifact introduced by the retinal pigment epithelium does not apply to studies of retinal or optic disc flow. However, it casts serious doubt on reports in which the choroidal and retinal circulations are compared, especially those where intraocular pressure is altered. If the artifact is fully recognized it may be possible to investigate choroidal circulation dynamics, especially when perfusion pressure is stable; if, for example, a change is noted in the choroidal in comparison to the retinal vasculature in the second of two angiograms taken one year apart, the intraocular and systemic blood pressures being the same at the two angiograms, it is probable that the change is real. Hyvarinen, Maumenee, George, and Weinstein have illustrated the usefulness of fluorescein angiography in the study of the choroidal circulation.[40] They investigated humans having albinotic fundi, lesions permitting clear visualization of the choroid, and conditions in which the choroidal circulation appeared defective. Extensive data regarding the temporal aspects of the choroidal circulation were not given, but the authors mentioned that it was possible to study "both the rapid intravascular circulation and the slow diffusion of extravasated fluorescein." They pointed out that some parts of the choroidal bed appeared to be devoid of dye even though the surrounding capillary bed had already become filled; in normal subjects the time differences in the filling of the choriocapillaries were described as spanning "only a few seconds" and also as being present in repeated angiograms. The phenomenon described by Ben-Sira and Riva, then, does not invalidate all attempts to study with fluorescein the choroidal circulation of animals with pigmented fundi (including humans); it does, however, highlight the precautions that must be taken in interpreting the angiograms. Not only must data from studies of induced ocular hypertension be examined in the framework of Ben-Sira and Riva's observation,

but also absolute time considerations regarding the choroidal circulation must be considered only approximate. The importance of their observation in regard to the study of patients with glaucoma is mitigated by the availability of filter systems which make it possible to study the circulation of the disc itself, which may be the matter of primary importance. Moreover, if direct study of the choroid is considered important this can be accomplished by the use of indocyanine green.[16,17,41]

A report by Laatikainen and Mäntylä has added to the controversy regarding the peripapillary choroid in glaucoma.[42] These authors obtained satisfactory fluorescein angiograms before and one to six months after glaucoma surgery in 33 eyes with chronic open-angle glaucoma; apparently unsatisfactory angiograms eliminated 17 other eyes from the study. They found abnormalities of the peripapillary choroid in a high percentage of their subjects. When neither disc nor field changes were present "delayed filling" was noted in 22 percent, and "underfilling" of the choroid in 56 percent of the eyes. Eyes with early or moderate disease showed delayed filling in 11 and 29 percent respectively, and underfilling in 78 and 80 percent. "A postoperative fall in intraocular pressure did not result in disappearance of the choroidal filling defects in any of the eyes examined." They concluded, then, that filling defects of the peripapillary choroid and fluorescence of the disc were not clearly influenced by intraocular pressure, and that this indicated "the presence of permanent anatomic changes in the peripapillary choroidal vasculature." Three eyes showing "filling defects" were illustrated. However, in all three the latest phase shown was early venous filling, at which time the defects had already become less visible; one wonders whether the "defects" eventually filled completely, as several authors have pointed out is characteristic of these areas of hypofluorescence.[20,30,36,38,40] It seems probable that these angiographic patterns in fact represented normal variation rather than pathology, and therefore would not have been expected to change significantly. Timing considerations were not studied, so that small changes in the rate of filling which conceivably might have been a function of change in intraocular pressure would not have been observed. Furthermore, the persistence of the apparent defects postoperatively is probably a normal finding rather than a sign of persisting choroidal hypoperfusion. Hyvarinen, Maumenee, George, and Weinstein showed that these areas of late filling tend to recur in the same manner on repeat angiography.[40] Consequently the findings of Laatikainen and Mäntylä do not warrant either the conclusion that change in pressure appeared to be without effect or the contention that permanent defects in the peripapillary choroidal vasculature are present in chronic open-angle glaucoma.

An interesting observation by Laatikainen and Mäntylä was that "normal peripapillary fluorescence (was found) adjacent to an avascular part of the disc, . . . indicating that these adjacent areas were supplied by different branches of the posterior ciliary arteries." This finding casts further doubt on the initial hypothesis of Hayreh and Perkins that disc ischemia in glaucoma is a function of choroidal insufficiency.[27]

In summary, improvements in technique have made fluorescein angiography a potentially useful tool in the study of patients with glaucoma. Better understanding of the technical and interpretative problems has allowed more accurate differentiation between normal, artifact, and pathological. Angiograms in patients with glaucoma show changes not attributable to either artifact or normal variation. However, at least partially because of the considerable difficulties attendant to studying photographically patients with glaucoma (small and rigid pupils, elderly population with cataracts and limited ability to cooperate, difficult maintenance of fixation due to poor sight, corneal haziness associated with elevated intraocular pressure, and a potential risk of inducing a significant rise in pressure) a comprehensive study of patients with glaucoma has not been reported. Furthermore there have been no attempts to quantitate angiographic fingings, and few to relate them to a wide variety of clinical findings. It is the purpose of the present study to add new data developed by investigation of a large number of individuals, over a period averaging two years, and to evaluate the data as quantitatively as possible.

MATERIALS AND METHODS

This was a prospective study in which subjects were examined with an extensive battery of tests at six month intervals for periods up to five years.

TABLE I: DIAGNOSTIC CATEGORIES

Diagnosis
1. Normal
2. Glaucoma suspect
a. Intraocular pressure above 21
b. Cup-disc ratio greater than 0.5
c. Asymmetry of cup-disc ratio greater than 0.1
d. Suspicious disc pathology
e. Saucerization of the disc
f. Coefficient of aqueous outflow less than 0.16
g. Possible but not definite visual field loss
3. Chronic open-angle glaucoma
4. Low-tension glaucoma
5. Angle-closure glaucoma
6. Pigmentary glaucoma
7. Congenital glaucoma
8. Other glaucoma

TABLE II

Data Obtained	Frequency
1. Patient consent	Every visit
2. History — full (extensive medical and family history)	Initial visit
— interim (medications, illnesses, etc.)	Subsequent visit
3. Visual acuity	Every visit
4. Intraocular pressure (Goldmann applanation)	
Pre-dilatation	Most visits
Post-dilatation	Every visit
5. Refraction	Initial visit
6. Gonioscopy (Zeiss 4-mirror lens)	Initial visit
7. Goldmann perimetry (3 isopters)	Every visit
8. Slit lamp biomicroscopy	Every visit
9. Steroscopic ophthalmoscopy (Hruby lens)	Every visit
10. Tonography	Initial visit
11. Ophthalmodynamometry (Bailliart), diastolic and systolic	Every visit
12. Estimate of "disc blanch"	Every visit
13. Systemic blood pressure, pre- and post-angiography	Every visit
14. Photography of optic discs, stereoscopic	Every visit
15. Fluorescein angiography	Every visit
16. Decholin circulation time	Every visit

A list of the diagnostic categories included is shown in Table I, and of the tests performed in Table II. Initial description of all angiograms was in a "blind" fashion. Angiograms were than analyzed again, in an open fashion, and efforts made to find patterns in the angiograms, correlation between angiographic data and clinical findings. Information obtained was submitted to computer analysis.

The criteria for entry of patients into the study were the following: clear-cut diagnosis within the limits defined (see below), adequately clear optical media, ability to cooperate with the testing techniques, willingness to participate in the study, no history of allergy to previous injections, no known abnormality that might interfere with the flow of fluorescein from the antecubital fossa to the eye, and anterior chamber angles considered non-occludable. Normal controls were selected from those responding to a request for control subjects. They were age, race and sex-matched with the subjects diagnosed as having chronic open-angle glaucoma.

Chronic open-angle glaucoma was defined as intraocular pressure above 21 mm Hg together with optic nerve cupping and visual field loss characteristic of the changes caused by glaucoma; no other apparent cause for optic nerve damage could be present. In low-tension glaucoma, cupping and field loss compatible with that caused by glaucoma were both present, but the intraocular pressure was below 22 mm Hg. All patients with low-tension glaucoma had medical and neurological evaluations; laboratory tests included sedimentation rate, glucose tolerance test, serological test for syphilis, complete blood count, and radiological examination

TABLE III: BREAKDOWN OF PATIENTS STUDIED

1. Total cases entered into study	437
2. Patients having only one angiogram	92
3. Patients having more than one angiogram	170
4. Patients having technically satisfactory angiograms	247

of the skull; a diurnal curve of intraocular pressure was obtained over a two day period while in the hospital. Pigmentary glaucoma was defined as chronic open-angle glaucoma in conjunction with signs of the pigmentary dispersion syndrome (iris transillumination, Krukenberg spindle, pigmentation of the posterior trabecular meshwork). For a diagnosis of angle closure glaucoma to be made the subject needed to have closed angles and elevated intraocular pressure. "Other glaucomas" consisted of conditions with intraocular pressure above 21 mm Hg in association with an apparent cause for the elevated pressure, such as uveitus, essential iris atrophy, or previous trauma.

A complete evaluation was performed on each subject at the initial examination. At each subsequent visit all required data were obtained (Table II). Determination of the visual field at one visit and fluorescein angiography one month later, for example, was not permitted except in extraordinary circumstances.

Repeat evaluations were performed at six month intervals for the duration of the study unless the subject wished to withdraw, developed significant adverse reaction to the testing situation, or proved to be inappropriate for inclusion in the study because of technical reasons (development of cataract, inability to fixate).

When change occurred rapidly visits were scheduled more frequently. The data from all cases entered into the study were considered. However, where angiograms were not technically excellent the angiographic findings were not included in the statistical analysis (Table III).

Those individuals selected for inclusion in the study were examined in a standard fashion at each evaluation: the purpose, duration, method of performance, and hazards of the research project were discussed with each subject and consent obtained; the subject's name, date, age, sex, race, and other identifying data were recorded; the subject was questioned regarding allergies or adverse responses to injection or venepunctures; history was obtained and recorded regarding systemic and topical diseases and medications, best corrected visual acuity was measured and the intraocular pressure determined with a Goldmann applanation tonometer. No patients with occludable angles were included in the study with the exception of those in the process of a spontaneous angle closure attack. Goldmann perimetry was performed by a technician: the size of the pupil

was recorded; the patient's refractive error was measured and appropriate correcting lens utilized during the testing; at least 3 isopters were plotted, usually utilizing the smallest, dullest test object the patient could see, a test object whose threshold level visibility was determined just peripheral to the blind spot, and a test object visible well outside the blind spot, a semistatic technique was employed to define the isopters. After the pupils became maximally dilated in response to phenylephrine, 10% and tropicamide, 1% the pupil size was recorded and the optic discs photographed stereoscopically (1× and 2×) using a Zeiss Fundus camera and Kodachrome film. Stereoscopic photographs were also taken on Polaroid film. The systemic blood pressure was measured and recorded. Venepuncture using a Butterfly - 19 infusion set was made into a large vein deep in the antecubital fossa. Decholin circulation time was measured using a stopwatch. The infusion set was rinsed and a 6cc syringe containing 5cc of 10% sodium fluorescein attached. The patient was positioned at the Zeiss Fundus Flash II or III and readied for photography. Filters employed during fluorescein angiography were matched Baird Atomic B4 and B5, or Spectrotech SE4 and SB5. A control photograph was taken with a red-free filter and then with the blue excitor filter in position. Kodak Tri-X film was employed. Fluorescein was forcibly injected (within 1 second) through the infusion set into the antecubital vein. Utilizing the Decholin circulation time as a rough guide of the fluorescein circulation time photographs at intervals of approximately 0.4 seconds were taken with the blue filter in place so as to assure that the first entry of the eye was documented photographically. Rapid sequence photography was continued for approximately ten seconds after appearance of the dye. Stereophotography was performed 30 seconds after the dye appeared as well as one minute, two minutes and five minutes later. Throughout the period of angiography every effort was made to assure steady fixation, a constant degree of accommodation, maintenance of clear media, and absence of any head movement.

Immediately following fluorescein angiography intraocular pressure and systemic blood pressure were again measured. The ocular fundi were then examined stereoscopically with a Hruby lens at the slit lamp. The appearance of the optic disc was graded according to the following schema: the disc was divided into two major concentric areas, the width of each area depending upon the nature of the individual disc (Figure 2). The more central area included the ophthalmoscopically visible cup as defined by change in configuration of the surface of the optic disc. The more peripheral circle was composed of the neuroretinal rim of tissue, which may or may not have been normal. Both the central and

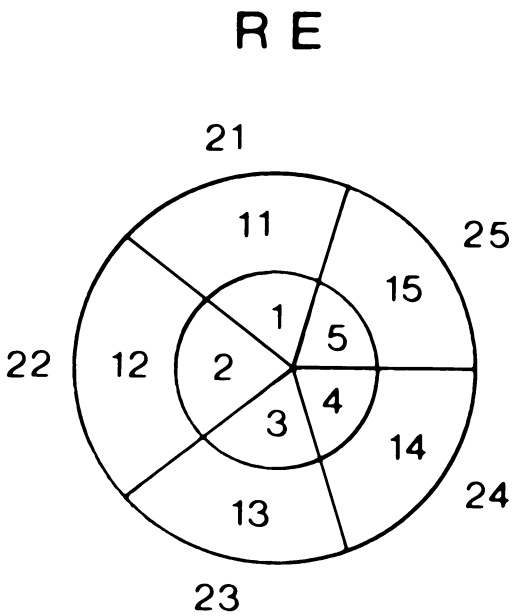


FIGURE 2 (See text)

the peripheral areas were again subdivided into five sections, specifically superotemporally, inferotemporally, inferonasally, and superonasally. The inner five areas were designated respectively 1, 2, 3, 4, and 5, the outer 11, 12, 13, 14, and 15, so that 11 was adjacent to and external to 1, 12 to 2, and so forth. Degree of optic nerve pallor was estimated in each area, ranging from 0, signifying no pallor to 4+, extreme pallor. The presence of Read's "laminar dots sign" or a "tinted hollow" was noted: a "tinted hollow" referred to an area of apparent tissue loss, where the color of the hollowed out area was still pink.[46] This contrasted with the presence of a definite "notch" where the remaining portions of the neuroretinal rim could be quite normal, but the area of tissue loss was white and atrophic. The presence of a notch in any of areas 11, 12, 13, 14, or 15 was recorded. The presence or absence of increased transparency of the tissues between the anterior surface of the lamina and the internal limiting membrane of the retina, that is, the prelaminar portion of the optic nerve head, was noted; where abnormal transparency was observed its location and stage of development were recorded.

Nerve fiber bundle defect of the retina were searched for as described by Hoyt and Newman, using both white and red-free light and recorded.[44]

The cup-disc ratio was estimated, utilizing change in configuration rather than change in color as the criterion for edge of cup, in both the horizontal and vertical directions.[45]

Ophthalmodynamometry was performed with a Bailliart ophthalmodynamometer and the direct ophthalmoscope; diastolic and systolic pressures were measured. In addition, an attempt was made to determine the level of pressure at which the temporal disc tissue first started to blanch in a pulsatile fashion; this was recorded as the level of diastolic "disc blanch." That point at which the temporal portion of the neuroretinal rim became persistently blanched was recorded as the systolic "disc blanch" pressure. The determination of the diastolic disc blanch was difficult and not always possible. Especially was this the case in nerves where little neuroretinal rim was left. The systolic disc blanch, however, was relatively easily measured. This measurement was made independent of the appearance of pulsation in the central retinal veins.

The color photographs, both 1X and 2X were developed by one of the laboratories of the Eastman Kodak Company. Film was processed in undiluted Kodak D-76 developer at 75°F for 10 minutes. Prints for publication were made on Agfa Brovira BEH 1 #6. Exposure was in most instances adjusted to the characteristics of each negative, so as to make comparison between different angiograms possible. The light intensity of the exposure standard was ten foot-candles at the enlarging easel. Exposure time for this standard was set for a negative density of 1.15. Because the negatives in the very earliest phases of dye entry occasionally showed only the barest amount of fluorescence, and because high contrast paper was utilized in printing, it was necessary in a few instances to increase the exposure slightly. This was done only in the prints of the earliest phases, and is recognizable by the lighter background.

