DIABETIC RETINOPATHY: FIBROTIC PROLIFERATION AND RETINAL DETACHMENT*

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DIABETIC RETINOPATHY IS now a common late complication of diabetes mellitus.[1] It is one of the three major causes of blindness in the United States having onset in adults. The other two are glaucoma and ocular trauma. Proliferative retinopathy is the type most often associated with permanent profound visual loss. Exudative changes alone never cause total visual loss and angiopathic lesions in the absence of proliferation lead to blindness only infrequently. Therefore, most blindness due to diabetic retinopathy is related to proliferative retinopathy, which consists of new formed tissue on the retinal surface or in the vitreous cavity. It has both vascular and fibrotic components. As the fibrotic changes are responsible for traction on the retina and its sequelae, this aspect of proliferative retinopathy will be emphasized in this study of the relationships between fibrotic proliferative diabetic retinopathy, retinal traction, retinal detachment, and visual prognosis.

Diabetic retinopathy has been studied in three ways, clinically, histopathologically, and by special techniques.

Historically, there are three periods in the clinical study of proliferative diabetic retinopathy. The first period, prior to the discovery of insulin, begins in 1855 when Jaeger[2] first described the ophthalmoscopic picture of diabetic retinopathy. Reports in the literature were rare, as few diabetics survived long enough to develop retinopathy. In 1876, Manz[3] reported three cases that had new tissue growing from the disk and suggested the term retinitis proliferans. This term has been used to describe the proliferative form of retinopathy; however, none of these three cases was diabetic. The first report of retinitis proliferans in a diabetic was by MacKenzie[4] in 1877. In 1888, Nettleship[5] described an eye with vascular proliferation in a diabetic of maturity onset type. The

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proliferation extended into the vitreous and was seen best with a +6 sphere. The fellow eye was blind and had secondary glaucoma associated with enlarged vessels on the iris (rubeosis iridis?).

Hirschberg[6] was the first to study diabetic retinopathy systematically. In 1891, he divided his cases into two groups: (1) Retinitis centralis punctata – a characteristic inflammation of the central retina with small clear spots and usually punctate hemorrhages; (2) Retinitis hemorrhagica diabetica – retinal hemorrhages with consequent inflammation and degeneration. In the latter group, hemorrhagic glaucoma and central vein thrombosis were seen in addition to the less advanced changes of the small and large intraretinal hemorrhage. In a survey of diabetics prior to the use of insulin, Wagener and Wilder[7] in 1921 reported an incidence of diabetic retinopathy of 8.3 per cent.

The second period began with the discovery and use of insulin in 1921 as treatment for diabetes mellitus. Insulin drastically changed the entire disease complex, including its ocular aspects. Instead of sporadic cases of retinopathy that warranted a report in the literature, the ocular changes in longstanding diabetes were to become a major ophthalmic disease entity. Within 15 years after the introduction of insulin, several large series of patients with diabetic retinopathy were reported.

Although the less severe aspects of diabetic retinopathy were relatively common, proliferative retinopathy was still infrequent. In 1935 Waite and Beetham[8] reported their ocular findings in 2001 diabetics. Twenty-six (26) eyes had proliferative retinopathy, 0.7 per cent of the 3915 visible fundi. Wagener et al.[9] in 1934 also reported 8 cases (0.8 per cent) of retinitis proliferans in their series of 1052 eyes studied. In 1954, Dekking[10] reported proliferative retinopathy in 7 per cent of 383 patients examined; Portsmann (1954)[11] noted proliferative diabetic retinopathy in 1.7 per cent of 720 patients. These data show that proliferative retinopathy was still uncommon only twenty years ago.

The relationship between vitreous hemorrhage and proliferative retinopathy has been a matter of controversy for many years. Hanum (1938)[12] described six cases of proliferative diabetic retinopathy. All were associated with vitreous hemorrhage and occurred in maturity onset diabetes. Abnormal new vessels or fibrous tissue were present in each fundus. Because vitreous hemorrhage occurred in both treated and untreated diabetics, he doubted any relationship with diabetes. He considered the vitreous hemorrhage as the stimulus for the formation of the new fibrous tissue. In 1947, von Bahr[13] described neovascular proliferation in diabetics with no previous history of vitreous hemorrhage.

Bedell (1945)[14] documented early vessel formation at the disk, with

extension, and then development of connective tissue. He noted wrinkling of the proliferative membrane, obscuration of the retina by a dense membrane, and shrinkage of new vessels as the membrane atrophied. All these findings have frequently been described in more recent literature.

The third period began slightly more than a decade ago when reports of large numbers of patients with proliferative diabetic retinopathy first appeared. The first series reporting more than 100 patients with proliferative retinopathy was that of Kornerup[15] in 1958. Of 1402 nonselected diabetics examined, 117 (8.4 per cent) had proliferative diabetic retinopathy. Appearance of proliferative diabetic retinopathy was most frequent in the group having diabetes for 15–19 years. Age at appearance of proliferative diabetic retinopathy ranged from 25 through 49 years. Root et al.[16] analyzed 847 cases with proliferative diabetic retinopathy in 1959. They stated that proliferative retinopathy was rare in patients developing diabetes after age 60. They felt close regulation of diabetes was an important factor in reducing the incidence of proliferative changes. Their data supported the assumption that simple and proliferative diabetic retinopathy were two processes that frequently occurred in the same eye.

Beetham in 1963 stated, "No one doubts the marked increase in frequency of proliferating retinopathy during the past few decades." He reported that 30 per cent of the patients he had seen with diabetic retinopathy in the twenty years prior to his report in 1963 had had proliferative disease. Of 1149 patients with proliferative retinopathy, he examined 351 on two or more occasions. Of the 351, approximately 30 per cent were legally blind, and 7 per cent totally blind. Two hundred fifty-six showed an advancement in the degree of proliferation, but no specific descriptions of proliferative disease were recorded. Thirty-five patients had a spontaneous arrest of proliferative diabetic retinopathy. In these cases there was no recurrent vitreous hemorrhage, the new vessels atrophied and retinal hemorrhages became less common. Eight patients in this quiescent, "dried out," stage had vision better than 20/200 in at least one eye.[17]

Dobree,[18] in 1964, carefully documented the progression of proliferative retinopathy in twenty-five eyes. He described the progression from the formation of the early, small naked new vessels, through the stage of extension of new vessels and appearance of connective tissue to the final phase of regression of the neovascularization and contracture of the connective tissue. Different stages might be present in one eye. In 1968,[19] he reported the evolution of proliferative diabetic retinopathy in 112

eyes from 58 patients, observed from 9 months to 8½ years. He also discussed the secondary changes in these eyes. They were as follows: (1) vitreous retraction; (2) thickening of the posterior vitreous face; (3) formation of retino-vitreal bands; (4) traction on retinal vessels; (5) retinoschisis; (6) flat holes and retinal detachment; (7) late choroid-retinal changes; (8) pathological arterioles, rubeosis iridis and secondary glaucoma; (9) subhyaloid, vitreous and choroidal hemorrhages. The first six are related to fibrotic proliferative retinopathy or retinal detachment and will be discussed later.

Larsen,[20] in 1960 demonstrated numerous instances of proliferative retinopathy, with both neovascular and fibrotic proliferation. Contraction of the extensive connective tissue formations of the late stage of proliferation were identified as the cause for the traction that wrinkled the hyaloid membrane. He also photographed regression of early vascular networks. Reports of clinical regression have been noted by Babel and Rilliet (1958),[21] Fischer (1961),[22] and Beetham (1963).[17]

The reports of Davis (1965)[23] and Tolentino et al. (1966)[24] on patients with proliferative retinopathy studied with contact lens and slit lamp biomicroscopy will be examined in the section on special studies.

Although both non-proliferative and proliferative retinopathy (retinitis proliferans) frequently are present in the same eye, they may occur independently of one another. The histopathologic study of each occurred at approximately the same time. The study of the microscopic changes of non-proliferative retinopathy within the retina will be discussed first although the study of Klien on diabetic proliferans antedated the work of Ballantyne by several years. The understanding of the pathogenesis of diabetic retinopathy rests primarily upon the work of Ballantyne and co-workers.[25–27] They revived the concept that diabetic retinopathy was a distinct entity, as recognized by MacKenzie,[4] Nettleship,[5] and Hirschberg[6] in the late nineteenth century and not merely a variant of hypertensive or arteriosclerotic retinal change. The subsequent work of Ashton,[28] Friedenwald,[29] Wise,[30] Kuwabara and Cogan,[31] elaborated on Ballantyne's original findings and theories.

The changes from the early manifestations of diabetic retinopathy to ophthalmoscopically visible proliferative retinopathy have been well documented. The early microscopic changes noted by Ballantyne[25] were minute aneurysms in the retinal capillaries which he termed microaneurysms. They were conspicuous lesions microscopically, easily distinguished from punctate hemorrhages, being round and clearly outlined, about 50 microns in diameter, and situated in the nerve fiber or inner nuclear layers. Some had an elongated sausage-like form. Although

not pathognomonic of diabetes, their presence in large numbers was indicative of this disease. He suggested that microaneurysms were an abortive attempt at neovascularization in an hypoxic retina, as did Wise in 1956.[30] Ashton (1963),[28] however, felt microaneurysms might result merely from stasis and engorgement of retinal capillaries. Kuwabara and Cogan,[31] on the basis of their trypsin digestion preparations of the retina contended that microaneurysms might be associated with the loss of the mural cell in the wall of the capillary. They also noted areas of capillary closure, with adjacent microaneurysms and dilated capillaries.