Angiograms were analyzed without knowing the name of the subject or the diagnosis. In the initial phases of the study contact prints or photographic enlargements were examined. However, this method was discarded as too costly and too inaccurate. The print failed to give as much or as reliable information as the negative itself. Projection of the negatives was tried and abandoned; not only was the risk of scratching the negatives considerable, but enlargement was not associated with increased resolution. The best method proved to be direct examination of the negative with a high quality magnifying glass; the Nikon 20 diopter lens intended for indirect ophthalmoscopy was a help in this regard, but much greater magnification was needed for fine analysis. A light-table with a thickly frosted glass surface proveded even illumination for viewing. Stereoscopic photographs were usually examined with decen-

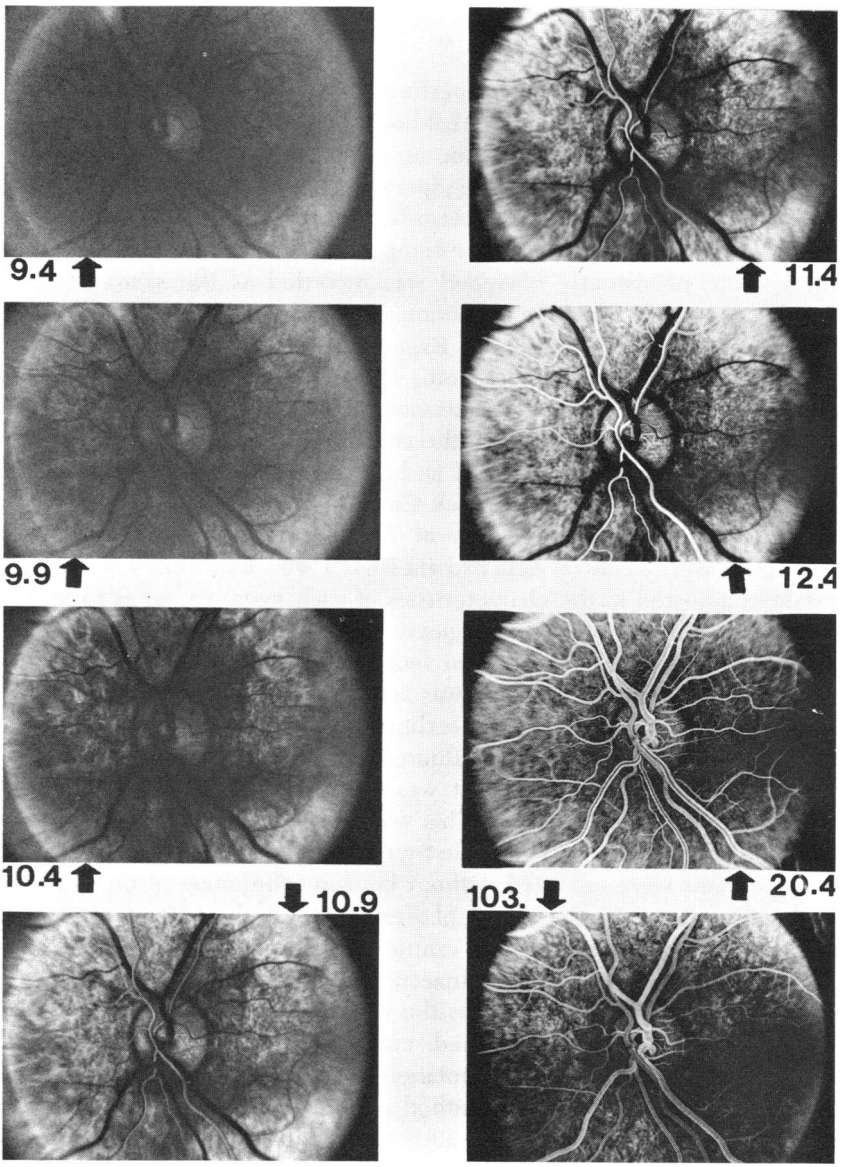


FIGURE 3A
Angiogram of #1, an apparently healthy 17-year-old black male.

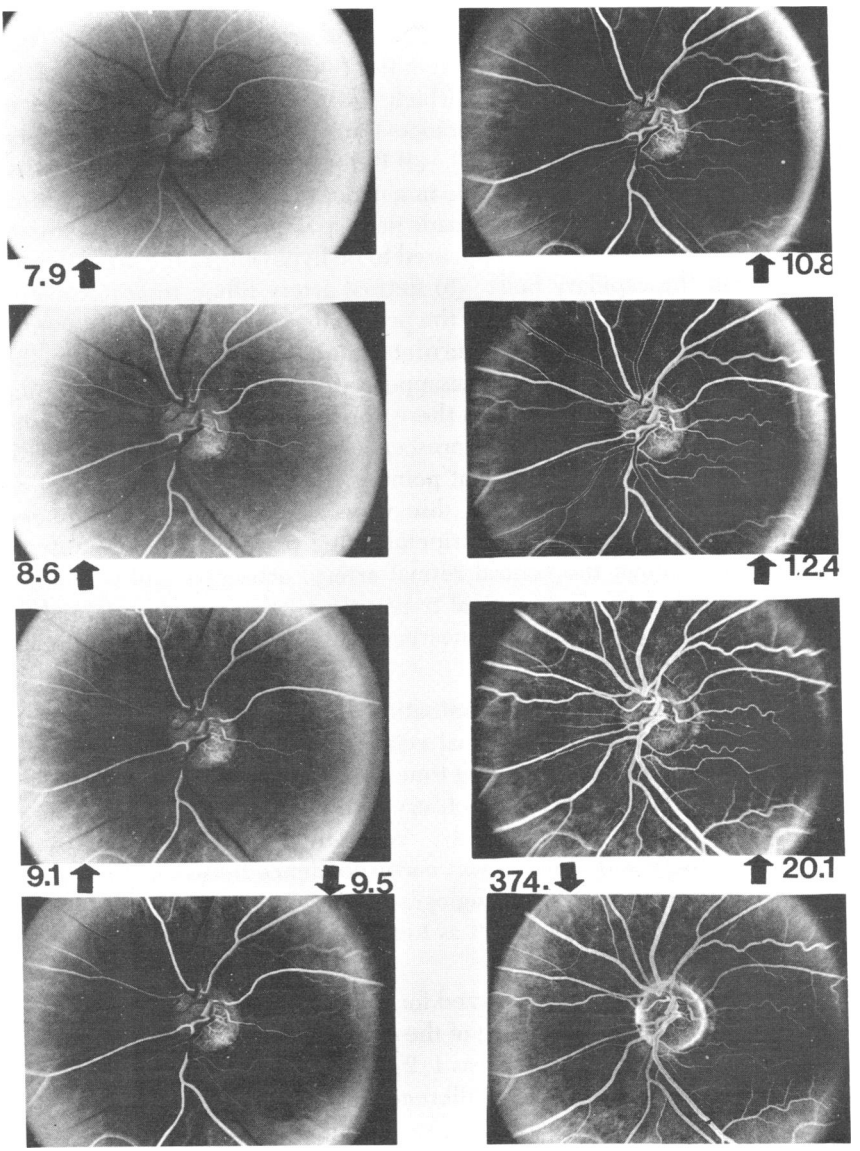


FIGURE 3B
Angiogram of #2, a 58-year-old black normal control.

tered plus 12.00 aphakic spectacles, though the Donaldson viewer was occasionally used.

The following were determined: (1) Retinal artery appearance time (that point at which dye was first visible in the central retinal artery). (2) Disc appearance time (that point at which the disc tissue first appeared to fluoresce). (3) Choroidal appearance time (when fluorescein was first visible in any area of the choroid). (4) Retinal vein appearance time (that time at which dye was first visible in a major branch of the central retinal vein; this measurement was not made in areas where arteriovenous shunts were present or where there appeared to be bypassing of the normal transit through the capillary bed). (5) Retinal artery filling time (estimated as the time at which the filling of the precapillary arterioles was first complete). (6) Retinal vein filling time (determined as the time when lamellar flow in retinal veins had just disappeared). (7) Choroidal filling time (estimated as that point at which there appeared to be no increase in the intensity of diffuse choroidal fluorescence at any in the choroidal bed). (8) Disc filling time (taken at that point at which there was visualization of fluorescein in the superficial disc veins, those vessels having been identified as veins by their centripetal filling pattern). The rapidity of dye transit through the central retinal artery, arterioles and capillaries was expressed as the "intraretinal transit time;" this was determined by subtracting the retinal artery appearance time from the retinal vein appearance time (Figure 3).

In actual practice the determination of retinal artery appearance time, disc appearance time, retinal vein appearance time, retinal artery filling time, and retinal vein filling time could be made quite easily. This was tested by having a separate observer make the determinations on a series of angiograms independently. When the angiogram was of excellent quality there was almost exact correspondence between the two independent evaluations of the angiogram in regard to these appearance times; there was good agreement as to the retinal artery and retinal vein filling times.

The angiogram was then analyzed for the presence or absence of a "delay" or a "decrease" in the filling of the disc. This was separately considered for each of the ten areas, areas 1, 2, 3, 4, and 5, or 11, 12, 13, 14, and 15. "Delay" was defined as any difference in the rate of appearance of dye within the disc. That is, when dye was visible in one area prior to being visible in another, a delay was said to be present. In contrast a "decrease" signified a delay which persisted past the time of venous filling. Thus a decrease appeared as a persistently hypofluorescent area in contrast to its surroundings.

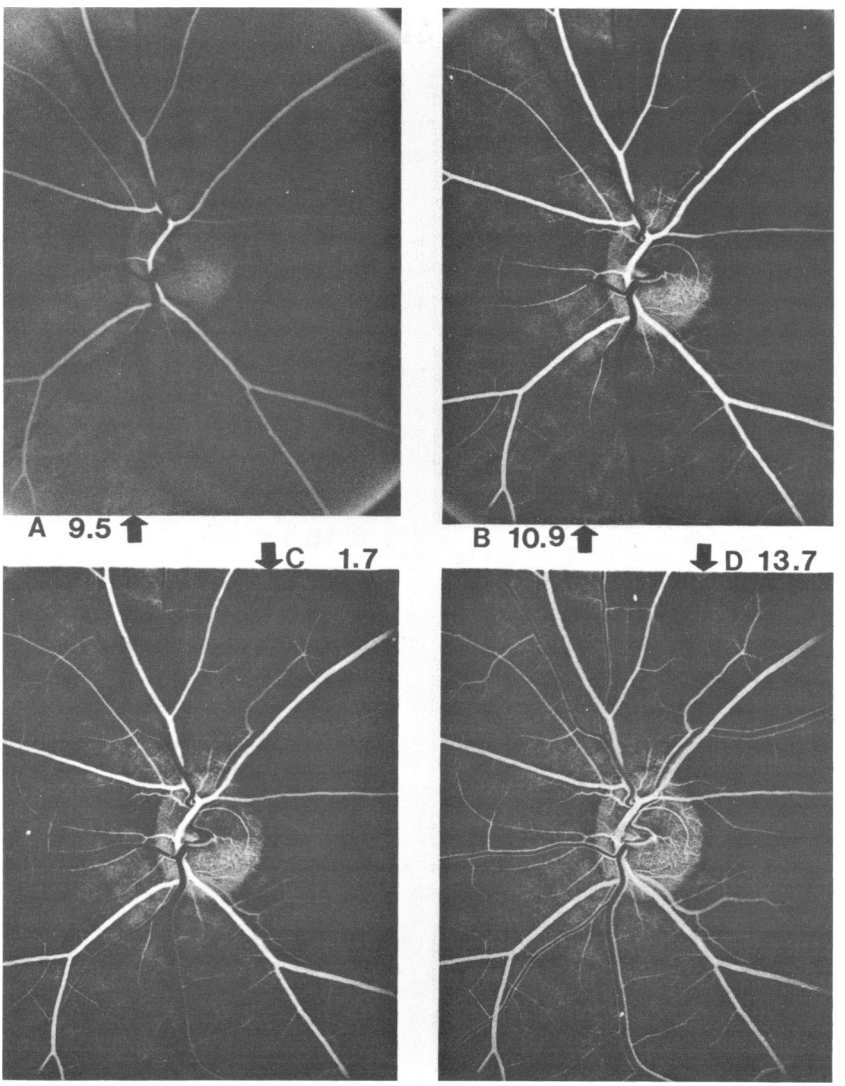


FIGURE 4
Disc filling delay in a 41-year-old white woman with early but definite chronic open-angle glaucoma; nerve fiber bundle type visual field loss was present. Intraocular pressure was 21 mm Hg.

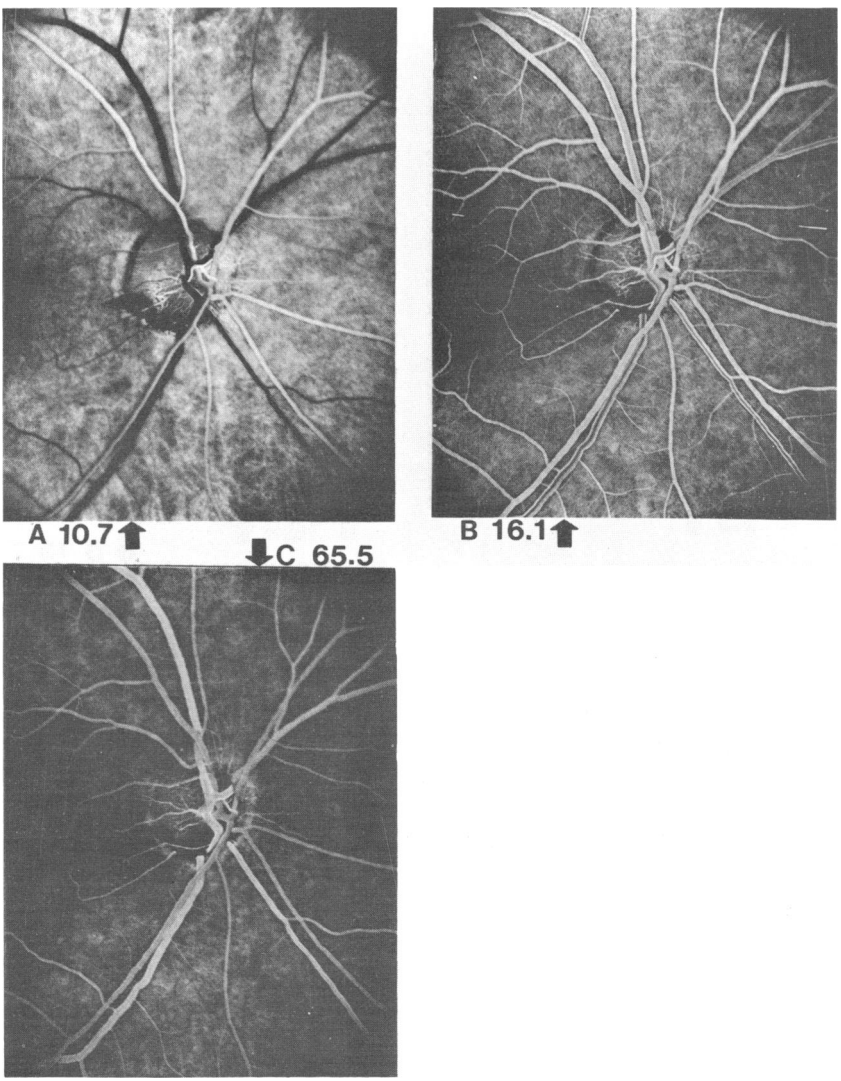


FIGURE 5
Disc decrease in a 48-year-old woman with "low-tension glaucoma" and a disc hemorrhage. The area of decrease is inferotemporal.

A filling delay, then, was considered present when a particular region of the disc or choroid became fluorescent later than the other regions, but eventually appeared to fill completely. An example of such a delay is illustrated in Figure 4. Nine and one half seconds after injection of dye the nasal and the inferotemporal portions of the disc started to fluoresce, but not the superotemporal region (Figure 4A). There was a "filling delay" in areas 1 and 11, and in part of areas 2 and 12. This was more apparent 1.4 seconds later (Figure 4B). After two seconds the difference in intensity of fluorescence between the superior and inferior portions had lessened (Figure 4C), though there was still less dye in the superior rim. Two seconds later, or four seconds after injection of dye, however, the entire disc fluoresced in a seemingly homogeneous manner; that is, the "delay" was no longer visible (Figure 4D).

A "filling decrease" in contrast, was an area of hypofluorescence lasting well into the late venous phase. The angiogram of a 48 year-old woman with a dense superior visual field defect is illustrated in Figure 5. In the arterial phase less fluorescence was noted in area 13 (Figure 5A). This was still hypofluorescent six seconds later, by which time the veins had filled (Figure 5C); had the intensity of fluorescence returned to normal this would have been labeled a filling "delay", but since localized hypofluorescence was still visible one minute after injection of dye, this constituted a "filling decrease." The angiogram in Figure 5 was chosen to illustrate a different and unrelated type of hypofluorescence. At the temporal edge of the disc, just inferior to the midline, was an unchanging spot of total non-fluorescence due to hemorrhage, and not to absence of dye. This type of "blocked fluorescence" which was not a reflection of blood flow was identified as a "disc defect," not as a decrease. The nature of the defect was determined by reference to colored fundus photographs routinely reviewed immediately after reading the angiogram.

Edema of the disc was considered to be present when the disc showed venous and peripapillary capillary dilatation, and leakage from the disc vessels that extended beyond the margins of the disc itself.

When disc fluorescence lasted longer than five minutes after the injection of dye the angiogram was said to show "fluorescent staining of the disc." This was graded in terms of none, mild, moderate or marked. Examples of disc staining are shown in Figure 6A, B and C. In the illustrated case, that of a young woman with far-advanced chronic open-angle in the right eye and moderate disease in the left, the difference between moderate (right eye) and mild (left eye) can be observed. Figure 6D shows marked disc staining in a young man with long-standing secondary glaucoma.

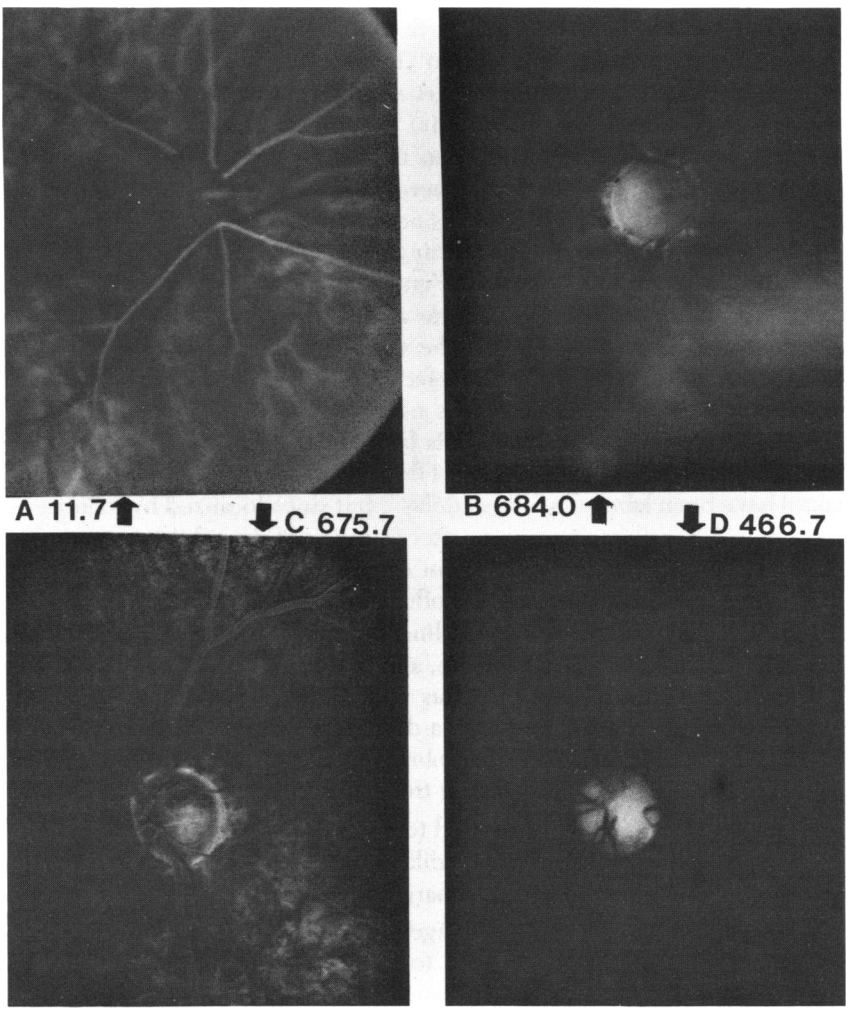


FIGURE 6

Staining of the optic disc in a 35-year-old woman with bilateral chronic open-angle glaucoma. 6A demonstrates absence of pseudofluorescence. 6D shows marked staining of the disc.

In some cases a halo of peripapillary hyperfluorescence was noted. The intensity and pattern of this was difficult to grade. Such a halo occurring in a normal control, age 57, is shown in Figure 7.

It should be noted here that terms such as "delay," "decrease" and "staining," do not signify normalcy or pathology. The words are merely descriptive. Whether or not such "delays," "decreases," and "stainings" represent pathology can be determined only by correlation of the angiogram with other data including angiograms of normal individuals. No value judgment was made at the initial angiographic description; the goal at that time was to describe findings, not to attribute mechanisms.

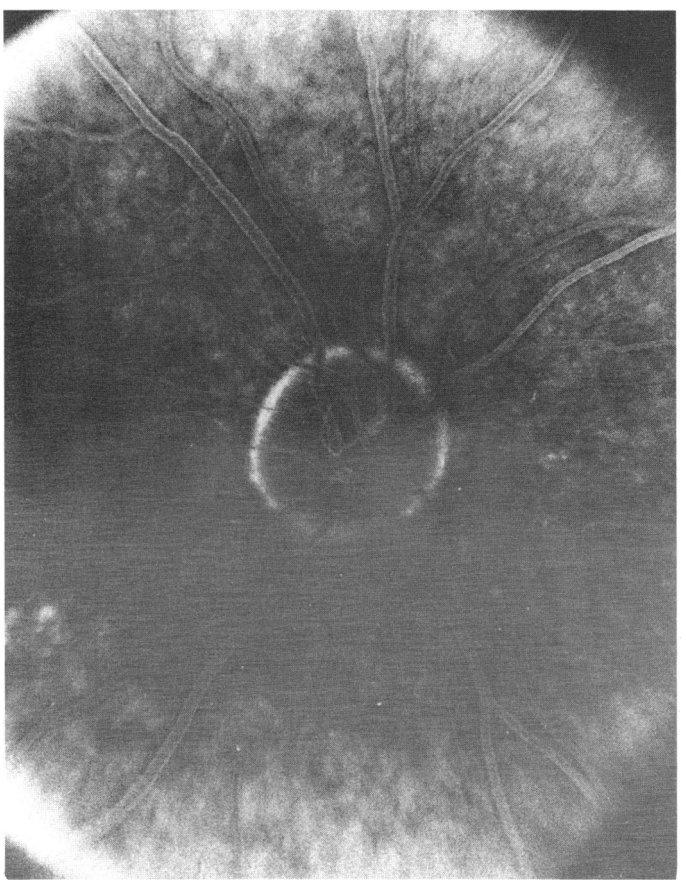


FIGURE 7
Peripapillary hyperfluorescence in a 57-year-old white man with apparently normal eyes.

Fluorescence originating in the choroid was described; of interest were the peripapillary areas designated 21, 22, 23, 24, and 25 (those areas being contiguous with disc areas 11, 12, 13, 14, and 15) and the more distal choroid, designated 31, 32, 33, 34, and 35 (those areas respectively being contiguous with the peripapillary choroid). A "delay" signified localized hypofluorescence in a particular area. A "decrease" denoted a delay persisting well into the venous phase at which time the remainder of the angiogram showed intensive fluorescence. Once again the phrases "delay" and "decrease" are solely descriptive. In fact, they do not even indicate that an actual delay or decrease occurred. The apparent change in fluorescence may be only a function of a variable degree of pigmentation of the retinal pigment epithelial layer.

The findings just described were transferred onto computer punch cards and analyzed by a program designed in cooperation with the University Computer Center. The basic computer program utilized was the Statistical Package for the Social Sciences, version 5.5 of the Vogelback computing center of Northwestern University, modified specially for the present study. This program was intended to search out possible correlations between the data utilizing the Spearman and Kendall coefficient correlations, Chi square, Student's t-test comparison of means, Kruskal-Wallis one-way analysis of variance, and other appropriate statistical methods.

Densitometric evaluation of the intensity of fluorescence was individually made in each numbered region using a West, MacBeth Quantilog densitometer with the smallest available aperture. The uncertainty of the method however, was great. For example, were the reading taken overlying a large vessel the result was vastly different than if taken 1 mm away. Furthermore, unavoidable variations in the technique of photography (such as difference in pupil size) and processing caused dissimilarities in "background". This varied most markedly from case to case, but also from frame to frame within the same angiogram depending upon the clarity of focus and perhaps other factors. The attempt to make densitometric determinations was consequently abandoned.

STATISTICAL ANALYSIS OF DATA

This section summarizes relevant findings derived from a "blind" inspection of the angiograms.

Four hundred thirty-seven subjects were studied. Angiograms satisfactory for coding were obtained in 247 subjects. Primary attention will be given to a comparison between normal controls and subjects with chronic open-angle glaucoma. Since cases with missing data were ex-

TABLE IV: DIAGNOSTIC CATEGORIES OF PATIENTS STUDIED

Total subjects with satisfactory angiograms		247
Normal control (N.C.)	50	
Glaucoma suspect (Gl.Susp.)	87	
Other glaucoma (O.Gl.)	32	
Low-tension glaucoma (L.T.Gl.)	16	
Chronic open-angle glaucoma (C.O.A.Gl.)	62	

cluded from the computations the base number remains the same regardless of the variable.

The number of cases in each major diagnostic category serves as the reference throughout the analysis (Table IV). In order to present the data in readily comprehensible form percentages of cases rather than absolute numbers will be used wherever feasible. This is acceptable because of the stability of the base number.

The values for several of the variables are shown in Table V; included in this are all 247 subjects on whom angiographic data was coded.

The mean values for several variables broken down by diagnostic category are shown in Table VI.

Of the four categories listed the only two strictly comparable are the normal controls and the chronic open-angle glaucoma cases. These two populations were closely matched with the same mean age and age distribution, and the same racial and sex distribution. The glaucoma

TABLE V: MEANS AND STANDARD DEVIATIONS FOR ENTIRE POPULATION STUDIED (247 SUBJECTS)

	Mean	Standard Deviation	Units
Intraocular pressure			
Post-angiography, right eye	21.7	8.7	mm Hg
Post-angiography, left eye	22.2	9.8	mm Hg
Systemic blood pressure			
Systolic	131.5	23.2	mm Hg
Diastolic	85.7	10.3	mm Hg
Ophthalmodynamometric pressure			
Systolic, right eye	67.8	12.2	mm Hg
Systolic, left eye	67.6	13.5	mm Hg
Diastolic, right eye	34.7	13.4	mm Hg
Diastolic, left eye	36.0	12.2	mm Hg
Arm-tongue circulation time	15.3	6.0	seconds
Circulation times — Fluorescein			
Arm-choroid	12.4	3.9	seconds
Arm-retinal artery	12.1	3.5	seconds
Arm-disc	12.7	4.2	seconds
Arm-retinal vein	14.4	4.2	seconds
Fluorescein "filling times"			
Choroid	3.6	0.8	seconds
Retinal artery	1.9	0.5	seconds
Disc	1.7	0.6	seconds
Retinal vein	9.7	1.6	seconds

TABLE VI: FINDINGS IN VARIOUS DIAGNOSTIC CATEGORIES (MEAN AND STANDARD DEVIATION)
(ALL TIMES IN SECONDS)

	N.C.*	Gl.Susp.*	O.Gl.*	L.T.Gl.*	C.O.A.Gl.*
Intraocular pressure (mm Hg)	15.4 ± 5.6	23.5 ± 4.9	30.3 ± 8.6	17.6 ± 6.1	24.0 ± 9.1
Systolic "retinal artery pressure" (mm Hg)	55.6 ± 19.1	65.4 27.0	60.1 ± 15.0	56.6 8.3	59.6 ± 6.4
Arm-tongue circulation time	14.1 ± 3.2	15.2 ± 4.6	16.6 ± 3.3	17.3 ± 61.0	13.4 ± 2.4
Arm-choroid circulation time	10.9 ± 4.0	14.3 ± 5.9	13.7 ± 3.7	13.3 ± 4.3	13.7 ± 3.9
Arm-disc circulation time	10.7 ± 3.8	14.2 ± 5.3	14.1 ± 3.5	13.3 ± 8.6	15.2 ± 8.4
Arm-retinal artery circulation time	10.3 ± 3.9	13.9 ± 2.8	12.3 ± 2.1	12.8 ± 3.9	12.5 ± 3.3
Arm-retinal vein circulation time	13.4 ± 5.2	16.1 ± 5.4	15.8 ± 9.1	14.8 ± 3.8	16.6 ± 5.6
Disc filling time	12.1 ± 4.2	15.4 ± 4.9	16.1 ± 5.1	15.2 ± 4.1	15.8 ± 4.0
Retinal artery filling time	12.7 ± 5.1	15.1 ± 5.2	18.1 ± 3.1	14.1 ± 3.7	15.7 ± 5.7
Retinal vein filling time	23.1 ± 6.6	26.4 ± 8.9	25.4 ± 6.9	26.4 ± 7.1	27.3 ± 10.2
Intraretinal transit time	2.0 ± .3	1.9 ± .3	2.7 ± .3	2.1 ± .6	2.7 ± .5
Cup-disc ratio/horizontal	.39 ± .19	.55 ± .29	.52 ± .26	.60 ± .18	.78 ± .19

*N.C. = normal controls; Gl.Susp. = glaucoma suspect; O.Gl. = other glaucomas; L.T.Gl. = low-tension glaucomas; C.O.A.Gl. = chronic open-angle glaucoma.

suspects were slightly younger. Mean age for subjects with "other glaucoma" was 40 and low-tension glaucoma 52 years. Seventy percent of low-tension glaucoma subjects were female.

Statistically significant differences were present between the normal controls and the glaucoma subjects for the variable in Table VI (probability less than 0.01) except for the arm-tongue circulation time, systolic "retinal artery" pressure (probability was 0.02), retinal artery filling time, retinal vein filling time, and choroidal filling time. This last was not listed as the standard deviation was so large that the value of the mean was questionable; there was no significant difference between the calculated mean choroidal filling times of the various groups.

Mean circulation time for subjects whose intraocular pressure was between 10-20 mm Hg was compared with that of subjects whose pressure was above 30 mm Hg; this comparison was statistically significant (probability = .01) for arm-disc and intraretinal transit time, and more so (.001) for arm-choroid circulation time. Comparisons between measurements within each group were not significant. Similar breakdowns were not possible in other diagnostic categories because of the limited number of cases.

Several statistical methods were employed to investigate inter-relationships within the data. Only those most pertinent will be listed here. Results of the Spearman correlation coefficient for non-parametric data are shown in Table VII.

With one exception all the comparisons listed in Table VII are statistically significant, most of them highly so. Apparently unrelated comparisons are not shown except for a correlation coefficient describing the relation between "disc filling time" and "decreased perfusion of the disc". The lack of correlation between these two seems worthy of mention. There was also no correlation between intraocular pressure measured prior to fluorescein angiograph and the circulation times, in contrast to the clear correlation present when pressure was measured post-angiography.

The Kruskal-Wallis one-way analysis of variance showed a high correlation ($p-.001$) between degree of pallor of the optic nerve and diagnostic catagory, and extent of visual field loss and diagnostic category.

Cross tabulations of the individual diagnostic categories with specific findings yielded interesting correlations.

A correlation between staining and other variables was noted in Table VII. Staining was almost never present in normals, but was observable in over a third of the subjects with glaucoma; it was seen in a few subjects

TABLE VII: SIGNIFICANT CORRELATIONS OF DATA

Variable	Correlation Coefficient	Probability
Visual field loss		
Arm-choroid circulation time	.16	.01
Arm-disc circulation time	.23	.001
Arm-retinal artery circulation time	.21	.001
Arm-retinal vein circulation time	.23	.001
Decreased disc fluorescence	.61	.001
Retinal artery filling time	.16	.01
Retinal vein filling time	.15	.02
Decreased disc perfusion		
Arm-choroid circulation time	.20	.004
Arm-disc circulation time	.22	.001
Arm-retinal artery circulation time	.19	.005
Arm-retinal vein circulation time	.21	.002
Intraretinal transit time	.16	.01
Disc staining	.19	.003
Stage of disease	.70	.001
Control of disease	.39	.001
Visual field loss	.61	.001
Delayed disc fluorescence	.30	.001
Disc filling time	.01	.40
Pallor of the optic disc		
Arm-choroid circulation time	.26	.001
Arm-disc circulation time	.22	.001
Arm-retinal artery circulation time	.18	.007
Arm-retinal vein circulation time	.20	.003
Staining of disc	.11	.05
Decreased disc circulation time	.51	.001
"Retinal artery" pressure systolic		
Arm-choroid circulation time	.27	.004
Arm-retinal artery circulation time	.17	.04
Stain of disc	.24	.005
Intraocular pressure (post fluorescein angiography)		
Arm-choroid circulation time	.16	.01
Arm-disc circulation time	.16	.01
Arm-retinal artery circulation time	.15	.02
Arm-retinal vein circulation time	.12	.04
Intraretinal transit time	.14	.03
Disc filling time	.26	.001
Retinal artery filling time	.19	.005
Intraretinal transit time		
Arm-choroid circulation time	.36	.001
Arm-disc circulation time	.41	.001
Arm-retinal artery circulation time	.35	.001
Arm-retinal vein circulation time	.57	.001
Disc filling time		
Arm-choroid circulation time	.28	.001
Arm-disc circulation time	.29	.001
Arm-retinal artery circulation time	.32	.001
Arm-retinal vein circulation time	.35	.001
Retinal vein filling time		
Arm-choroid circulation time	.48	.001
Arm-disc circulation time	.49	.001
Arm-retinal artery circulation time	.40	.001
Arm-retinal vein circulation time	.40	.001
Staining of disc		
Control of disease	.29	.001
Stage of disease	.25	.001
Decreased disc perfusion	.19	.003
Pallor of optic disc	.11	.05

suspected of having glaucoma. Chi square analysis yielded a p. of .001 for the entire grid.