Ashton (1963)[28] stated capillary closure was an important early development associated with hypoxia, which might also be the stimulus to endothelial proliferation. This not infrequently leads to neovascularization, as shown in Stage 1 retrolental fibroplasia which he produced experimentally in kittens.

Later changes noted by Ballantyne[26] were thickening of venous walls with narrowing of their lumina, periphlebitis and phlebosclerosis, plus knots, coils and loops in the distended veins. Erosion of the internal limiting membrane was occasionally noted over these vessels if they lay close to it. Kornerup[15] noted clinically that when venous changes of this type were present, proliferative retinopathy was also present in 91 of 117 eyes (78 per cent).

Early histopathologic studies of retinitis proliferans were done by Weeks (1897),[32] Fleming (1898),[33] and Marple (1901).[34] Diabetes was present in 2 of the 16 cases reported by Marple, but not in Fleming's one case or Weeks' 18 cases. All three authors documented retinal detachment in association with proliferation. Also, they noted the absence of the internal limiting membrane at the sites where proliferation extended into the vitreous cavity.

Wolff (1937)[35] noted the internal limiting membrane stained like collagenous tissue with the Mallory stain. It was smooth on the vitreous surface, but irregular on the retinal surface. However, when a retinal vessel lay close, it was smooth on its retinal surface and also became very thin.

The understanding of proliferative retinopathy was greatly enhanced by the work of Klien.[36] In 1938 she described two types of retinitis proliferans. The first was proliferation from a formation of connective tissue, preceding blood vessel formation. The primary event was an inflammatory or traumatic change in the retina. From diseased retinal blood vessels, a hemorrhage or exudate extended from the retina into the vitreous. The causes were tuberculous periphlebitis, neuroretinitis

papulosa secondary to syphilis, injury to retinal blood vessels, or uveal inflammation.

The second type was primarily a vascular formation. Once the blood vessels had formed, a secondary scaffolding of delicate connective tissue developed. She felt the etiology was primarily circulatory impairment found in diabetes, tertiary syphilis, and arteriosclerosis. In comparing the two types of retinitis proliferans, she noted that the connective tissue type was a dense opaque gray-white membrane that rarely had new vessels and then only in advanced disease. The primarily vascular type had delicate semitransparent, connective tissue between the vessels. In a case of vascular proliferation a delicate membrane containing new thin-walled vessels covered the retina, inside the internal limiting membrane. On serial sections, sites of perforation of the internal limiting membrane by new blood vessels could be found. This membrane was not perforated when vessels originating at the disk entered the vitreous. The connective tissue framework was delicate, consisting of fibroblasts and a few wandering cells. In other cases the connective tissue was much more dense.

In one case she observed clinically a brush-like fan of new vessels that extended into the vitreous and initially had no connective tissue between the vessels. But during the next six months, the vessels enlarged and a delicate gray connective tissue became visible between the veins.

Gartner (1950)[37] noted that shrinking connective tissue of retinitis proliferans pulled retina away from pigment epithelium to cause a malignant form of retinal detachment. He stated he had never seen retinitis proliferans in children, and postulated it was because of better circulation in early life.

Lee[38] reported the clinical and histologic findings in a 32-year-old male, diabetic since age 12, who had been carefully studied clinically before his eyes became available for postmortem examination. The patient had hypophyseal stalk section at age 27 after two years rapid progression of diabetic retinopathy. After surgery the retinopathy went into remission which continued until death at age 32 from a myocardial infarction. Fundus examinations had shown fibrovascular proliferative tissue extending into the vitreous cavity in the posterior polar region of each eye. In the left eye traction lines plus a traction detachment extended into the macular area. With biomicroscopy, flat proliferative tissue was noted on the inner surface of the retina over the posterior pole. Some also extended forward and adhered to the posterior vitreous surface.

Postmortem, the flat proliferative tissue was found to be more extensive than ophthalmoscopy and slit lamp biomicroscopy had demonstrated. Microscopically, there was extensive degeneration of the nerve fiber and ganglion cell layers of the retina. Pigment migration along the border of the traction detachment in the left eye represented a demarcation line. Retinal gliosis was present but did not affect the outer layers of the retina. Trypsin digestion preparations showed capillary shunts, microaneurysms, and over-sized capillaries bordering zones of capillary occlusion.

In the vitreous, microscopic sections showed that new vessels traveled along the posterior aspect of the detached hyaloid membrane in one area but proliferated into the vitreous in another. Near the posterior pole the posterior surface of the hyaloid membrane and the proliferative tissue derived from the retina were firmly attached. A change noted microscopically but not clinically was the fine preretinal membrane that covered the retina from the posterior pole to the equator. Lee felt this was newly formed tissue rather than cortical vitreous.

The posterior hyaloid membrane of the left eye was attached to the disk margin by proliferative tissue but extended directly to the region of the ora serrata rather than along the contour of the globe. This conforms to descriptions of vitreous shrinkage by Davis[23] and Dobree.[19]

Ashton (1967)[39] studied the histology of retinitis proliferans in the mature human eye. He observed it in cases of venous occlusion and chronic inflammation as well as in diabetic retinopathy. The ingrowing tissue was an advancing band of vasoformative mesenchyme with endothelial cells that differentiated into blood vessels slightly behind the advancing front of mesenchymal tissue. The mesenchymal cells failing to differentiate into endothelial cells developed into fibroblasts to form fibrous tissue. He felt hypoxia was the stimulus for formation of this tissue because he had demonstrated that an almost identical pattern of vasoformative tissue was associated with retrolental fibroplasia, Stage 1. In retrolental fibroplasia, where there is oxygen induced vaso-obliteration, pathologic neovascularization appears to be an exaggeration of the normal process of vascular response to hypoxia.

The third approach to the study of diabetic retinopathy is by special techniques. Fluorescein angiography has been most important in the study of early change. This technique has demonstrated capillary closure, capillary dilatation, altered blood flow patterns, and leakage of fluorescein dye through the abnormal walls of retinal vessels (Figure 1). These changes may all occur in the pre-proliferative phase of retinopathy (Kohner and Dollery).[40] Once fibrotic proliferation has become estab-

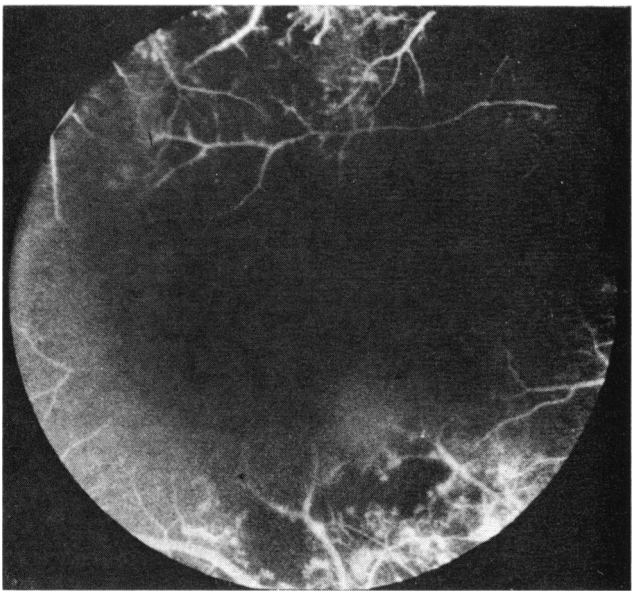


FIGURE 1A

The macular area is devoid of retinal capillaries, and surrounding it are areas of capillary closure. Abutting the areas of capillary closure are microaneurysms and dilated capillaries.

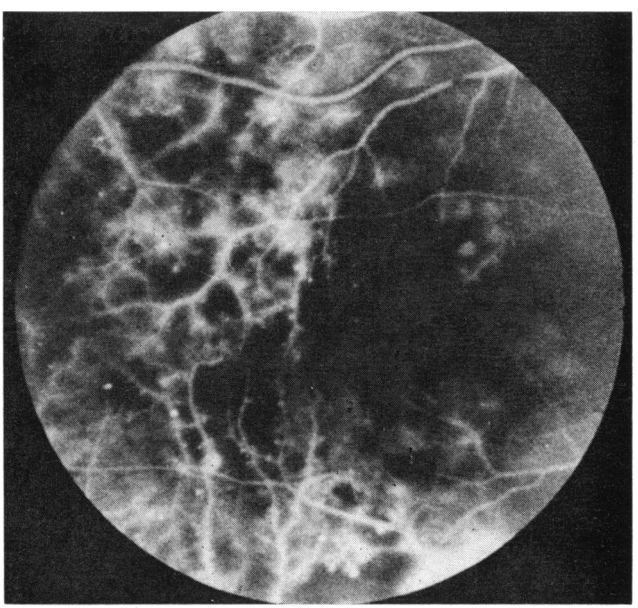


FIGURE 1B

A late photo of the same area shows fluorescein leakage.

lished, this technique becomes less important. Study of proliferative retinopathy with slit lamp biomicroscopy and contact lens has emphasized the importance of the relationship of the vitreous gel to the proliferating tissue. With the slit beam, variable illumination, and stereopsis, one can discern changes not visible by ophthalmoscopy. Hruby (1942)[41] reported shrinkage of the vitreous gel associated with "retinitis proliferans." One of the eight cases in this series was diabetic.