An additional statistical task was to define the relationship between state of control or extent of disease and the dynamics of circulation as indicated by fluorescein angiography. When subpopulations were examined no apparent correlation between the stage of disease and circulatory measurements was observed. That is, when the cases were matched for level of intraocular pressure, individuals with far advanced disease did not have significantly different circulation times than those without disease. In contrast there was a good correlation between the state of control of disease and the circulation times. Control of disease was defined in terms of change of the optic nerve or visual field; it was not synonymous with elevation of intraocular pressure. However, in most instances where control was poor the intraocular pressure was also elevated. As such, then, the apparent relation between state of control and circulation times may be a consequence of the already demonstrated effect of increased intraocular pressure on these variables.

The normal controls (NC) and the subjects with chronic open-angle glaucoma (COAGl) were comparable populations with regard to age, race and sex. Therefore they can be validly compared. The data in Table VI suggest that blood flow in the glaucomatous eye as revealed by fluorescein angiography is abnormal. Of the variables studied the greatest deviation from normal was noted for the arm to disc circulation time, but other measurements also show a generalized retardation of circulation in glaucoma. Whether this is a function of the damage caused by the elevated pressure or of the elevated pressure itself cannot be determined with certainty, but there are indications that in one subpopulation, glaucoma suspects, the slowing is due to pressure. This was borne out by the studies of patients having angiography at elevated intraocular pressure and at lower pressure. (Cases #7, 8, 12, 14, 15, 16 and 21). Similar "high-low" studies were not carried out in normal controls, so there is no population to compare, but in the subjects with disease lower intraocular pressure was invariably associated with more rapid circulation.

The conclusion appears valid, then, that increased intraocular pressure is accompanied by prolongation of circulation time; further, as a general rule the higher the pressure the slower the flow. Elevated pressure itself may have been responsible for the circulatory retardation.

The location of this slowing was not the vessels between the arm and the eye. Both arterial and venous segments of ocular circulation were about equally impeded.

Retardation of dye passage through the optic disc was greater than elsewhere. The 2.7 second difference between the arm-retinal artery and arm-disc circulation times is significantly larger (p. = .01) in cases with chronic open-angle glaucoma than the 0.4 seconds in normal controls. This implies a selective impairment of the optic disc vasculature in chronic open-angle glaucoma.

In low-tension glaucoma the difference between arm-retinal artery and arm-disc circulation times was similar to that in normal controls. Since the intraocular pressure in the low-tension glaucoma population was only slightly greater than in the normal controls the greater difference in subjects with chronic open-angle glaucoma may be a factor of elevated intraocular pressure.

Optic disc staining occurred significantly more often in glaucoma than in normal controls. The incidence of staining was about the same in patients with chronic open-angle glaucoma and low-tension glaucoma. This suggests that elevation of pressure per se was not responsible for the finding. Furthermore, staining was present less often in glaucoma suspects than in subjects with chronic open-angle glaucoma, yet the mean intraocular pressure of the two groups was not significantly different.

The complete lack of correlation between perfusion "delay" and detectable pathology implies that the observed retardation of circulation times was not pathogenetically significant. There was no observed relationship between delayed disc or choroidal circulation and optic pallor or visual field loss (Table VII).

Several isolated correlations relating to disc flow were observed, such as the prolonged arm-disc circulation time already discussed. Furthermore there was a positive correlation between disc circulation time (the time for dye to cross the surface of the disc) and pallor of the optic nerve head, as well as between temporary hypoperfusion (disc delay) and lasting hypoperfusion (disc decrease).

In marked contrast to the apparent lack of significance of "delay", was the striking correlation between persisting hypoperfusion of the disc and definite pathology, namely, visual field loss and optic nerve pallor. The correlation was almost absolute. Wherever one was found the other was also. Moreover, there was an inference in Cases #16 and #17 that hypofluorescence of the disc actually preceded the visual field loss. In every instance the zone of hypofluorescence of the disc reflected the corresponding area of visual field loss.

In low-tension glaucoma there was a consistent pattern of localized hypofluorescence of the optic disc, usually in area 13 (inferotemporally) without any other apparent vascular changes.

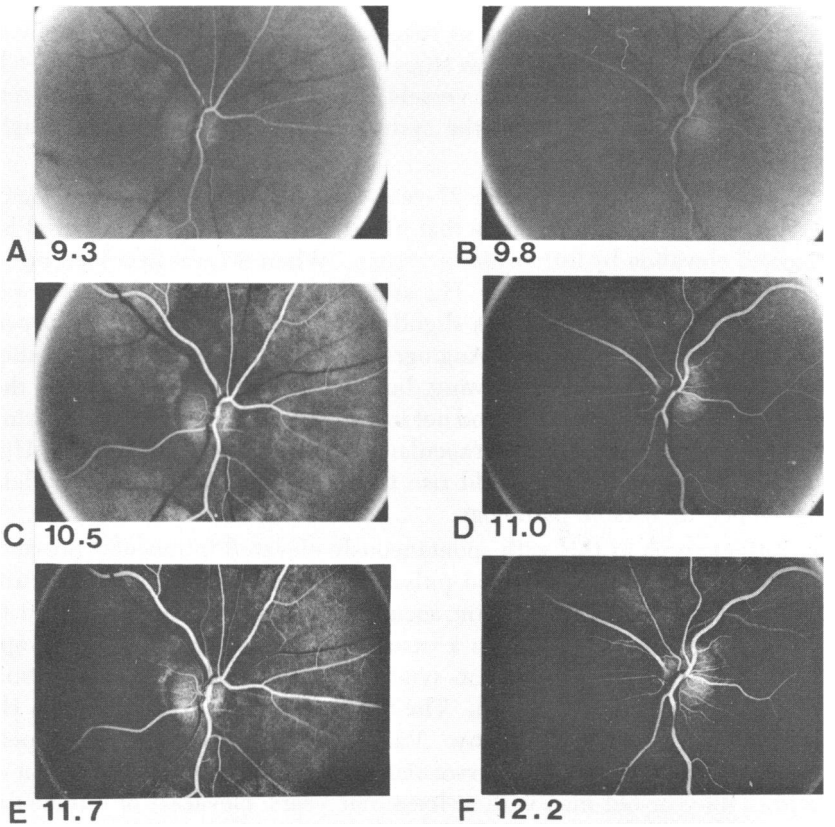


FIGURE 8

A 49-year-old white male, #10, had persistent asymmetry of intraocular pressures, the left higher than the right. At the same time of the angiographies illustrated here the intraocular pressure was 20 mm Hg in the right eye (A, C, E) and 32 in the left (B, D, F) yet the angiograms are highly similar.

QUALITATIVE ANALYSIS OF THE ANGIOGRAMS

As the angiograms were reviewed several questions were asked. These included: (1) Is there a relation between level or intraocular pressure and vascular perfusion of the optic nerve and retina as demonstrated by fluorescein angiography? If so, what? (2) Is there a relation between the angiographic pattern and optic nerve or retinal disease? If so, can fluorescein angiography help define its nature? and (3) Can fluorescein angiography help in a classification of glaucoma?

The relationship between level of intraocular pressure and perfusion of the optic nerve and retina as revealed by fluorescein angiography is complex. Clearly all blood flow stops when intraocular pressure exceeds the pressure within the blood vessels. Angiography suggests, however, that at pressures lower than the systolic the responses are surprisingly variable.

Some cases, such as #7, a 27-year-old black man with glaucomatocyclitic crisis, seemed to show that blood flow was almost unaffected by marked elevation by intraocular pressure. When #7 was first seen intraocular pressure was 60 mm Hg and the central retinal artery was pulsating; the visual field was slightly contracted, but the disc showed no glaucomatous atrophy. Angiography was performed; the quality was poor due to corneal bedewing, but the dye entered the disc and the retinal circulations promptly and not in a grossly reduced amount. During the next four years the intraocular pressure averaged 15 mm Hg, though during attacks it would rise to the 50's. Neither disc nor field developed detectable pathology.

Patients such as this with spontaneously elevated intraocular pressure high enough to induce arterial pulsations are uncommon. In contrast, more moderate elevation of intraocular pressure in the range of 30 to 40 mm Hg is not rare. Such a case is #9, a 28-year-old male myope with the pigmentary dispersion syndrome whose optic discs and visual fields were considered normal. The intraocular pressure was 36 mm Hg at the time of the angiography. Vascular details are clear and appear unaffected by the elevated intraocular pressure. A similar case is that of #10, a 49-year-old man with at least four years' elevation of intraocular pressure in the left eye; both the discs and fields seemed normal and completely symmetrical. The pressure in the left eye was, however, consistently 32 mm Hg, in contrast to the right whose pressure was a steady 20 mm Hg. Angiography was unable to demonstrate any difference between the two eyes (Figure 8).

The angiograms of a 60-year-old man with primary angle closure glaucoma showed only slight retardation in the rate of circulation through the fundus when the intraocular pressure was 58 mm Hg in comparison to when the pressure was 28.

The cases just illustrated were chosen to document an important finding; namely, that elevation of intraocular pressure to a level that may be associated with eventual development of glaucomatous change of the optic nerve need not be accompanied by abnormal fluorescein angiographic findings such as selective involvement of the circulation of the disc or retina. In the present study 82 percent of subjects diagnosed

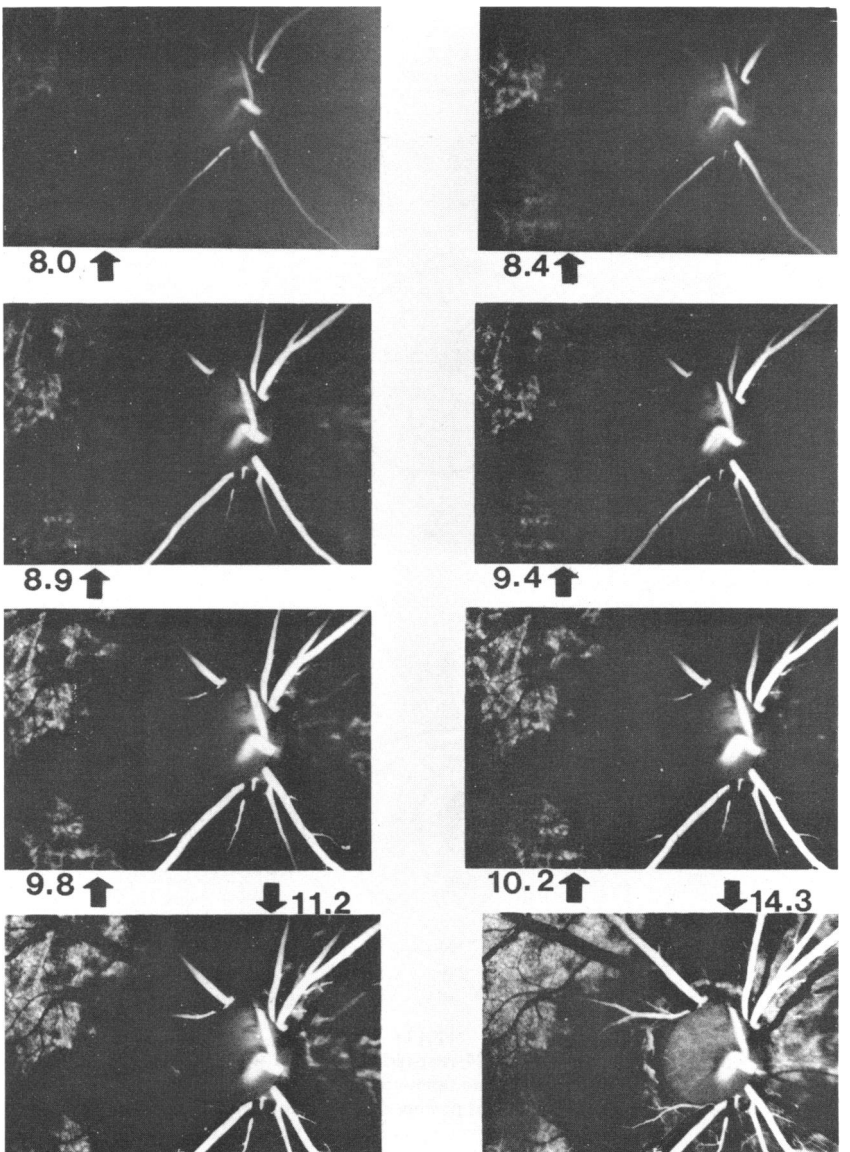


FIGURE 9
Angiogram of #13, a 13-year-old girl with no light perception in her right eye due to far-advanced glaucomatous damage. Dye is first visible 7.6 seconds following injection, but advances slowly thereafter.

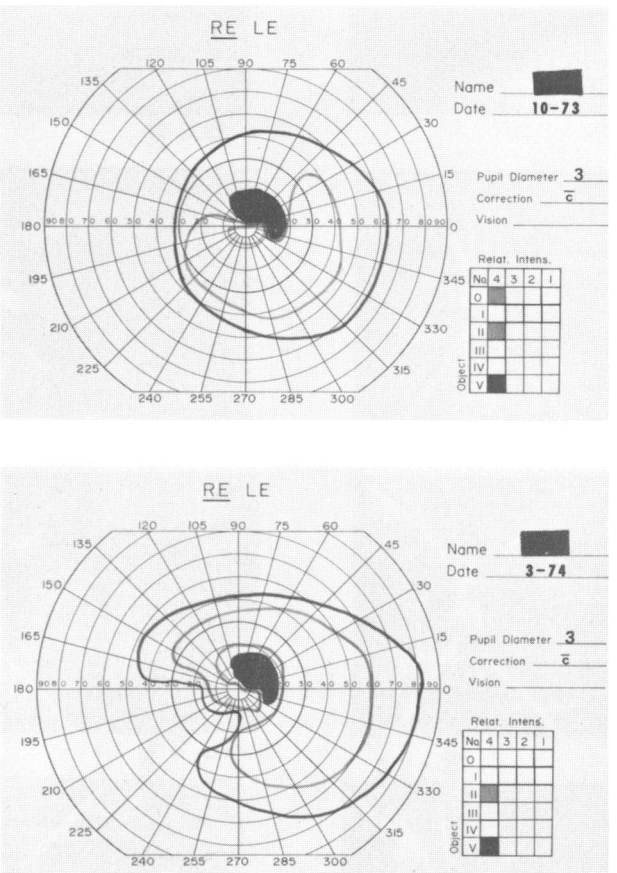


FIGURE 10
Visual fields of #14, a 24-year-old white man with moderately advanced bilateral chronic open-angle glaucoma, preoperatively and postoperatively.

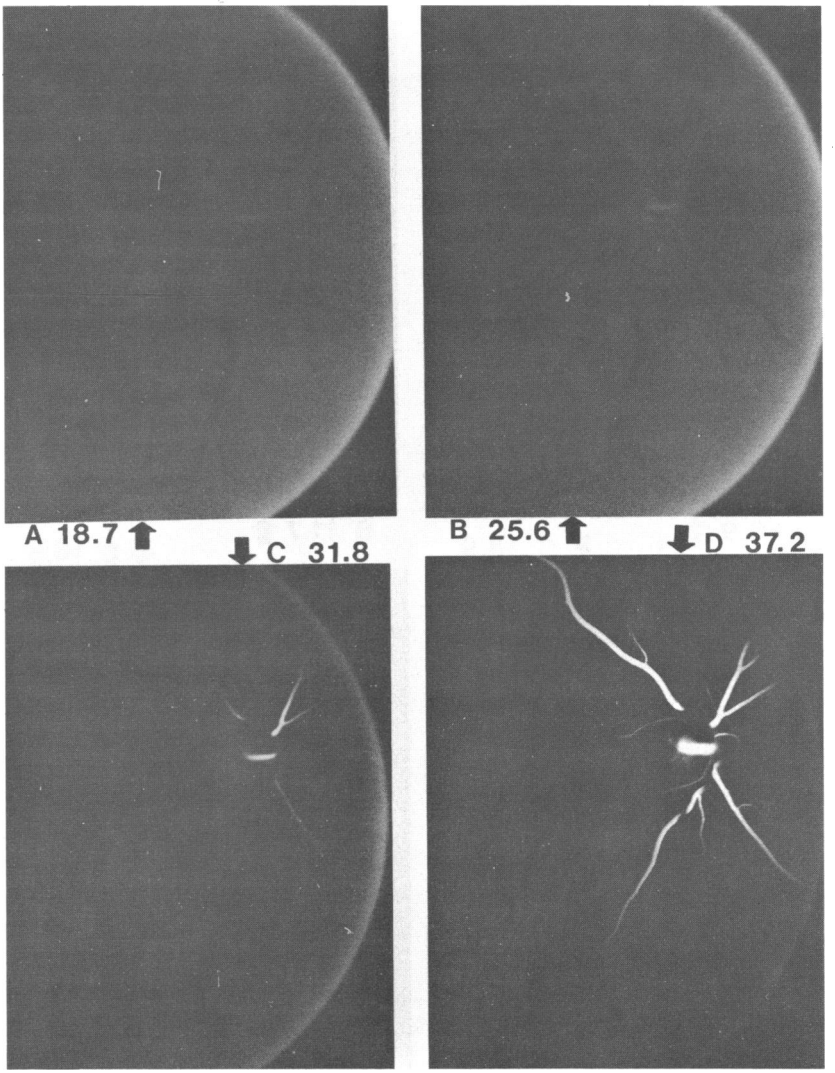


FIGURE 11
Angiogram of #14 when the intraocular pressure was 42 mm Hg.