The most extensive studies of diabetics by this method are those of Tolentino et al.[24] and of Davis.[23] Although they classified the progressive stages differently, they agreed on the following findings. The vitreous cortex that lies over an area of new vessel formation is altered and becomes adherent to it. These sites are usually at or near the posterior pole. Vitreous shrinkage occurs and may pull new vessels off the surface of the retina into the vitreous cavity. More extensive traction may rupture these vessels or produce traction detachment or retinoschisis.

After vitreous shrinkage, new vessel growth was noted primarily along the posterior hyaloid surface or in the retrohyaloid space, only rarely penetrating the gel itself. The region of the optic nerve was usually the site of new vessel penetration of the gel when it occurred.

The small new blood vessels commonly remained adherent to the posterior hyaloid surface as the vitreous gel shrank and drew them into the vitreous cavity. During the phase of vitreous shrinkage, hemorrhages, minimal or massive, might occur due to rupture of the weak, abnormal blood vessels. The chances that a large hemorrhage would occur were less if the retina and vitreous were still in contact throughout their interface, or if the vitreous had totally detached from the retina.[23]

CLASSIFICATION

The first classification of diabetic retinopathy was by Hirschberg[6] in 1891. Scott[42] presented a classification system in 1951 in which the stages I through III had changes of non-proliferative retinopathy and stages IV through VI were those of proliferative retinopathy. Although there was a separation of two types of retinitis proliferans into stages V(a) and V(b), there was no system for documenting a combination of the two forms or for the gradations of severity of each. Despite these limitations, it represented a significant advance in the cataloguing of changes in diabetic retinopathy.

Until recently a precise classification of diabetic retinopathy was not urgent because there was no treatment for retinopathy. Now an accurate classification of diabetic retinopathy has become imperative because

optimal use of photocoagulation or pituitary ablation depends on the proper selection of cases. Also, a good classification serves as a framework for logical interpretation of pathological changes, as well as a convenient means of describing cases individually or for statistical survey.

In the last five years, classifications have been developed that not only differentiate between non-proliferative and proliferative retinopathy but also document the finer gradations of the various forms of each as well as degrees of vitreous hemorrhage.[43–45]

The Airlie classification,[46] which was the result of a group effort, is probably the most comprehensive one developed to date. Its most precise gradations are in the non-proliferative and early proliferative changes of diabetic retinopathy. Less definition is given to the more severe gradations of proliferative disease.

In this study, the classification of retinopathy developed by Lee et al.[43] was used. As with the other recent classifications, it was designed to distinguish the changes of non-proliferative and proliferative retinopathy, particularly the more severe form.

As most patients in this study had moderate to severe diabetic retinopathy, the classification of Lee et al. was considered to be more revealing of the changes of moderate and severe retinopathy than the Airlie classification, which provided less precise information once the eye was beyond early stages of retinopathy.

Classifications of the extent of traction detachment and of vitreous changes are also valuable in understanding the relationships between the various anatomic changes in the diabetic eye, and so are included.

Slight quantitative revisions made the limits between the less severe grades of retinopathy more discrete and allowed this classification to be used interchangeably with the Airlie House classification, which will probably be the standard for classification in the future (Davis et al.).[46] The two classification tables given are for non-proliferative (Table 1) and proliferative (Table 2) retinopathy.

Background retinopathy includes exudates and the non-proliferative aspects of angiopathy, such as intraretinal hemorrhages, microaneurysms, retinal edema, and venous change (Table 1). In the classification of non-proliferative angiopathy the changes of early indolent retinopathy are classified as grade 1. These include only the microaneurysms and hard exudates of limited number. If changes are present that indicate progressive retinopathy, the appropriate grades are recorded. Since some angiopathic changes occur infrequently in early retinopathy, their presence indicates a more advanced stage. Thus, in classifying back-

TABLE 1. CLASSIFICATION OF BACKGROUND RETINOPATHY

A—ANGIOPATHY

	Type of hemorrhage	Extent of hemorrhage and microaneurysms	Retinal edema	Venous abnormalities		
				Dilation	Tortuosity	Segmentation
A_1	Small, round micro-aneurysm	Less than 10 sites		Trace		
A_2		Area of sector from macula to 45° anteriorly	Trace	Slight	Slight	
	All types of intraretinal hemorrhage	Less than 30° segment				
A_3	including blot and flame shaped	30° to 90° segment	Moderate and severe	Moderate	Moderate	Slight moderate and severe
A_4		Over 90° segment		Severe	Severe	

B—EXUDATES

	Type of exudate	Extent of exudates
E_1	Refractile, discrete border–"hard"	Less than 10 sites
E_2	All types of exudates including "cottonwool" variety	Area of sector from macular to 45° anteriorly Less than 30° segment
E_3		30° to 90° segment
E_4		Over 90° segment

TABLE 2. CLASSIFICATION OF PROLIFERATIVE RETINOPATHY
(N Neovascular proliferation, F Fibrotic proliferation)

	Area of proliferation	Arc of proliferation
Grade 1 (Figure 2A)	Less than four disk areas	
Grade 2 (Figure 2B)	Segment extending anteriorly from macula 45° less than 30°	Less than 90°
Grade 3 (Figure 2C)	30° to 60° segment	90° to 270°
Grade 4 (Figure 2D)	Over 60° segment	Greater than 270°

ground retinopathy the most advanced stage of the various changes is recorded. For instance, if segmentation of veins is noted, the classification must be grade 3 background angiopathy even if classification by intraretinal hemorrhages or severity of retinal edema would be of a lesser grade.

Proliferative retinopathy includes both new fibrotic tissue and neovascularization, as angiopathy has proliferative as well as non-proliferative features. In classifying, both the neovascularization and new fibrotic tissue are graded independently so that not only the extent of proliferative tissue is determined but also its predominant form. The classification of proliferative retinopathy is shown in Table 2. The gradations are determined not only by the area of the proliferative tissue, but also by the number of degrees of arc of proliferative tissue about the posterior pole since both factors are significant (Figure 2). Examples show how this classification of proliferative retinopathy is used. In Figure 3, the photograph shows a moderate amount of neovascularization about the disk with naked vessels, no fibrosis having yet developed. This classification is N_2F_0. In Figure 4, the proliferative tissue is primarily fibrotic with very few new vessels. This is classified as N_1F_3. It is important to recognize each form of proliferative tissue, because treatment and prognosis differ depending upon the relative amounts of each type.

A classification to record the extent of non-rhegmatogenous detachment due to traction is necessary to correlate as accurately as possible the severity of the detachment with various factors. There are four grades classified in Table 3 and illustrated in Figure 5. The gradations in the illustration refer to the area of the detachment, not to the specific geographical area described.

A classification of changes in the vitreous body was developed by Van Heuven (1968)[48] to evaluate the results of photocoagulation

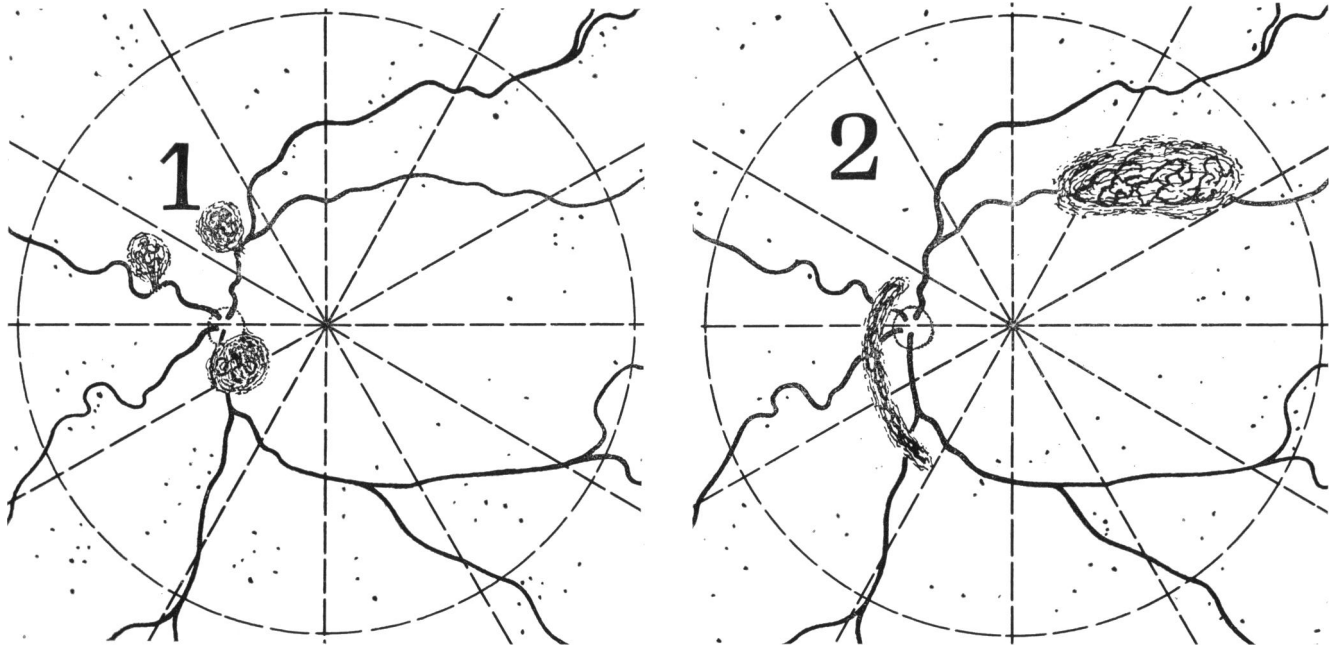


FIGURE 2

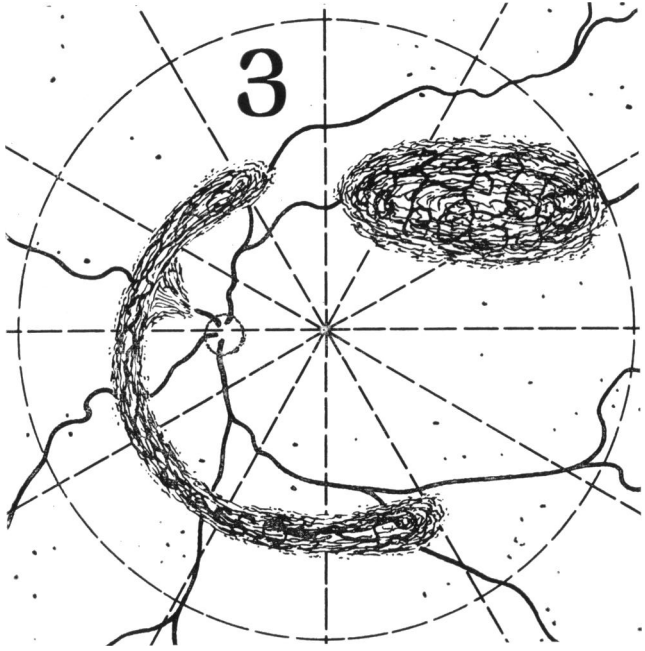
The four grades of classification of proliferative retinopathy are shown in schematic drawings. The fundus is divided into 30° segments by broken lines meeting at the macular area of the left eye. The outermost broken line represents the equator; and the inner line represents a distance of 45° from the macula to the equator.

A

Grade I Proliferative retinopathy has a total area of involvement less than the area of four disks.

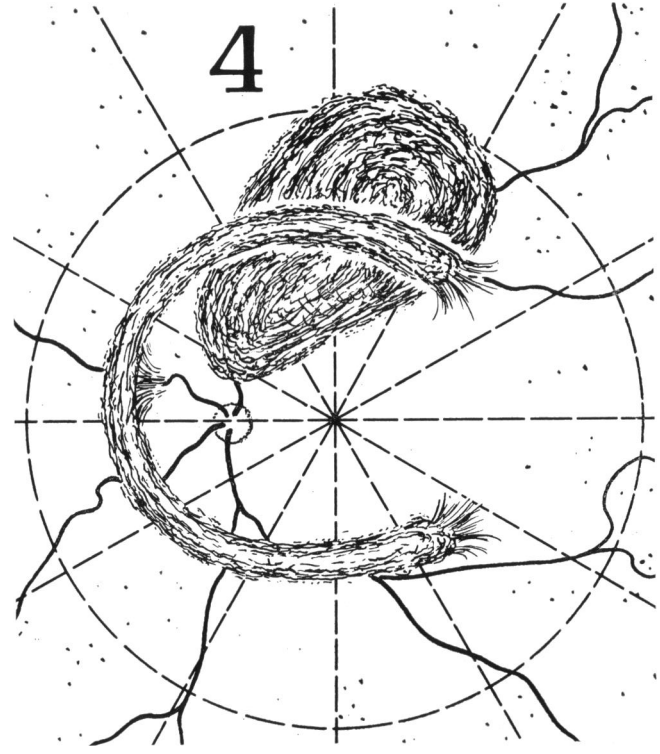
B

Grade II The area of proliferation pictured in the upper temporal quadrant covers an area larger than grade I, but less than the area of a 30° segment of the fundus extending anteriorly from the macula 45°. The other parameter, the arc of proliferation extends for less than 90°.



C

Grade III The area of proliferation illustrated in the upper temporal quadrant is larger than a 30° but less than a 60° segment of the fundus extending 45° anteriorly from the macula. The arc of proliferation is over 90° but les than 270°.



D

Grade IV Due to the large size of each lesion these had to be superimposed. The area of proliferation was larger than a 60° segment of the fundus from the macula anteriorly 45°. The arc of proliferation was greater than 270°. Classification is made on the basis of either the area or the arc of proliferation. Sometimes a combination is present. In that instance the more advanced grade is the one classified.

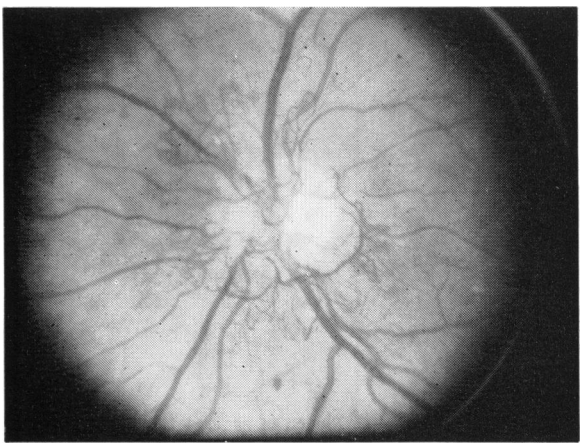


FIGURE 3
Neovascularization about the disk with naked vessels and no intervening fibrotic tissue.

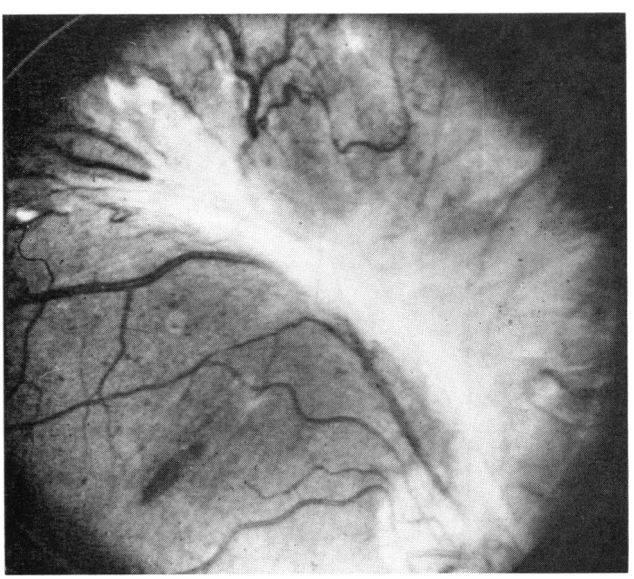


FIGURE 4
The arc of proliferative tissue extending supratemporally from the right disk. It is primarily fibrotic, with only a minimal amount of neovascularization at the temporal periphery. Traction lines and distortion of the macula are also visible.

TABLE 3. CLASSIFICATION OF EXTENT OF RETINAL DETACHMENT DUE TO TRACTION

	Total area of detached retina
Grade 1	Less than a circle four disk diameters across.
Grade 2	Greater than a circle four disk diameters across, but less than a 30-degree segment that extends 45 degrees anteriorly from the macula.
Grade 3	A segment of the fundus 30 degrees to 90 degrees that extends 45 degrees from the macula.
Grade 4	A segment of the fundus over a 90-degree segment that extends 45 degrees from the macula.

therapy in patients with diabetic retinopathy. The eyes could be divided into three groups (Figure 6). In group 1 the vitreous body had not yet detached from the retina. In group 2 there were vitreoretinal adhesions with partial detachment of the vitreous from the retina. These were seen with the slit lamp and contact lens, but indirect evidence of vitreous shrinkage or traction might also be present (Figure 7). This included the crescentic type posterior hyaloid hemorrhage lying in the trough between the attached hyaloid and retina, traction retinal detachment, and ophthalmoscopically visible elevation of new vessels into the vitreous cavity. In group 3 the posterior hyaloid face had detached completely from the retina. These are the classification systems that will be used to evaluate the data presented later.

DISCUSSION

In discussions of proliferative retinopathy two basic types have been described, frequently by different terminology.* Klein made a definite distinction between two types: one was primarily vascular initially and ultimately became fibrotic, and the other was primarily fibrotic from the beginning.

A division of avascular connective tissue was proposed by Duke-Elder and Dobree (1968).[47] They reported on the formation of avascular connective tissue bands in proliferative diabetic retinopathy. They described two types, retinal avascular bands or sheets and vitreous bands. The retinal avascular bands were formed by contracture of tissue between two fixed points, one often at the disk. The other was peripheral, at sites where connective tissue had arisen in association with new vessel forma-

*Refs. 18, 19, 20, 23, 24, 36, 38, 43, 47.