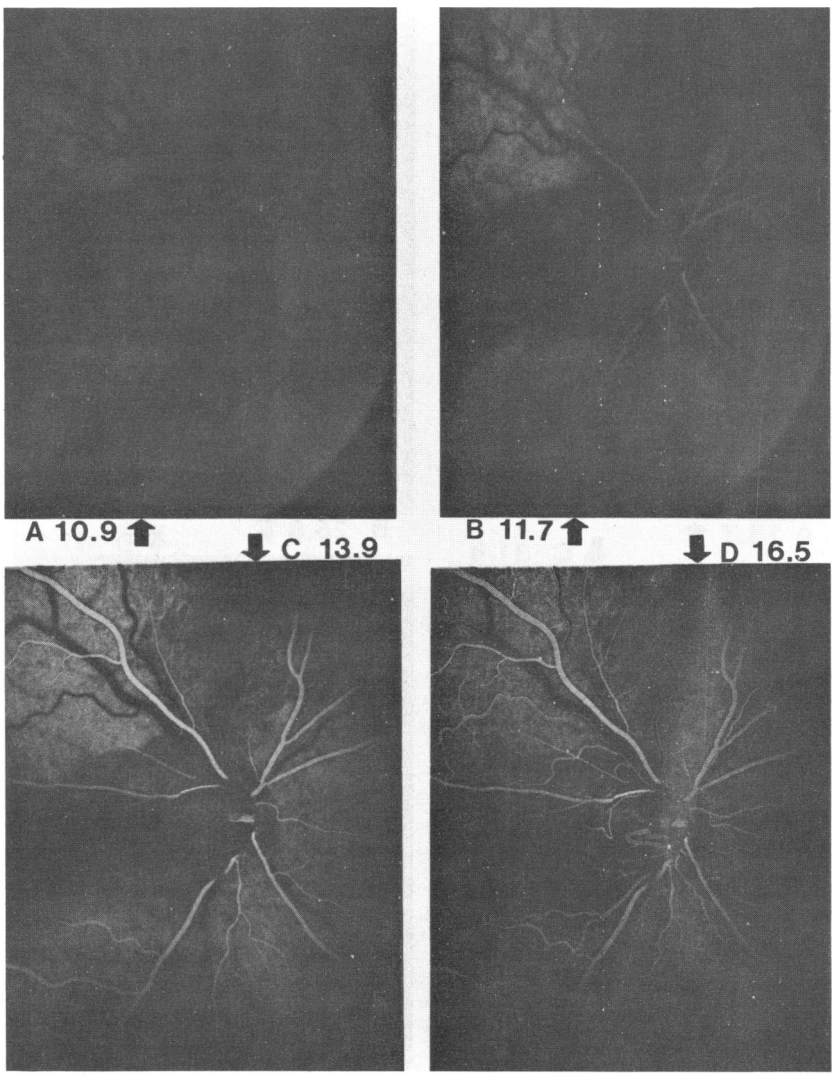


FIGURE 12
Angiogram of #14 one month after that in Figure 11; the intraocular pressure was 21 mm Hg on medical therapy.

"ocular hypertension" (intraocular pressure above 21 mm Hg without disc or field changes), had fluorescein angiograms thought to be normal. In fact, the gross fluorographic pattern can be normal even at intraocular pressures high enough to cause intermittent collapse of the blood vessels. Such apparent normalcy of the angiogram may be misleading, however. In the first place, the technique may simply not be adequate to demonstrate alterations of flow that are physiologically, and in the second, biologically significant changes may be missed because they are incorrectly considered variants of normal.

It does not follow from the point just made, namely, that the relationship between vascular perfusion of the optic nerve and retina as evidenced by angiography is not linear, that intraocular pressure is devoid of effect on the fluorescein angiogram. Some subjects showed an obvious relation between the two. In this regard it may be helpful here to introduce a definition of the "elevated pressure pattern." This pattern, as arrived at by inspection of individual angiograms and by statistical analysis of the entire patient population, is primarily characterized by damped dye passage through the vasculature. This shows a delayed "filling" of the disc, central retinal artery, retinal veins and choroid, associated with less intense fluorescence, most conspicously in the early phases. "Filling" is quoted because degree of fluorescence is not necessarily an accurate measure of blood flow. Disc filling and intraretinal transit times are about equally retarded. The effect of pressure change on choroidal circulation is open to question because of the masking effect of the retinal pigment epithelium. As demonstrated in Figure 8 this pattern is not always present when the pressure is elevated, that is above 21 mm Hg. It need not be present even with considerably greater elevation. Findings such as hypoperfusion of the optic disc are not essential elements in the "elevated pressure pattern."

The effect elevated intraocular pressure may have on vascular dynamics is illustrated by #11, a 19-year-old black girl with congenital glaucoma, whose intraocular pressure was 38 mm Hg at the time of angiography. Extensive field loss and deep cupping of the optic nerve were present. Dye was first visible 36 seconds after injection; this slow entry was unrelated to abnormality of systemic circulation as indicated by the normal Decholin circulation time of 8 seconds. Intraretinal transit time was unable to be measured with accuracy due to the slow entry of dye into the veins; it was certainly extremely prolonged, being about two minutes as opposed to the two seconds that would be normal in a young adult. Sluggish flow was indicated by the scalloped trickle of dye along the inferior temporal vein walls in Figure 15 A and B.

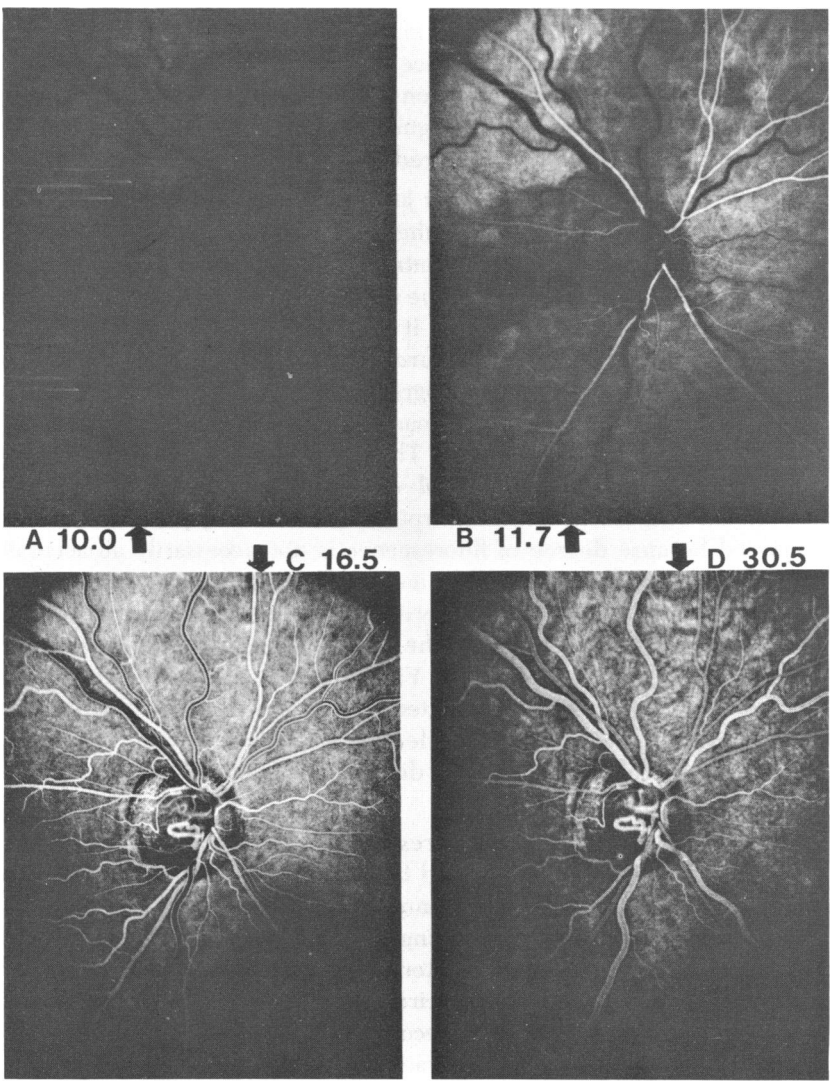


FIGURE 13
Angiogram of #14, 2 months after that in Figure 11; intraocular pressure was 15 mm Hg.

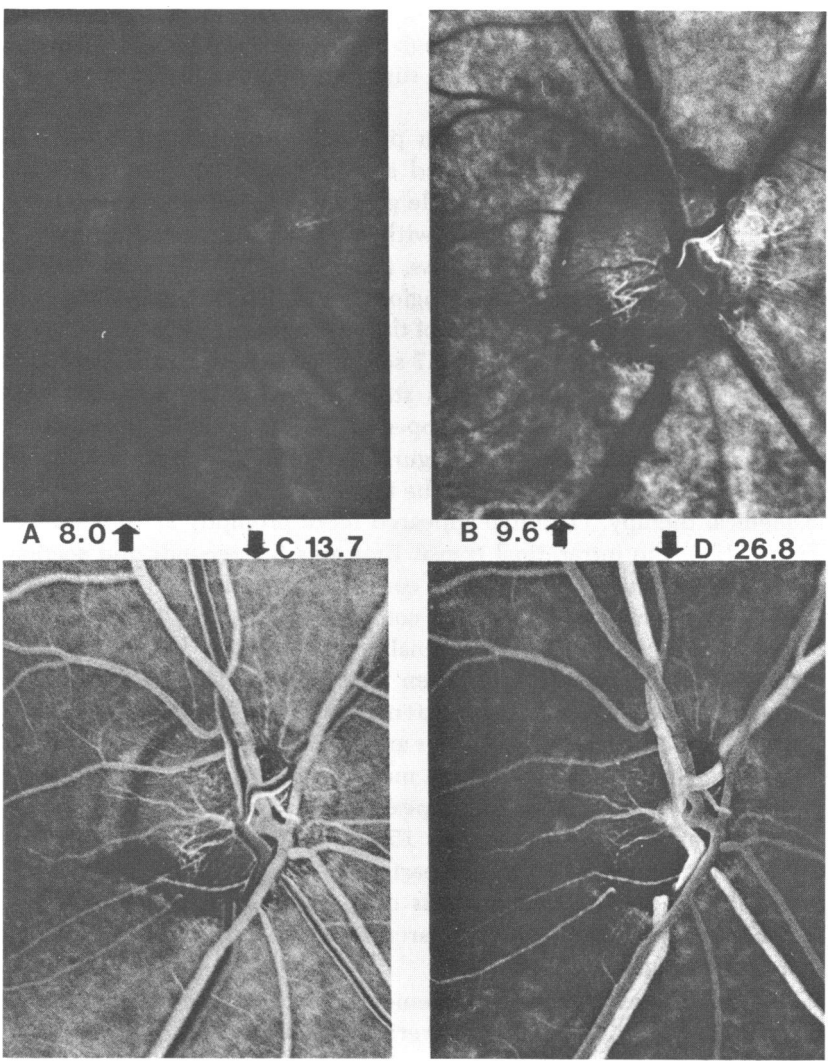


FIGURE 14
Angiogram of #4, three years after a superonasal loss had been noted in the right eye.

A similar pattern was observed in a 13-year-old girl, #13, with unilateral glaucoma whose right optic nerve was severly damaged; there was no perception of light. Angiography was performed when the intraocular pressure was 40 mm Hg (Figure 9). Dye was visible promptly (7.6 seconds), but advanced through the vessels with great lassitude. This was most clearly seen in the superior temporal artery which was not filled after seven seconds.

The effect of elevated intraocular pressure was most clearly manifest where angiography was performed at different intraocular pressures in a subject with chronic open-angle glaucoma. Consider, for example, #14, a 24-year-old white male with elevated intraocular pressure, moderately advanced visual field loss, and definite glaucomatous cupping of the optic nerves (Figure 10). Angiography when the intraocular pressure was 42 mm Hg showed delay of the entire transit of dye (Figure 11). A trickle of dye was first visible 18.7 seconds post injection (Figure 18A). Seven seconds later the disc was still not visible (Figure 18B). Not until 13 seconds after dye first appeared in the central retinal artery was it visible in the disc itself (Figure 18D). This angiogram contrasts with that three months later when the intraocular pressure was 21 mm Hg on medical therapy. The dye appeared more promptly at 10.9 seconds (Figure 12A), the intraretinal transit time was 5.2 seconds and sections of the disc eventually filled almost completely (Figure 12D). However, filling of the disc was still delayed, commencing 3 seconds after the dye was first visible in the central retinal artery, and not reaching its first plateau until 17 seconds later; even then area 13, the inferotemporal portion of the rim, and to a lesser extent area 11, the most superior part of the rim, appeared relatively ischemic. Surgery was performed one month later because of inability to maintain intraocular pressure below 35 mm Hg. Angiography was repeated one month following surgery when the intraocular pressure was 15 mm Hg (Figure 13). There was little further improvement in comparison to Figure 12, though 13C suggests that the vascularized portions of the disc were better filled; the less vascular segments (especially area 13) seemed even more ischemic than before (Figure 12D).

This case shows definite improvement in blood perfusion of the optic nerve and retina in response to lowering intraocular pressure medically. Further lowering of pressure was not associated with further improvement in the fluorescein angiographic pattern. Apparently permanent defects in the vasculature of the disc were associated with persisting visual field loss. This type of response was frequent in patients with chronic open-angle glaucoma.

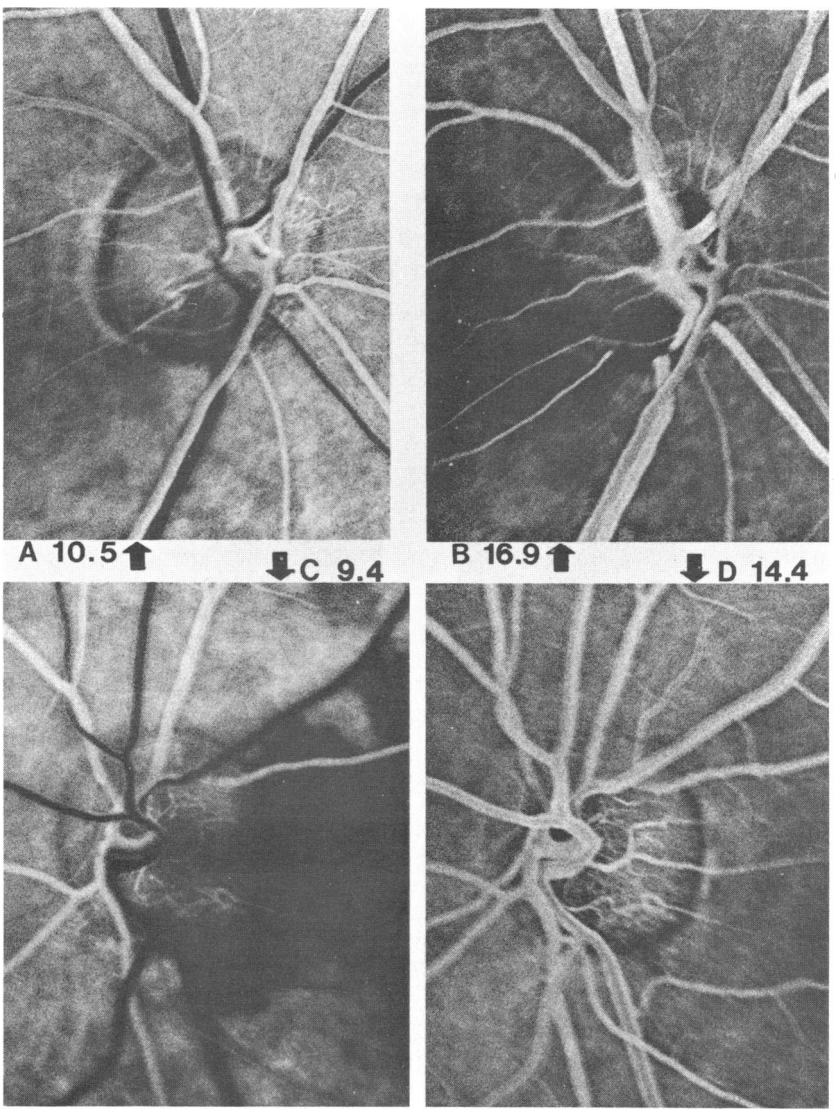


FIGURE 15
Angiogram of #4; right eye: A and B, six months after angiogram in Figure 14. C and D are from the left eye which had a visual field loss similar to that of the right eye.