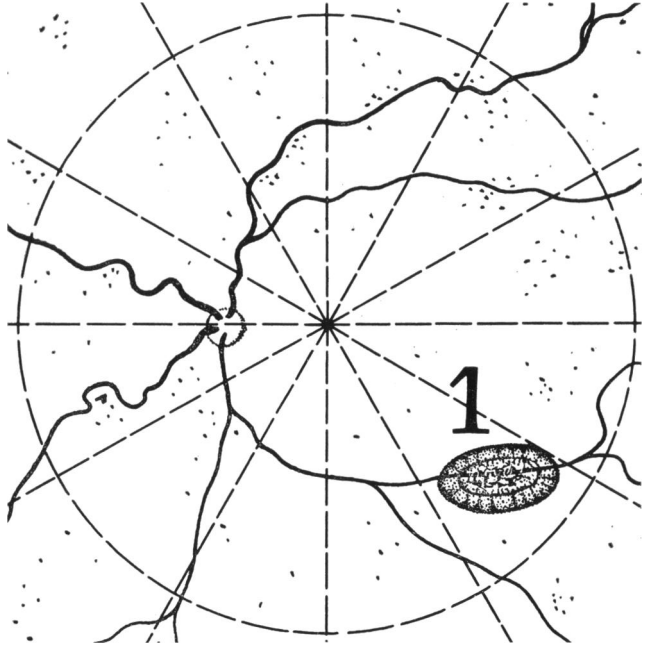


FIGURE 5A

Grade I The area of traction detachment is less than a circle 4 disk diameters across.

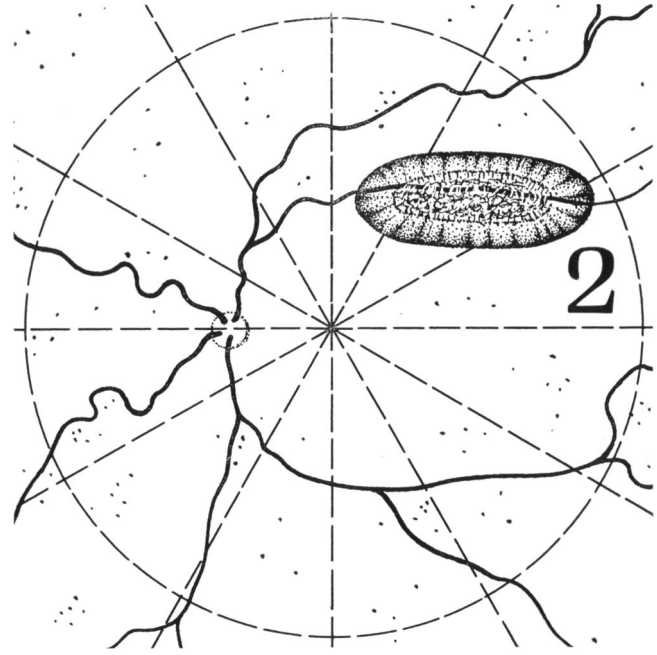


FIGURE 5B

Grade II Total area of the traction detachment schematically represented in the upper temporal quadrant is greater than a circle 4 disk diameters across but less than a 30° segment of the fundus extending 45° anteriorly from the macula.

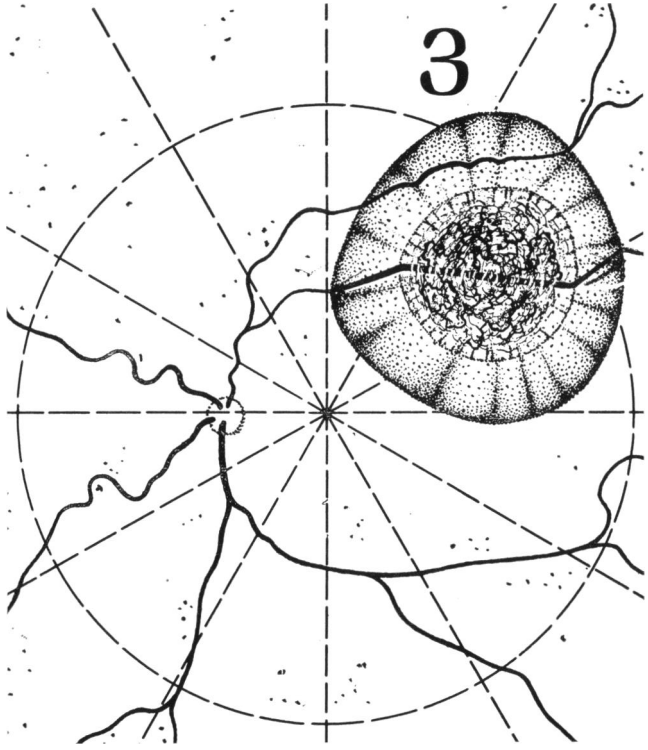


FIGURE 5C

Grade III The area of the traction detachment, schematically represented in the upper temporal quadrant, shows a central area of fibrotic proliferation surrounded by the sloping side of the traction detachment. The total area of detachment covers a segment of the fundus 30° to 90° that extends 45° anteriorly from the macula.

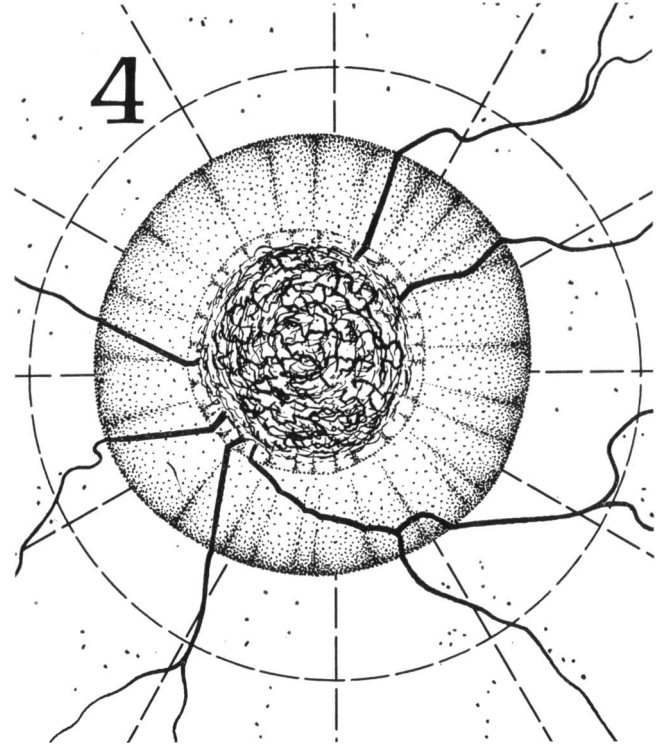


FIGURE 5D

Grade IV The total arc of the traction detachment is greater than a 90° segment of the fundus extending 45° anteriorly from the macula.

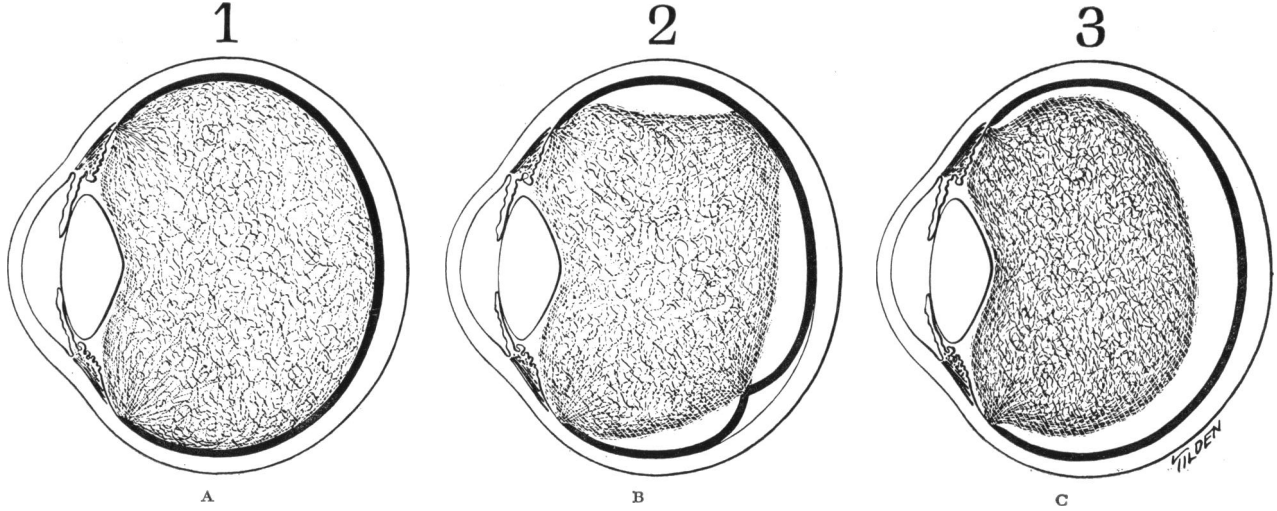


FIGURE 6

Stages of vitreous retraction. A Group 1 The vitreous body has not yet detached from the retina. B Group 2 Vitreoretinal adhesions are present with partial detachment of the vitreous from the retina. The retina may or may not be detached. C Group 3 The vitreous body is detached from the retina, but no vitreoretinal adhesions are present.

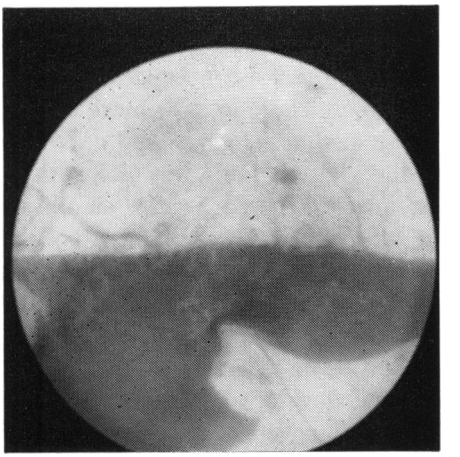


FIGURE 7

Preretinal hemorrhage lies in a trough between the posterior hyaloid face and the retina. The area of retina visible in the lower right hand corner is probably where the posterior hyaloid is adherent to the retina. Thickening of the posterior hyaloid surface can be seen with the blood as a background. The horizontal upper level of the blood suggests it has settled into the retrohyaloid space.

tion. The internal limiting membrane of the retina participated in the formation of the band and possibly also the hyaloid face of the vitreous. Retinal attachment explained the localized retinoschisis and wrinkling of the retinal surface noted at areas of traction.

The vitreous bands they noted were formed in the posterior face of the vitreous and were separated by clear fluid from the retina. The bands often tented the retina at their sites of attachment or dragged vessels toward this site. The scimitar-shaped retinal bands were observed to displace vessels and the macula by their traction, as well as produce a localized retinoschisis. In one case, the vitreous bands had pulled a hole in the retina.

The author's observations of patients with fibrotic proliferative diabetic retinopathy reveal that there are two general types of naturally occurring fibrotic tissue plus an infrequently occurring type of iatrogenic origin. The two former will be referred to as fibrovascular proliferative tissue and avascular proliferative tissue. The more common is fibro-

vascular tissue. It develops in association with the abnormal new vessels on the surface of the retina or disk, as well as those which extend into the vitreous cavity. The other form consists of amorphous avascular membranes of three types. There may be more than one source of these membranes since they seem to be associated not only with the posterior hyaloid surface of the vitreous body but also with a thickening of the internal limiting membrane. The avascular membranous types are less distinct entities than the fibrovascular tissue. All of the above types may merge with one another so that an amalgam of proliferative forms is frequently seen. The relative proportion of each component may vary greatly.

A third type of fibrotic proliferation is of iatrogenic origin. It is a fibrovascular tissue that develops at sites where photocoagulation was applied to areas of flat neovascularization as treatment for diabetic retinopathy.

The fibrovascular form, the one most commonly seen, has a wide spectrum of severity. New vessels, either naked or within a fibrous network, are its identifying feature. Klien[36] and Friedenwald[29] both noted an increase in the fibrous tissue of proliferative retinopathy. Dobree (1964)[18] described the progression of the early phases of neovascularization of naked vessels to the late avascular proliferative tissue as occurring in three stages. The naked new vessels develop either from the surface of the retina or at the optic disk. They apparently come from the superficial plexus or capillaries of the retina. Initially, the abnormal new vessels have no intervening fibrous tissue. However, as this early stage, which may be of variable duration, merges with the intermediate stage, grayish translucent fibrotic connective tissue gradually fills the spaces between the vessels. Thus, in the end stages of this process there may be a dense white scar which is virtually avascular (Figure 4). Different stages of this fibrovascular spectrum may be present in the same eye. If so, the new peripheral areas are usually the sites of the highly vascular portions of the proliferation and the more fibrotic avascular areas occur where fibrovascular proliferation has been present longer (Figure 8). The more prominent the vascular component, the greater the tendency for the proliferation to progress. It is only after the relatively avascular "burned out" end stage has been reached that no further fibrovascular proliferation is to be expected (Figure 9).

Fibrovascular proliferation most often arises from the disk or along the course of the superior and inferior temporal vessels. If it arises from the disk, it may extend along the course of these vessels (Figure 10). Initially, this network is usually flat. It can be seen by noting the ab-

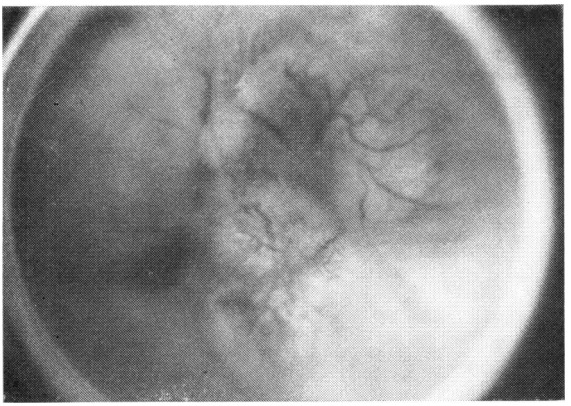


FIGURE 8
The central area of the proliferative retinopathy is less vascularized than the periphery.

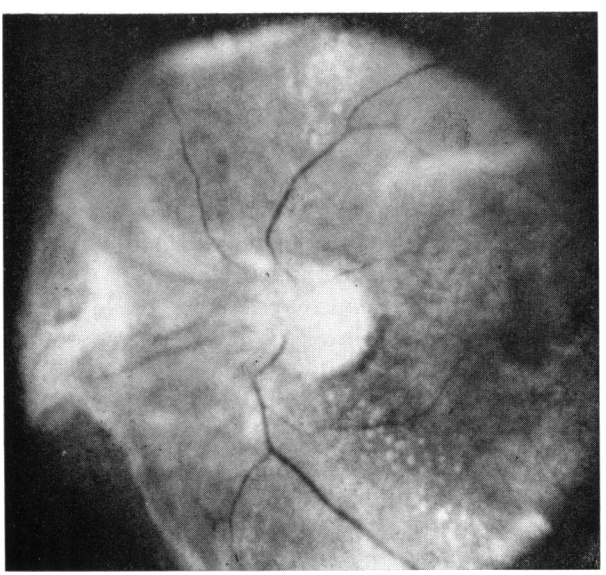


FIGURE 9
Fibrotic proliferative retinopathy is noted nasal to the disk as well as superiorly. There is no significant vascular component.

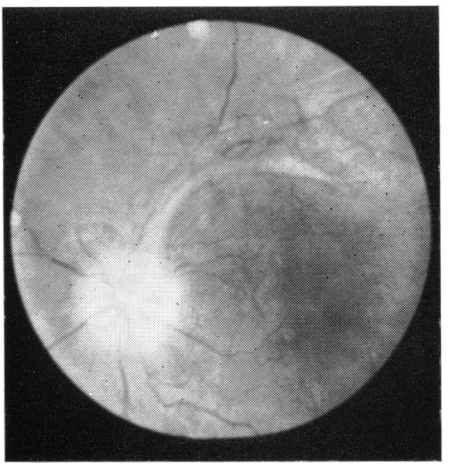


FIGURE 10

Fibrovascular proliferation arising from the disk and arcing superiorly along the course of the superior temporal vessels. The proliferation is exerting traction lines across the macula area.

normal vascular pattern overlying normal vessels. Although adherence between retina and new vessels may be the rule, in some instances the vascular network is a separate layer of tissue overlying the retina with no adhesion between them. This is demonstrated in a sequence of two photographs (Figure 11). It clearly shows a fibrovascular membrane on the retinal surface contracting to form an arc of tissue nasal to the disk without producing traction on the areas of the retina previously covered by this membrane. A similar phenomenon has not been noted with the peripheral patches of fibrovascular membranes.

The fibrovascular proliferation may later protrude into the vitreous cavity after partial vitreous shrinkage has occurred so the posterior vitreous face is no longer in apposition to the retina. Occasionally, vessels may extend directly into the vitreous cavity from the disk, possibly via the canal of Cloquet (Figure 12), although the vitreous has not yet collapsed.

Fibrovascular tissue usually has a polarity that extends peripherally from its origin (Figure 12). However, in some cases where the fibrovascular tissue has originated at the disk this does not occur. Instead, there is an apparent amorphous cluster of new vessels resembling a Medusa's head (Figure 13). With time, connective tissue becomes inter-

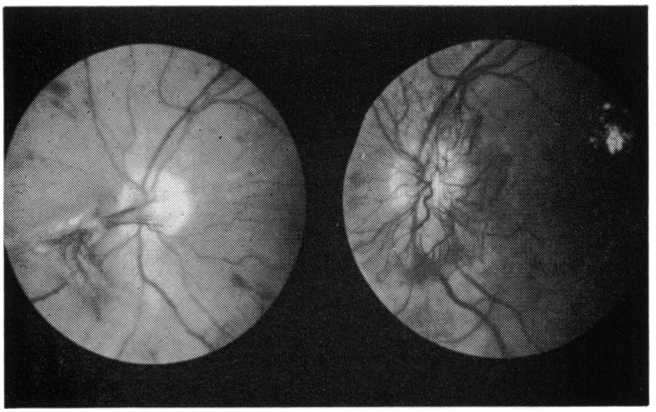


FIGURE 11

Abnormal new vessels about the disk in the photograph on the right subsequently were drawn nasally by contraction of the new fibrotic tissue. The underlying vascular pattern was not altered. There was a nine-month interval between the two photographs.

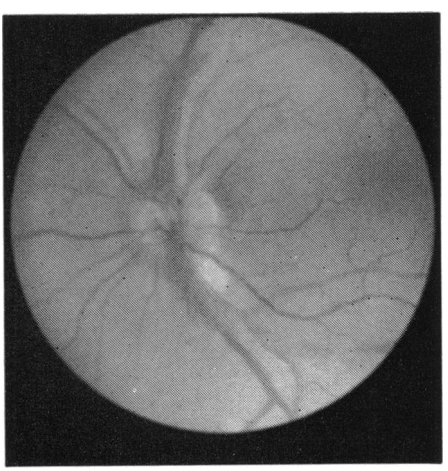


FIGURE 12

Fibrovascular tissue extends into the vitreous from the disk in a spoke-like polarity.