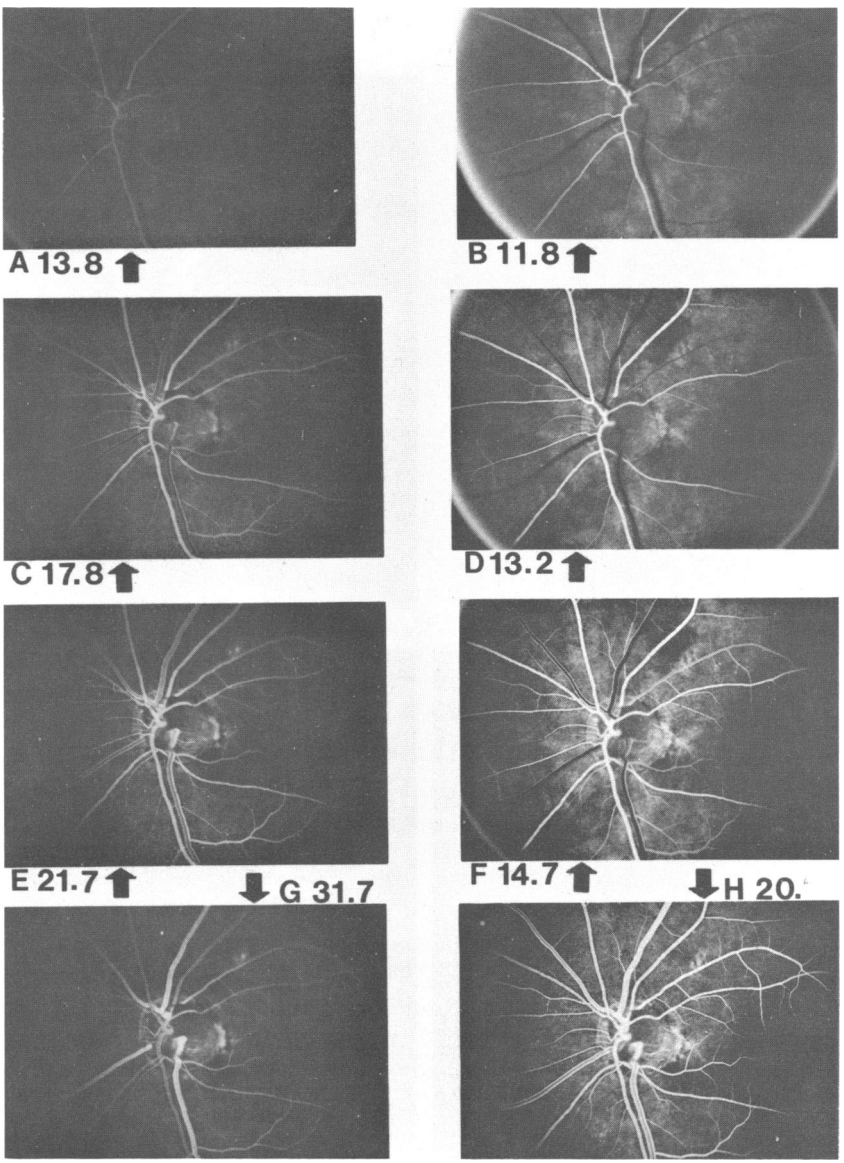


FIGURE 16

Angiogram of #20, left preoperatively when intraocular pressure was 19 mm Hg (A, C, E, and G) and postoperatively when 6 mm Hg (B, D, F and H). Disc filling occurs more rapidly and completely at the lower intraocular pressure (times in the right should be compared with those in the left column).

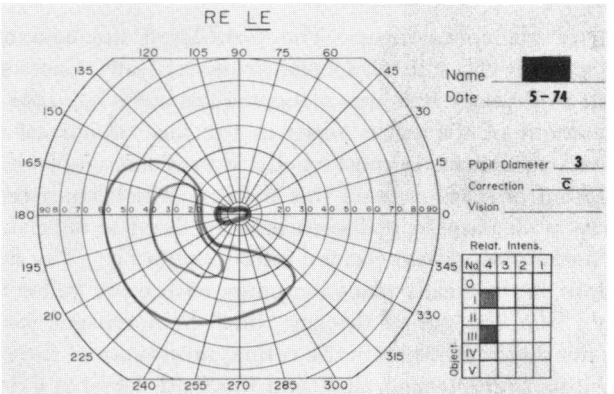
A 48-year-old white woman, #4 was first seen because of the sudden awareness of a small superonasal scotoma in the right eye. The intraocular pressure was 12 mm Hg and the coefficient of aqueous outflow high; a neurological evaluation was unrevealing. Three years later the same sensation was noted in the other eye; a tiny scotoma just nasal and superior to fixation was found in the left eye. The right eye had developed a superior arcuate scotoma and a flame-shaped hemorrhage at 8:00 o'clock on the rim of the optic nerve head. Inferior notching of both optic discs were noted. The intraocular pressure ranged between 12 and 23 mm Hg over a two-day period. The coefficient of aqueous outflow was 0.23 in the right eye and 0.25 in the left. Repeat neurologic, hematologic and general medical evaluations were within normal limits. Over the next year small hemorrhages were noted inferotemporally on both optic discs. However, the clinical course was not seemingly related to the occurrence of these hemorrhages. There was no change in the visual fields, there being dense superior arcuate scotomas and peripheral nasal steps bilaterally. Figure 14 illustrates the results of the angiography performed three years after the initial scotoma was noted. The entry of dye was rapid and in the normal sequence. However, there was an area of hypoperfusion at the inferior pole of the disc that persisted through all phases. The blocked fluorescence superotemporal to the hypoperfusion was due to a superficial hemorrhage. Six months later the area of hypoperfusion was still present (Figure 15A and B). The spot where the hemorrhage had been seemed normal in appearance, and did not connect directly to the hypoperfused sector. A similar region of decreased perfusion corresponding to the visual field defect was also present in the other eye, though to a lesser degree (Figure 15C and D). The occurrence of localized disc hypoperfusion and an isolated scotoma in the corresponding region of the visual field with subsequent stability of both the angiogram and field suggests that the initial cause for the field loss may have been the hypoperfusion itself. The lack of spatial relationship between the hemorrhage and the hypoperfused zone and the subsequent observation of new hemorrhages without either further field loss or further hypoperfusion indicated that the hemorrhage was not the primary pathological event causing the visual loss.

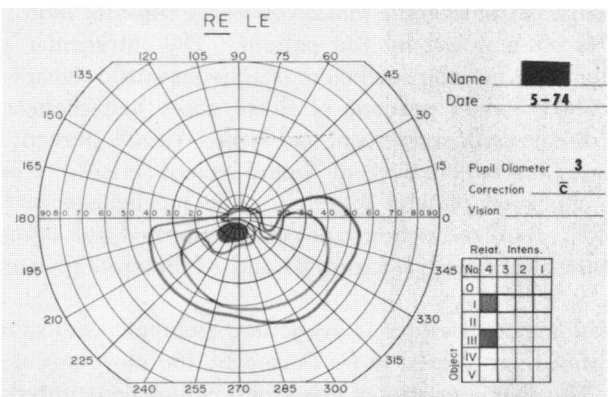
Number 20, a 58-year-old white man, had advanced chronic open-angle glaucoma when first seen. He related that he had had progressive field loss despite "controlled" intraocular pressure. The discs were severely cupped pathologically, but the degree of visual loss in the left eye seemed even greater than the appearance of the disc suggested. There was complete loss of the superior field in both eyes. Fluorescein

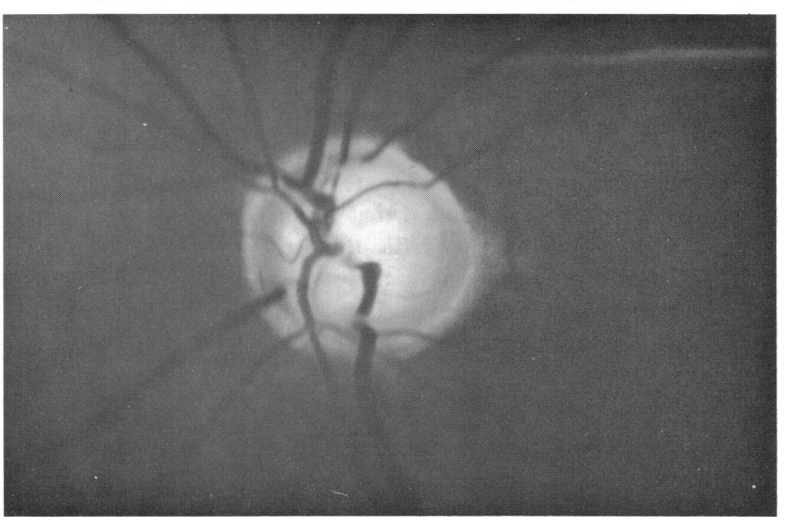
angiography was performed when the intraocular pressure was 19 mm Hg. The rate of dye transit appeared within normal limits, though there was hypoperfusion of the disc rim at 1:00 to 3:00 o'clock and at the inferior pole (Figure 16A, C, E, and G). When the inferior loss progressed so that only a central and temporal island remained surgery was performed despite pressures averaging 18 and consistently below 20 mm Hg (Figure 17). Postoperatively the intraocular pressure ranged between 6 and 8 mm Hg; the visual field loss did not progress. Repeat angiography one year postoperatively showed absolute filling defects almost exactly similar to those noted before. However, there was seemingly more rapid and more complete filling of the remainder of the optic nerve (Figure 16B, D, F, and H). The demarkation between the perfused and the hypoperfused areas became more clearly delineated. An additional change was the appearance at 1:30 o'clock of small vessels crossing the rim. These were not visible in the preoperative angiogram.

These few illustrative cases should be enough to demonstrate what shows in the statistical analysis as a large range of values even in rather narrowly defined groups. The variability of expression of the findings being studied is great. For example, Cases #11 and #13 exhibit the full "elevated pressure pattern" with intraocular pressures around 40 mm Hg. Yet neither case #9 nor #24 shows the pattern with similar pressures; nor did case #8 with even higher pressures. In contrast, case #14 did with pressure of only 21 mm Hg. Expression of vascular insufficiency is clearly related to the perfusion pressure in the central retinal artery and the short posterior ciliary arteries; fluorescein angiography may help define this perfusion pressure in a more meaningful manner than ophthalmodynamometry has been able to provide. In this study the correlation between the pressure necessary to collapse the central retinal artery and the intraocular pressure needed to evoke the "elevated pressure pattern" was not statistically significant.

The impression gained from the preceding section was that fluorescein angiography may be of help in classifying glaucoma cases according to the basic mechanism of visual loss. Four categories can be postulated: (1) primary hyperbaric, (2) primary ischemic, (3) secondary ischemic, and (4) mixed. Primary hyperbaric glaucoma is characterized by progressive nerve damage in the absence of apparent ischemia. Individuals within this group have elevated intraocular pressure as the primary finding. They also have a normal fluorescein angiogram. The anterior surface of the disc is displaced posteriorly, there is symmetrical, round enlargement of the optic cup, and visual field loss tends to be more peripheral than central. This combination of features was seen in 12% of the present


RE LE
Name [redacted]
Date 5-74
Pupil Diameter 3
Correction C
Vision
Relat. Intens.
No 4 3 2 1
0
I
II
III
IV
V
Object


RE LE
Name [redacted]
Date 5-74
Pupil Diameter 3
Correction C
Vision
Relat. Intens.
No 4 3 2 1
0
I
II
III
IV
V
Object



population of glaucoma cases. The postulated mechanism is nerve damage as a direct effect of intraocular pressure itself. Cases #23 and 24 are examples. Primary ischemic glaucoma has as its hallmark glaucoma-like involvement of the optic nerve in the face of normal intraocular pressure, and is comprised almost wholly of cases of low-tension glaucoma. Eleven percent of cases showed this pattern, which consisted of a well defined area of absolute hypofluorescence in the disc unrelated to pressure level and almost always located inferotemporally. The discs usually show shallow, eccentrically placed cupping with more pallor than would be expected from the size of the cup; small hemorrhages may occur on the rim of the disc reaching into the retina, most often at the 4:00 or 6:00 o'clock position (inferotemporally), and the field defect is a dense, often absolute, paracentral scotoma that involves the superior field. The visual field loss is often noted by the patient. The intraocular pressure is in the upper teens and the coefficient of aqueous outflow characteristically normal. Thirty-seven percent of these cases had diabetes mellitus (all newly discovered), six percent had syphis, twelve percent had severe heart disease, and twelve percent "hemodynamic crises." Four of seven cases had abnormal platelet function. The mechanism in these cases appeared to be localized ischemia of the optic nerve head, often associated with systemic abnormality. Cases #4 and 17 illustrate primary ischemic glaucoma.

The third major category is secondary ischemic glaucoma in which hypoperfusion is presumed to be caused by the elevation of intraocular pressure. The characteristics of this group, which constituted 36 percent of glaucomas, are infero- or superotemporal cupping of the nerve, arcuate scotomas that change in size and density in relation to pressure level, and optic nerve hypoperfusion that varies directly with the intraocular pressure. Cases #14 and 15 are examples of secondary ischemic glaucoma.

Forty-one percent of the population was unable to be placed in any of the three groups. It is postulated that in many of these the same basic mechanisms are operative, specifically pressure damage or ischemic damage. Fluorescein angiography, however, was not able to discriminate between these groups; this may be a function of the technical difficulties of performing fluorescein angiography in a glaucoma population, of the experimental design, or, further, of the limitations inherent in the technique as presently practiced.

FIGURE 17 *(overleaf)*

Optic disc and visual fields of #20, a 58-year-old white man with progressive chronic open-angle glaucoma despite intraocular pressure below 20 mm Hg.

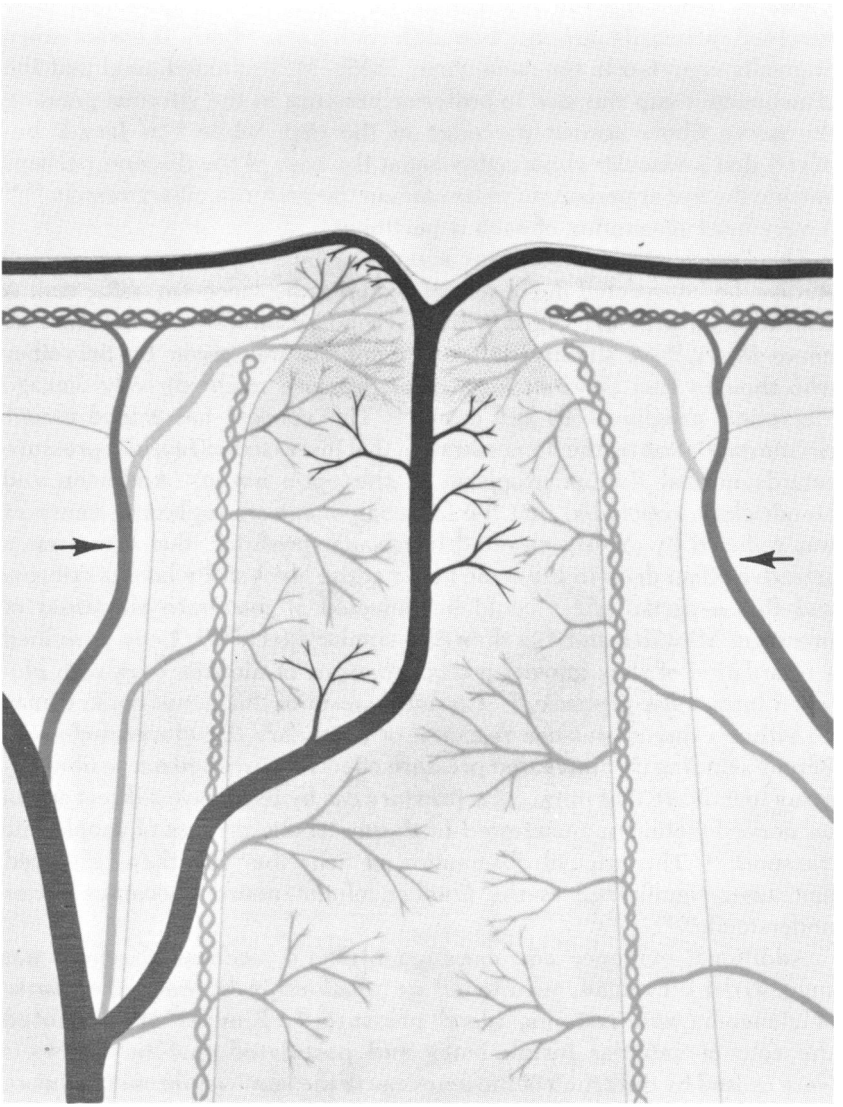


FIGURE 18
The blood supply to the optic nerve head. This illustration is a component intended to convey the possible sources of blood flow to the optic nerve head. It is unlikely that in any single case all of the illustrated vessels would be functional. The short posterior cilliary artery system is marked with arrows.