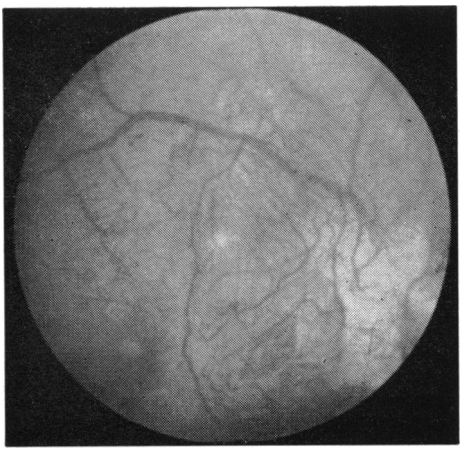


FIGURE 13

A mass of new vessels at the disk with no specific polarity, that have a "Medusa's head" appearance.

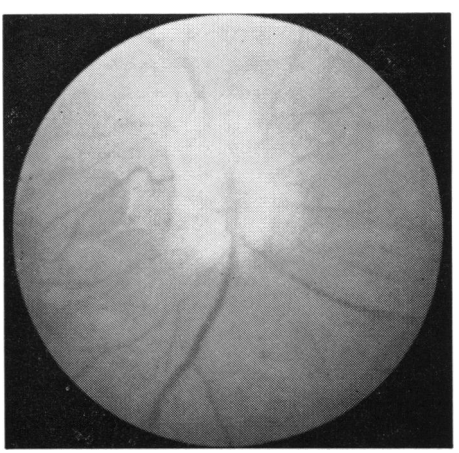


FIGURE 14

Nonpolarized amorphous primarily fibrotic fibrovascular tissue about the disk. A "Medusa's head" had been present in the active angiopathic stage.

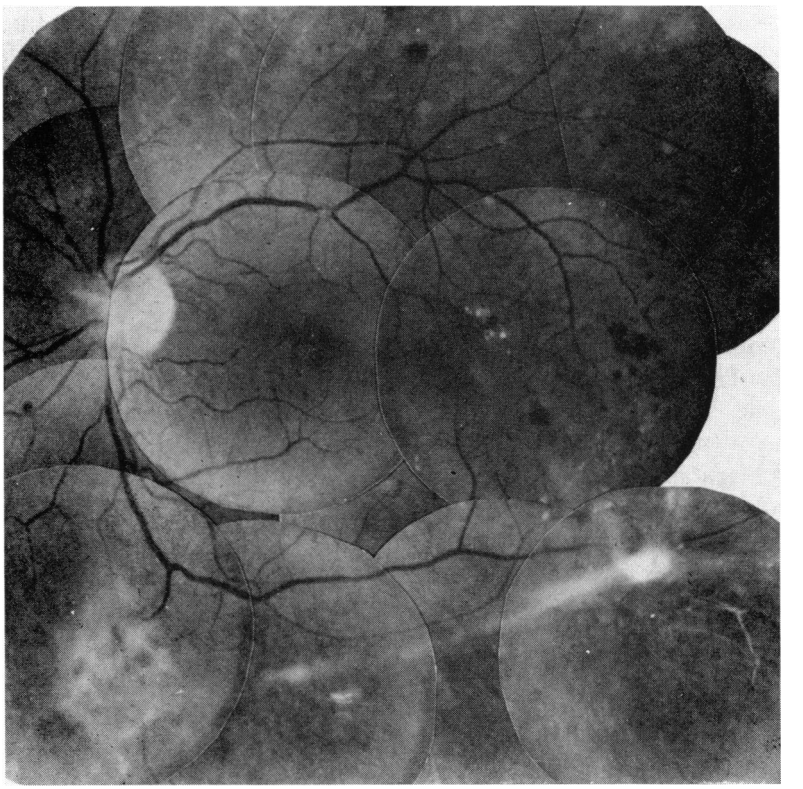


FIGURE 15

Two areas of peripheral fibrotic proliferation appear in the two lower corners of the photograph. They lie just outside the arc of the inferior temporal vessels, connected by a fine avascular strain.

spersed between the vessels. This, too, has a nonpolarized amorphous character. Occasionally, there are sharp arcuate borders of thin sheets of connective tissue which overlie this nonpolarized network of vessels and connective tissue (Figure 14). The macula is more apt to be involved by this type of fibrovascular extension from the disk than when there is polarization of the fibrovascular tissue arcing above and below the macula along the temporal vessels.

Sites of neovascularization other than at the disk may be associated with thickening of the overlying posterior vitreous face and subsequent vitreoretinal adhesions. Although these sites appear sporadically, they usually lie in an arc 20 to 30 degrees from the posterior pole (Figure 15). Careful examination of the intervening areas along this arc may show

fine avascular vitreous strands connecting the ostensibly isolated areas of neovascularization and preretinal thickening.

The avascular form of fibrotic proliferation can be divided into three types. The first is the extension from the fibrovascular tissue; the second type is vitreous membranes unassociated with fibrovascular tissue; and the third type is preretinal membranes, often described as preretinal gliosis, preretinal organization, or thickening of the posterior hyaloid face (Larsen).[20]

The first type of avascular tissue consists of strands or thin membranes that extend from the edges of elevated fibrovascular proliferation. It may extend circumferentially, posteriorly, or anteriorly toward the ora serrata. Partial shrinkage of the vitreous body is necessary before this can occur. These strands may be almost invisible, but careful observation may reveal them and their connection with a distant area of fibrovascular proliferation (Figure 16). Sometimes it is an extension of fibrovascular proliferation that has begun to encircle the posterior pole. This faint tissue high in the vitreous may complete a 360° arc about the posterior pole. In other cases a membranous sheet that extends anteriorly toward the region of the equator or ora serrata may become quite obvious if vitreous hemorrhage is deposited on its posterior surface (Figure 17). This membrane may represent the taut thickened posterior surface of a shrunken vitreous body. It occasionally has new vessels of adjacent fibrovascular tissue extending along its surface.

Another type of avascular tissue is one which has maintained a vitreoretinal adhesion and thus exerts traction on the retina that may produce a traction detachment, schisis, or retinal holes. It appears as a small area of thickened translucent tissue to which is attached a strand of avascular tissue that projects from the shrunken vitreous body (Figure 18). These "sucker feet" located away from the disk often produce the small localized detachments peripheral to the posterior pole. This lesion is frequently stable.

The last type is an avascular membrane (or flat fibrosis) on the surface of the retina that differs from the others (Figure 19). The other types are usually seen without difficulty by indirect ophthalmoscopy, but this form may be easily overlooked. It is usually visible as a glistening flat sheet on the retinal surface seen best when the light is reflected at a specific angle. This form is characteristically on or adjacent to the posterior pole and usually has a definite border except near the disk or where it may be continuous with other proliferative tissue. This membrane may slowly extend over the surface of the posterior pole. It often spares the macula, but if it covers the macula visual acuity may decrease

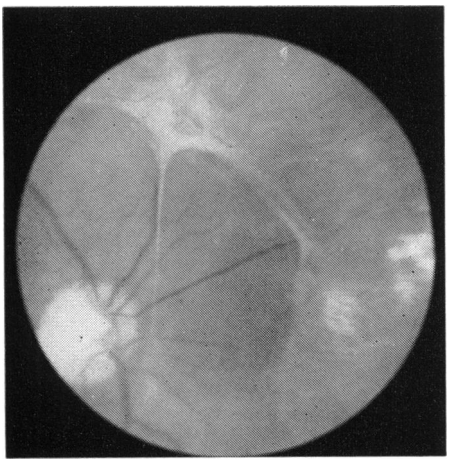


FIGURE 16

An avascular strand crosses the posterior pole just nasal to the disk connecting superior and inferior portions of a peripheral fibrovascular arc. This strand lies approximately 3 mm anterior to the surface of the retina.

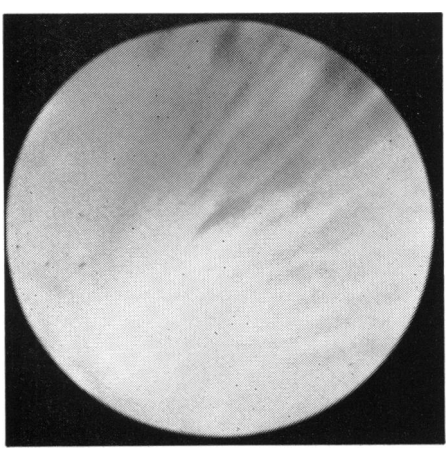


FIGURE 17

Hemorrhage in the vitreous cavity lies on the taut thickened posterior surface of a shrunken vitreous body.