DISCUSSION

Concepts regarding the mechanism for visual loss in glaucoma have revolved primarily around two different axes. Both theories were originally reported in the same year, 1858. Müller maintained that the glaucomatous cup was due to posterior pressure in the vitreous pressing the nerve fibers against the edge of the cup, while von Jaeger believed that a vascular abnormality lay at the base of the disease, perhaps outside the eye or perhaps in some cases in the posterior ciliary vessels.[46,47] A very brief accounting of each is pertinent.

The "mechanical school" was supported by Fuchs' histopathological studies; he interpreted the observed posterior displacement of the lamina cribrosa as a pressure effect with a secondary atrophy of the glia and nerve fibers.[48] A slightly different emphasis was given by Schreiber who thought that elevated intraocular pressure might directly damage the retinal ganglion cells and axons.[49] This concept has gained recent circumstantiation by the demonstration that increased intraocular pressure retards normal flow of axoplasm in the optic nerve. Anderson and Hendrickson concluded that the fast component of axoplasmic transport was reduced by grossly elevated intraocular pressure, that there was a selective effect deep in the optic nerve at the level of the lamina cribrosa and that a partial effect could be detected at moderate elevations of pressure; Minckler and Tso showed a similar effect.[50,51] Levy described a retardation of slow moving protein in axons of monkey eyes with elevated intraocular pressure.[52] The mechanism of this is not clear; it may be either a direct pressure response or secondary to induced ischemia. Barany's finding that increased pressure effects the isolated nerve fiber appears to indicate that intraocular pressure can by itself have a direct action on nerve function as manifested in the metabolic process of axoplasmic transport.[53] The original observation of Schreiber has then, gathered increasing significance as the function of the neuron becomes better understood.[54-57]

Additional evidence corroborating Müller's mechanical school was suggested by Fruhauf, who found no relationship between the course of glaucoma and systemic blood pressure.[58] Lindsey also doubted the role of vascular insufficiency and postulated that field defects were caused by distortion of the fenestrae of the lamina cribrosa secondary to a direct pressure effect.[59] This idea is basically a restatement of Fuchs' concept, and has been given considerable support by the scanning electron microscope studies of Emery and co-workers, who reported striking and permanent distortion of the lamina cribrosa in experimentally induced glaucoma.[60]

The initial concepts of von Jaeger have also gathered considerable backing. LaGrange and Beauvieux believed that the vascular supply of the lamina was exclusively from the "posterior scleral wreath" and that rises in intraocular pressure compressed these vessels, leading to the isolated foci of necrotic nerve tissue previously described by Schnabel.[61-63] Cristini found decreased capillarity of the optic disc in patients with glaucoma, and in another pathologic study of humans, Kornzweig, Eliasoph and Feldstein described selective atrophy of the radial peripapillary capillaries.[64,65] Loewenstein found cavernous changes of the optic nerve in a variety of ischemic conditions and postulated that vascular insufficiency was the fundamental abnormality in glaucoma.[66]

A variety of clinical considerations tend to confirm the von Jaeger-vascular school. Reese and McGavic's observation that elevated systemic blood pressure seemed to protect the glaucoma patient from field loss has been substantiated by others (in contrast to the report of Fruhauf noted before), the most convincing documentation being that of Harrington, who observed deterioration in association with reduction of blood pressure.[67-72] Feldman, Drance and Goldman found cerebrovascular disease in 60 percent of cases with chronic open-angle glaucoma.[35] Ekbom, studying normal individuals by inducing hypotension with a tilt-table discovered the development of an oval scotoma filling the Bjerrum area, and in so doing elegantly confirmed the results that Gafner and Goldmann, Jaeger, Weeks and Duane, and Drance had reported by utilization of different means of reducing vascular perfusion.[25,74-76]

The von Jaeger-vascular school includes within it different theories; one major subdivision conceives the basic problem to be inadequate perfusion to the optic nerve, as occurs in systemic hypotension or ocular hypertension;[77] the other subdivision postulates disease in the ocular blood vessels themselves.[78] The thrust of the matter, nevertheless, is basically the same, namely inadequate vascular supply to the neurons. Hayreh has suggested that glaucoma and ischemic optic neuropathy are essentially the same entity, and Morgan has gone so far as to suggest that chronic open-angle glaucoma be renamed chronic ischemic glaucoma.[79,80] However, there are significant clinical and histopathological differences between ischemic optic neuropathy and the usual case of chronic open-angle glaucoma that make acceptance of such a concept difficult.

Experimental studies have established that increased intraocular pressure decreases blood flow in the eye, and more specifically in the choroid, a tissue without autoregulatory capacity.[81,82] Alm and Bill demonstrated that even slight increases of intraocular pressure cause a

decrease in blood flow in both the choroid and the prelaminar portion of the optic nerve, and further that the consequence is reduced oxygenation of tissues supplied by the uveal circulation, including most specifically the deep portion of the prelaminar optic nerve.[83,84]

The retinal blood vessels possess autoregulatory ability.[85] Ernest has shown that the anterior surface of the optic nerve head can maintain a stable oxygen tension in view of changing intraocular pressure or blood pressure.[86] However, when intraocular pressure was raised and the blood pressure then lowered in addition, the autoregulatory capacity of the surface of the optic nerve head was overcome and oxygen tension fell. Blood supply to the retina, then, is also decreased by elevated intraocular pressure when the pressure rises above the level the autoregulatory mechanisms can compensate for. Two studies in humans indicate that retinal oxygenation decreases with increasing intraocular pressure.[87,88] The rate of blood flow through the retinal capillaries has been measured in humans by observing the entopic phenomenon of the speed of the passage of leucocytes; a steady decrease in the rate of flow was found with increasing intraocular pressure.[89] Additional evidence of possible role of vascular insufficiency has been given by Alterman and Henkind, who noted an effect of pressure on the radial peripapillary capillaries.[90]

Histopathological studies of experimental glaucoma, as with the fluorescein angiographic studies of induced ocular hypertension, have not unraveled the mechanism of visual loss in chronic glaucoma, which is the matter under consideration. Acute occlusion of part or all of the vascular supply of the optic nerve and retina indicates that there is probably little validity in hypotheses concentrating on a single vessel system. Anderson and Davis have shown, for example, that occlusion of the short posterior ciliary arteries in monkeys does not produce changes like those in glaucoma; the optic nerve is almost totally spared.[91] However, if the pial as well as the short posterior ciliary vessels are occluded then significant optic nerve damage occurs. The experimental studies show that the emphasis put on the choroidal circulation is almost certainly unwarranted.[79] It is also interesting to note that the anoxia caused by pulseless disease does not produce alterations mimicing chronic glaucoma.[92]

Both the "mechanical school," then, and the "vascular school" have their strong points and their serious weaknesses. The major conceptual problem in both is the attempt to fashion a completely unitary hypothesis incorporating within it all glaucoma. As suggested by Duane and Jaeger an integrating, rather than a unitary hypothesis is probably most appropriate for glaucoma; some glaucoma cases are best described by one

theory and others by another, a comment made by von Hippel 65 years ago.[93,94]

What insights can the present study give? Good data on circulation time in normals and several circulatory disturbances are available to use as the base line for the circulation times in the present study.[95-101] No evidence was found that vascular insufficiency of the choroid plays a significant role in the development of glaucomatous nerve damage. There was no sign of selective choroidal hypersensitivity to elevated intraocular pressure. The delay noted in choroidal filling that has in the past been thought typical of glaucoma is probably nothing more than a variation of normal in the normotensive cases and a technical artifact in those with elevated intraocular pressure.[28] The delay in arm-choroid circulation time previously commented on by several investigators is a real finding, but is probably only a function of the generalized retardation of circulation noted as a part of the "elevated pressure pattern." Furthermore, when considering cases with elevated pressure, the delay may be largely spurious, being nothing more than an artifact.[28] This investigation supports the views of those cautioning against accepting insufficiency of choroidal circulation as an adequate explanation for the pathogenesis of glaucomatous nerve damage.[30,93]

The present findings turn attention away from the choroid and onto the optic nerve and retina.

The evidence for vascular insufficiency of the optic nerve in glaucoma is great. This ischemia may be primary or secondary. One group of subjects consistently manifested disc hypoperfusion that seemed unrelated to level of intraocular pressure. Another population showed alterations in perfusion related to change in intraocular pressure. Analysis of individual angiograms suggested that hypoperfusion might precede visual loss, but the number of cases demonstrating this was too small to permit a definite conclusion. In this regard the comment made by other investigators that the extent of hypofluorescence exceeded the area of visible disc pallor should be recalled.[35,38] The observation in the present study that glaucoma suspects show a greater frequency of disc hypofluorescence than normal controls provides a further clue that ischemia may be an initiating factor in the development of neuronal damage, and portends a possible predictive value for the finding. Truly valid comparison cannot be made because the glaucoma suspects were not strictly comparable to the normal controls or to the chronic open-angle glaucoma subjects. Nonetheless, that the frequency of disc hypoperfusion in glaucoma suspects was intermediate between normals and those with certain disease lends a creditability to the thesis that these disc changes in glaucoma

suspects are a reflection of disease.

A suggestion of increased sensitivity of the prelaminar disc tissue in comparison to the central retinal artery circulation, was the finding that in some cases with glaucoma pressure on the globe collapses the disc circulation at a lower pressure than is needed to impede the central retinal artery circulation.

A further indication that in certain cases of glaucoma the prelaminar tissue is unhealthy was the 30 percent incidence of staining in subjects with glaucoma in contrast to almost none in normal controls. This implies that the integrity of the blood vessels within the disc tissue has been impaired. The presence of staining in subjects with low-tension glaucoma and its relative absence in glaucoma suspects implies that elevated intraocular pressure per se is not the cause of the staining, but rather that it is either a sign of damage to the disc caused directly by pressure or an indication of disease of the blood vessels themselves.

The role of retinal ischemia is less well defined. The number of cases showing a correlation between decrease in retinal peripapillary capillaries and progressive glaucoma was too few to allow more than speculation. An apparently selective loss of capillaries in the Bjerrum area of Case #22 was noted.

An additional case of interest will be introduced here. Case #25 is the brother of Case #20 whose optic disc was illustrated in Figure 17 and angiogram in Figure 16. Both Case #20 and his older sister have far-advanced glaucomatous damage of the optic nerve and visual field. Both have required surgery. Case #25, however has completely full vision fields despite pressures higher than those of his younger brother and older sister; while their disease progressed with pressures that averaged in the high teens, his was 29 mm Hg (on no therapy when first seen). Is the presence of a cilioretinal vessel in Case #25 in any way related to the apparently normal perfusion of the disc and the preservation of function in this case?

The finding of others that radial peripapillary capillaries may be selectively involved in glaucoma needs further study. High quality fluorescein angiography performed serially in a large number of ocular hypertensives may provide the answer to whether or not they are involved primarily in the pathogenesis of neuronal damage in some glaucoma patients.

Efforts have been made by others to establish a means of estimating the perfusion pressure ophthalmodynamometrically. Interpretation of results, however, has been conflicting, some reports suggesting that hypoperfusion is an invariable accompaniment of glaucoma and others dis-

senting.[102-104] An explanation for the disparity may be that in some cases the increased sensitivity to pressure lies in the central retinal artery system, while in others it is in the prelaminar capillaries supplied by the short posterior ciliary arteries (Figure 18). The prelaminar tissue is probably the meeting ground for a number of vascular systems, and it seems unlikely that insufficiency of blood flow is the result of isolated involvement of one set of vessels.[105,106]

Progression of disease was noted in cases without apparent vascular abnormality of the optic disc or retina. Furthermore, cases with markedly elevated intraocular pressure but no signs of disc hypoperfusion were observed. It is possible that ischemia is still a factor in the development of optic nerve pathology even though there is no fluorescein angiographic evidence. The technique has obvious limitations in its ability to describe optic disc and retinal circulation. Furthermore, change in blood flow posterior to the lamina may be caused by increased intraocular pressure, as suggested by Ernest and Potts, and such alterations would be undetected by fluorescein angiography.[107] Nonetheless, the apparent normalcy of circulation in the face of either known disease or elevated pressure suggested that within limits ischemia was not an invariable aspect of increased intraocular pressure and that damage to the optic nerve and retina could, therefore be a direct consequence of the elevated pressure itself. This led to the development of a tentative classification of glaucoma in which groups were separated into those in whom there was a direct effect of pressure, those in whom the pressure caused ischemia, and those in whom ischemia was present without elevated pressure. Cases with low-tension glaucoma showed the pattern of "primary ischemia," suggesting that ischemia is the basic pathological mechanism in this clinically definable group.

The final point to be made is that fluorescein angiography appears to be useful in helping to define the pathogenesis of visual loss in glaucoma. The complexity of this mechanism has been commented upon by Armaly.[108] Fluorescein angiography may provide an additional tool allowing a bit fuller description of glaucomatous process. Its usefulness in the diagnosis and management of patients with glaucoma appears limited, but it can help distinguish a subgroup in which disease of the optic nerve appears to be poorly related to intraocular pressure, specifically, patients with low-tension glaucoma. It is possible that fluorescein angiography may identify the ocular hypertensive who is going to get visual field loss in contrast to the ocular hypertensive who will not, and help determine the level intraocular pressure a particular eye is able to

tolerate, but futher studies are needed before such conclusions can be drawn.

CONCLUSION

This prospective study of 247 subjects shows the existence of significant differences between normal controls and subjects with chronic open-angle glaucoma in regard to blood flow to the optic nerve and retina as determined by fluorescein angiography.

Elevation of intraocular pressure causes retardation of rate of flow in the retina, optic nerve, and possibly choroid. Perfusion of the optic nerve as determined by fluorescein is effected in some cases by elevation of pressure to a greater degree than is flow to the retina or choroid. Selective sensitivity of the choroid was not noted. Observations of the peripapillary capillaries were too few to reach a firm conclusion.

Persisting hypoperfusion of the optic disc was a highly characteristic finding in subjects with glaucoma. This was particularly apparent in cases with low-tension glaucoma in whom lasting hypoperfusion of the infero-temporal area of the optic disc was almost invariably present. Persistent hypoperfusion was significantly correlated with visual field loss. Transient hypoperfusion of the disc, on the other hand, was not correlated with disease or with visual field loss.

Improvement in disc perfusion with decrease in intraocular pressure was documented in about one third of subjects with glaucoma.

Localized lasting hypoperfusion of the disc was noted in two cases prior to the development of corresponding visual field loss.

Progression of disease (cupping and visual field loss) in the absence of fluorescein angiographically demonstrable evidence of ischemia was noted in two cases. Marked elevation of intraocular pressure (above 35 mm Hg) without demonstrable ischemia was observed in 12 percent of the cases studied.

Staining of the optic nerve by fluorescein occurred in thirty percent of cases of glaucoma, and appeared to be unrelated to intraocular pressure. Staining was only rarely noted in normal controls.

A tentative classification based on the findings divides glaucoma into those cases in which there is damage to the neuron as a direct consequence of the intraocular pressure, those in which ischemia occurs without elevation of intraocular pressure, and those in which ischemia is the result of elevated pressure. These are called respectively, primary hyperbaric, primary ischemic, and secondary ischemic glaucoma. Undoubtedly in many cases more than one mechanism is involved.

Further studies appear warranted. Especially important will be the documentation by high quality angiograms of any changes that accompany the conversion from ocular hypertension to chronic open-angle glaucoma.

REFERENCES

1. Novotny HR, Alvis DL: A method of photographing fluorescence in circulating blood in the human retina. *Circulation* 24:82-86, 1961.
2. O'Day D, Crock G, Galbraith JEK, Parel JM, Wigley A: Fluroescein angiography of normal and atrophic optic discs. *Lancet* 2:224-226, 1967.
3. Hayreh SS, Walker WM: Fluorescent fundus photography in glaucoma. *Am J Ophthalmol* 63:982-989, 1967.
4. Yannuzzi L, Fisher YL, Levy JH: A classification of abnormal fundus fluorescence. *Ann Ophthalmol* 3: 711-718, 1971.
5. Hodge JV, Clemett RS: Improved method for fluorescence angiography of the retina. *Am J Ophthalmol* 61:1400-1404, 1966.
6. Haining WM, Lancaster RC: Advanced techniques for fluorescein angiography. *Arch Opththalmol* 70:1-15, 1968.
7. Machemer R, Norton EWD, Gass JDM, Choromokos E: Pseudofluorescence — A problem in interpretation of fluorescein angiograms. *Am J Ophthalmol* 70: 1-10, 1970.
8. Allen L, Frazier O: The results of tests on a broad band filter combination for fluorescence angiography. In: *Fluorescein Angiography* (ed Koichi Shimizu) Tokyo, Igaku Shoin Ltd., 1974, pp 48-59.
9. Wessing A: Erfahrungen mit neuen Filtern für die Fluoreszenz-Angiographie. *Klin Monatsbl Augenheilkd* 165:302-308, 1974.
10. Oosterhuis JA, Gortzak-Moorstein N: Fluorescein angiography of the optic disc in glaucoma. *Ophthalmologica* 160:331-353, 1970.
11. Shimizu K: Sectorial order of fluorescein filling in the disc area. In: *Fluorescein Angiography* (ed, Koichi Shimizu) Tokyo, Igaku Shoin Ltd., 1974, pp 349-356.
12. Yokoyama Y, Funahashi T, Horiuchi T, Mizuno T: Correlation of the fluorescein angiogram with the dye content in the blood. In: *Fluorescein Angiography* (ed Koichi Shimizu) Tokyo, Igaku Shoin Ltd., 1974, pp 72-76.
13. Amalric P, Bessou P, Biau C: Aspects fluoresceiniques de la papille et de la region peripapillaire. *Bull Soc Ophtalmol Fr* 334-365, 1967.
14. Gnad HD: A method for fluorescence cineangiography of the human retina. *Albrecht von Graefes Arch Klin Opththalmol* 182:82-88, 1971.
15. Haining WM: A new cine fluorographic technique and its application to investigation of the retinal circulation. *Trans Ophthalmol Soc UK* 92:169-172, 1972.
16. Hochheimer BF: Angiography of the retina with indocyanine green. *Arch Ophthalmol* 86:564-565, 1971.
17. Flower RW: Injection technique for indocyanine green and sodium fluorescein dye angiography of the eye. *Invest Ophthalmol* 12:881-894, 1973.
18. Hayreh SS: Blood supply of the optic nerve head and its role in optic atrophy, glaucoma, and oedema of the optic disc. *Br J Ophthalmol* 53:721-748, 1969.
19. Henkind P: New Observations on the radial peripapillary capillaries. *Invest Ophthalmol* 6:103-108, 1967.
20. Hayreh SS, Revie IHS, Edwards J: Vasogenic origin of visual fields defects and optic nerve changes in glaucoma. *Br J Ophthalmol* 54:461-472, 1970.
21. Rosen ES, Boyd TAS: New method of assessing choroidal ischemia in open-angle glaucoma and ocular hypertension. *Am J Ophthalmol* 70:912-922, 1970.
22. Raitta C, Sarmela T: Fluorescein angiography of the optic disc and the peripapillary area in chronic glaucoma. *Acta Ophthalmol (Kbh)* 48:303-309, 1970.
23. Spaeth GL: Pathogenesis of visual loss in patients with glaucoma. Pathologic and sociologic considerations. *Trans Am Acad Ophthalmol Otolaryngol* 75:296-317, 1971.

24. Cristini G: Common pathological basis of the nervous ocular symptons in chronic glaucoma. *Br J Ophthalmol* 35:11-20, 1950.
25. Gafner F, Goldmann H: Experimentelle Untersuchungen über den Zasammenhang von Augendruuksteigerung und Gesichtsfeldschädigung. *Ophthalmologica* 130:357-377, 1955.
26. Dollery CT, Henkind P, Kohner EM, Paterson JW: Effect of raised intraocular pressure on the retinal and choroidal circulation. *Invest Ophthalmol* 7:191-198, 1968.
27. Hayreh SS, Perkins ES: Clinical and experimental studies on the circulation at the optic nerve head. *The William Mackenzie Centenary Symposium on the Ocular Circulation in Health and Disease* (ed J Stanley Cant) St. Louis, C. V. Mosby Co., 1969, pp 71-86.
28. Ben-Sira I, Riva CE: Fluorescein angiography and ocular hemodynamics. Effect of ocular pigments on choroidal fluorescence during induced ocular hypertension. *Invest Ophthalmol* 12:896-903, 1973.
29. Blumenthal M, Gitter KA, Best M, Galin M: Fluorescein angiography during induced ocular hypertension in man. *Am J Ophthalmol* 69:39-43, 1970.
30. Archer DB, Ernest JT, Krill AE: Retinal, choroidal, and papillary circulations under conditions of induced ocular hypertension. *Am J Ophthalmol* 73:834-845, 1972.
31. Ernest JT, Archer D: Fluorescein angiography of the optic disc. *Am J Ophthalmol* 75:973-978, 1973.
32. Swietliczko I, David NJ: Fluorescein angiography in experimental ocular hypertenison. *Am J Ophthalmol* 70:351-363, 1970.
33. Blumenthal M, Best M, Galin M, Toyofuku H: Peripapillary choroidal circulation in glaucoma. *Arch Ophthalmol* 86:31-38, 1971.
34. Spaeth GL, Montalbo AA: A proposal for therapy of patients suspected of having glaucomatous disease utilizing fluorescein angiography as a measure of the adequacy of blood flow. In: *Fluorescein Angiography* (ed Koichi Shimizu) Tokyo, Igaku Shoin Ltd., 1974, pp 378-385.
35. Begg IS, Drance SM, Goldman H: Fluorescein angiography in the evaluation of focal circulatory ischemia of the optic nerve head in relation to the arcuate scotoma in glaucoma. *Can J Ophthalmol* 7:68-74, 1972.
36. Evans PY, Shimizu K, Limaye S, Deglin E, Wruck J: Fluorescein cineangiography of the optic nerve head. *Trans Am Acad Ophthalmol Otolaryngol* 77:260-273, 1973.
37. Halasa A: Vasogenic factors in the etiology of the field defects in glaucoma. In: *Current Concepts in Ophthalmology* (ed Frederick C. Blodi) St. Louis, C. V. Mosby Co., 1972, pp 131-141.
38. Oosterhuis JA, Boen-Tan RN: Choroidal fluorescene in the normal human eye. *Ophthalmologica* 162:246-261, 1971.
39. Ben-Sira I, Riva CE: Fluorophotometric recording of fluorescein dilution curves in human retinal vessels. *Invest Ophthalmol* 12:310-311, 1973.
40. Hyvarinen L, Maumenee AE, George T, Weinstein G: Fluorescein angiography of the choriocapillaris. *Am J Ophthalmol* 67:653-666, 1969.
41. Kogure K, David NJ, Yamanouchi U, Choromokos E: Infrared absorption angiography of the fundus circulation. *Arch Ophthalmol* 83:209-214, 1970.
42. Laatikainen L, Mäntylä P: Effects of a fall in the intraocular pressure level on the peripapillary fluorescein angiogram in chronic open-angle glaucoma. *Acta Ophthalmol (Kbh)* 52:625-633, 1974.
43. Read RM, Spaeth GL: The practical clinical appraisal of the optic disc in glaucoma. *Trans Am Acad Ophthalmol Otolaryngol* 78:OP 255-274, 1974.
44. Hoyt WF, Newman NM: The earliest observable defect in glaucoma? *Lancet* 1:692-693, 1972.
45. Schwartz B: Cupping and pallor of the optic disc. *Arch Ophthalmol* 89:272-277, 1973.

46. Müller H: Anatomische Beiträge zur Ophthalmologie: Ueber Nervean-Veränderungen an der Eintrittsstelle des Sehnerven. *Arch Ophthalmol* 4:1-39, 1858.
47. von Jaeger E: Ueber Glaucom und seine Heilung durch Iridectomie. *Z Ges der Aerzte zu Wien* 14:465-474, 484-491, 1858.
48. Fuchs E: Ueber die Lamina cribrosa. *Albrecht von Graefes Arch Ophthalmol* 91:435-485, 1916.
49. Schreiber L: Ueber Degeneration der Netzhaut naut experimentellen und pathologisch-anatomischen Untersuchungen. *Albrecht von Graefes Arch Ophthalmol* 64:237-339, 1906.
50. Anderson DR, Hendrickson A: Effect on intraocular pressure on rapid axoplasmic transport in monkey optic nerve. *Invest Ophthalmol* 13:771-783, 1974.
51. Minckler D, Tso M: Axoplasmic flow in the normal rhesus monkey optic nerve. Presented at the Association for Research in Vision and Ophthalmology meeting, Sarasota, Florida, April 26, 1974.
52. Levy NS: The effects of elevated intraocular pressure on slow axonal protein flow. *Invest Ophthalmol* 13:691-695, 1974.
53. Barany E: Effect of raised pressure on axoplasm flow of the isolated neuron. Presented at the International Symposium on the Pathogenesis of Glaucoma, Munich, Germany, October, 19, 1974.
54. Samson FE: Mechanism of axoplasmic transport. *J Neurobiol* 2:347-360, 1971.
55. Schonbach J, Cuenod M: Axoplasmic streaming and proteins in the retino-tectal neurons of the pigeon. *Acta Neuropathol (Berl)* 5:153-161, 1971.
56. Bunt AH: Effects of vinblastine on microtubule structure and axonal transport in ganglion cells of the rabbit retina. *Invest Ophthalmol* 12:579-590, 1973.
57. Levy NS: Functional implications of axoplasmic transport. *Invest Ophthalmol* 13:639-640, 1974.
58. Fruhauf A: Researches on the influence of the arterial blood pressure in the course of glaucoma simplex. *Dtsch Gesundheitsw* 26:273-275, 1971.
59. Lindsey A: Aetiology of field loss in chronic glaucoma. *Can J Ophthalmol* 6:212-217, 1971.
60. Emery JM, Landis D, Paton D, Boniuk M, Craig JM: The lamina cribrosa in normal and abnormal human eyes. *Trans Am Acad Ophthalmol Otolaryngol* 78:OP 290-297, 1974.
61. LaGrange F, Beauvieux J: Anatomic pathologique et pathogenie de l'excavation glaucomateuse. *Bull Soc Ophtalmol Fr* 37:462-480, 1924.
62. LaGrange F, Beauvieux J: Anatomie de l'excavation glaucomateuse. *Arch Ophtalmol (Paris)* 42:129-140, 1925.
63. Schnabel I: Entwicklungsgeschichte der glaukomatösen Exkavation. *Z Augenheilk* 14:1-22, 1905.
64. Cristini GL: Common pathological basis of the nervous ocular systems in chronic glaucoma. *Br J Ophthalmol* 35:11-20, 1951.
65. Kornzweig AL, Eliasoph I, Feldstein M: Selective atrophy of the radial peripapillary capillaries in chronic glaucoma. *Arch Ophthalmol* 80:696-702, 1968.
66. Loewenstein A: Cavernous degeneration, necrosis and other regressive processes in optic nerve with vascular disease of eye. *Arch Ophthalmol* 34:220-226, 1945.
67. Reese AB, McGavic JS: Relation of field contraction to blood pressure in chronic primary glaucoma. *Arch Ophthalmol* 27:845-850, 1942.
68. Nordmann J: Au sujet de quelques questions fondementales concernant le glaucome. *Ann Ophtal* 193:17-27, 1960.
69. Ebner R: Prognosis of glaucoma with reference to the arterial blood pressure. *Wien Med Wochenschr* 117:1024-1026, 1967.
70. Said A, Labib MAM, Abboud I, Hegazi A: The relationship between systemic hypertension and chronic simple glaucoma. *Bull Ophthalmol Soc Egypt* 60:71-81, 1967.
71. Leighton DA, Phillips CI: Systemic blood pressure in open-angle glaucoma, low-tension glaucoma, and the normal eye. *Br J Ophthalmol* 56:447-453, 1972.

72. Harrington D: The pathogenesis of the glaucoma field. *Am J Ophthalmol* 47:177-185, 1959.
73. Feldman F, Sweeney VP, Drance SM: Cerebrovascular studies in chronic simple glaucoma. *Can J Ophthalmol* 4:358-364, 1969.
74. Ekbom KA: Scotoma due to arterial hypotension. *Acta Ophthalmol (Kbh)* 51:375-383, 1973.
75. Jaeger EA, Weeks SD, Duane TD: Perimetric and visual acuity changes during ophthalmodynamometry. *Arch Ophthalmol* 71:484-488, 1964.
76. Drance SM: Studies in the susceptibility of the eye to raised intraocular pressure. *Arch Ophthalmol* 68:478-485, 1962.
77. Drance SM, Morgan RW, Sweeney VP: Shock-induced optic neuropathy: A cause of nonprogressive glaucoma. *N Eng J Med* 288:392-394, 1973.
78. Begg IS, Drance SM, Sweeney VP: Haemorrhage of the disc. A sign of acute ischaemic optic neuropathy in chronic simple glaucoma. *Can J Ophthalmol* 5:321-330, 1970.
79. Hayreh SS: The pathogenesis of cupping of the optic disc. *Br J Ophthalmol* 58:863-876, 1974.
80. Morgan RW: Open-angle glaucoma: An epidemiologist's view. *Can J Ophthalmol* 7:75-79, 1972.
81. Bill A: Intraocular pressure and blood flow through the uvea. *Arch Ophthalmol* 67:336-348, 1962.
82. Weiter JJ, Schachar RA, Ernest JT: Control of intraocular blood flow. I. Intraocular pressure. *Invest Ophthalmol* 12:327-331, 1973.
83. Alm A, Bill A: Ocular and optic nerve blood flow at normal and increased intraocular pressures in monkeys (macaca irus). *Exp Eye Res* 15:15-29, 1973.
84. Alm A, Bill A: Blood flow and oxygen extraction in the cat uvea at normal and high intraocular pressures. *Acta Physiol Scand* 80:19-28, 1970.
85. Alm A, Bill A: The oxygen supply to the retina, I. Effects of changes in intraocular and arterial blood pressures, and in arterial P_{O_2} and P_{CO_2} on the oxygen tension in the vitreous body of the cat. *Acta Physiol Scand* 84:261-274, 1972.
86. Ernest JT: Autoregulation of optic-disc oxygen tension. *Invest Ophthalmol* 13:101-106, 1974.
87. Oosterhuis JA, Bakker RB, Van Den Berge KM: Binocular fundus fluorometry and oximetry. *Ophthalmol Res* 2:236-241, 1971.
88. Zaretskaya RB, Trutneva KV, Zubareve TV: Oxyhemographia indices in persons with suspected glaucoma. *Oftalmol Zh* 27:276-280, 1972.
89. Riehm E, Podesta HH, Bartsch C: Researches on the blood flow in retinal capillaries in rises of intraocular tension. *Ophthalmologica* 164:249-251, 1972.
90. Alterman M, Henkind P: Radial peripapillary capillaries of the retina. II. Possible role in Bjerrum scotoma. *Br J Ophthalmol* 52:26-31, 1968.
91. Anderson DR, Davis EB: Retina and optic nerve after posterior ciliary artery occlusion. An experimental study in squirrel monkeys. *Arch Ophthalmol* 92:422-426, 1974.
92. Font RL, Naumann G: Ocular histopathology in pulsless disease. *Arch Ophthalmol* 82:784-788, 1969.
93. Duane TD, Jaeger EA: Glaucoma and ocular circulation: Theories of field loss. *Survey Ophthalmol* 15:364-369, 1971.
94. von Hippel E: Ueber die Schnabelsche Lehre von der Entstehung der glaukomatösen Excavation *Arch Ophthalmol* 74:101-167, 1910.
95. Flocks M, Miller J, Chao B: Retinal circulation times with the aid of fundus cinephotography. *Am J Ophthalmol* 48:306, 1959.
96. Hollenhorst RW, Kearns TP: The fluorescein dye test of circulation time in patients with occlusive disease of the carotid arterial system. *Mayo Clinic Proc* 36:457-466, 1961.
97. Pemberton JW, Britton WA: The arm-retina circulation time. *Arch Ophthalmol* 71:364-370, 1964.

98. Ferrer O: Retinal circulation times. Studies by means of fluorescein rapid sequence photography. *Ophthalmologica* 157:89-103, 1969.
99. Amalric P, Bessou P: The importance of the choroid time in the course of fluorescent angiography. *Bull Soc Ophtalmol Fr* 69:139, 1969.
100. Bulpitt CJ, Dollery CT: Estimation of retinal blood flow by measurement of mean circulation time. *Cardiovas Res* 5:406-412, 1971.
101. Matsui K: Studies of retinal circulation with fluorescein fundus angiography. *Folia Ophthalmol Jap* 21:483-495, 1970.
102. Palamarchuk GS: Prognostic Significance of the Lobstein index in glaucoma. *Vestn Oftalmol* 1:16-20, 1968.
103. Dobromyslov AN, Kvasova MD: Prognostic importance of tension in retinal capillaries in glaucoma simplex. *Vestn Oftalmol* 3:19-22, 1970.
104. Johnson DG, Drance SM: Some studies on the circulation in patients with advanced open-angle glaucoma. *Can J Ophthalmol* 3:149-153, 1968.
105. Henkind P, Levitzky M: Angioarchitecture of the optic nerve. I. The papilla. *Am J Ophthalmol* 68:979-986, 1969.
106. Anderson DR: Vascular supply to the optic nerve of primates. *Am J Ophthalmol* 70:341-351, 1970.
107. Ernest JT, Potts AM: Pathophysiology of the Distal Portion of the Optic Nerve. I. Tissue Pressure Relationships. II. Vascular Relationships. *Am J Ophthalmol* 66:373-387, 1968.
108. Armaly MF: The visual field defect and ocular pressure level in open-angle glaucoma. *Invest Ophthalmol* 8:105-124, 1969.