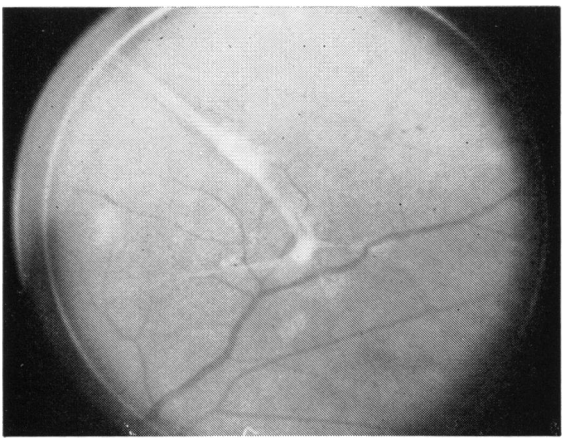


FIGURE 18

Avascular strands project to the retina from the shrunken vitreous body, attaching by "sucker feet" along the superior temporal vein. On stereoscopic view the membranes at the 9 and 10:30 meridians that merge in the center of the photograph are high in the vitreous. Minimal tenting of the retina in the areas of slightly altered light reflex over the vessel is also demonstrable with a steroscopic view.

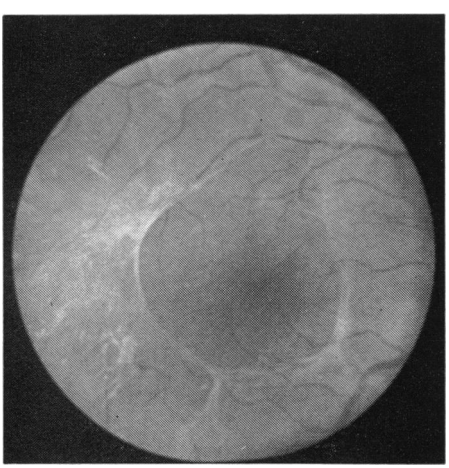


FIGURE 19

A glistening avascular membrane on the surface of the retina. The macula has been spared as revealed by the arcuate edges surrounding it.

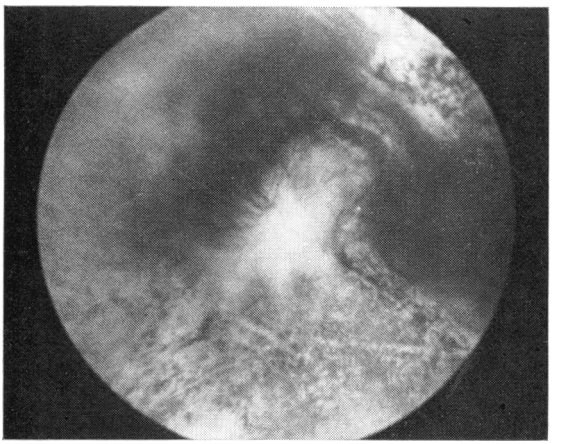


FIGURE 20
An iatrogenic tuft of proliferative tissue at a site of photocoagulation for diabetic retinopathy. The periphery is highly vascular but the base is densely fibrotic and avascular.

to 20/200. This membrane probably differs from the usual thickening of the vitreoretinal surface noted prior to shrinkage of the vitreous. This is suggested by the absence of any neovascularization beneath it and by the detachment of the overlying vitreous seen by examination with the slit lamp and contact lens. Also, this membrane is typically at the posterior pole whereas tenting of the retina due to vitreoretinal adhesion and traction most often lies along the course of the superior and inferior temporal vessels. Other considerations are that this flat fibrosis may represent a preretinal membrane similar to that seen in massive preretinal retraction in rhegmatogenous retinal detachment as suggested by Lee.[38] It could also be the remnant of the thickened vitreoretinal adhesions that remain on the retinal surface after shrinking vitreous has torn away the inner portion of the thickened posterior vitreous surface.

The third type of fibrotic proliferation, of iatrogenic origin, may appear as a fan-like mass of proliferative tissue that develops in the scar produced by photocoagulation (Figure 20). A tuft of highly vascular tissue appears a few months after photocoagulation. It slowly enlarges until its base is two to three disk diameters across and protrudes one to two millimeters into the vitreous cavity. The edges remain very vascular with a dense radiating network of fine vessels extending into the vitreous cavity, but the base becomes avascular and densely fibrotic. There does not appear to be vitreous traction on this new tissue, nor has hemorrhage been noted from it.

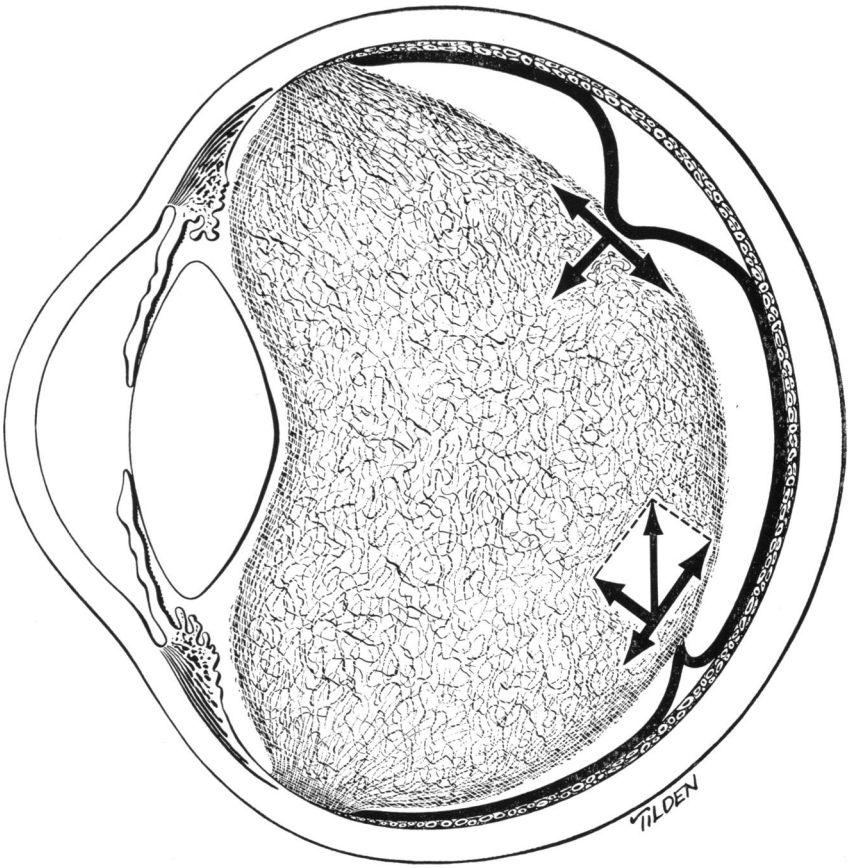


FIGURE 21

The vectors of traction determine the direction of retinal displacement. Traction forces due to vitreous shrinkage are primarily centripetal. However, force may also be exerted parallel to the retinal surface. The anterior traction is usually countered by equal posteriorly acting forces so that the retinal elevation is perpendicular to the surface of the globe. Occasionally, stronger vectors posteriorly will produce a rigid detachment about the posterior pole. The traction bands are like the bow strings described by Duke-Elder and Dobree (1968).

TRACTION PHENOMENA

Traction on the retina by fibrotic proliferative retinopathy may be parallel to the surface of the retina (flat traction) or inward, toward the vitreous cavity (centripetal traction). The vectors of traction determine the extent and direction of retinal displacement (Figure 21). Flat traction produces a lateral displacement of retinal structures; centripetal traction produces a detached retina.

Flat traction is most often due to fibrovascular tissue which distorts normal retinal architecture by exerting its pull parallel to the plane of the retina. An irregular washboard-like surface is a common early manifestation of flat traction. Traction lines usually radiate from the crescent of proliferative tissue that goes vertically past the disk and arcs along the course of the temporal vessels. Traction lines are more obvious if slivers of preretinal hemorrhage are caught in the troughs of the irregular retinal surface beneath the posterior hyaloid (Figure 22). If the macula is involved, visual acuity may be decreased to 20/200.

The more severe degrees of flat traction will drag retinal structures from their normal sites. The macula may be distorted or actually moved, by this traction. The accompanying photographs show various forms of macular dragging (Figures 23, 24). Although the macula may be drawn in any direction, it is most commonly displaced nasally, toward the disk. The displacement itself does not lower visual acuity. This occurs only when an irregularity of the retinal surface is associated with the traction. Blood vessel architecture may also be distorted (Figure 25).

Centripetal traction on the retina can cause detachment because the forces are not parallel to the surface of the retina. Some vector components are inward, toward the vitreous cavity. This inward traction may be from two sources. One is shrinkage of the vitreous pulling the retina via the vitreoretinal adhesions and the other is due to contraction of the fibrovascular tissue itself.

It is important to differentiate between non-rhegmatogenous detachment due to traction and rhegmatogenous detachment in an eye with fibrotic proliferation, as the treatment and prognosis differ. The non-rhegmatogenous retinal detachment due to traction can usually be differentiated from one that is rhegmatogenous.

TRACTION DETACHMENT

Traction detachment is carried into the vitreous cavity by pull on the retina associated with vitreous shrinkage or proliferative retinopathy. Due to the variations in the type and degree of proliferative change and extent of vitreous contraction, the size, placement, and progression of traction detachment differed. The most common direction of traction was perpendicular to the surface of the retina. It was produced by vitreoretinal adhesion along ridges of fibrovascular tissue that arched along the temporal vessels (Figure 26), by a plateau of fibrovascular tissue overlying the posterior pole, or by isolated strands just anterior to the posterior pole.

Occasionally the vector of traction crossed the posterior pole, with the sheet of fibrotic tissue forming a geometric chord, the posterior pole of

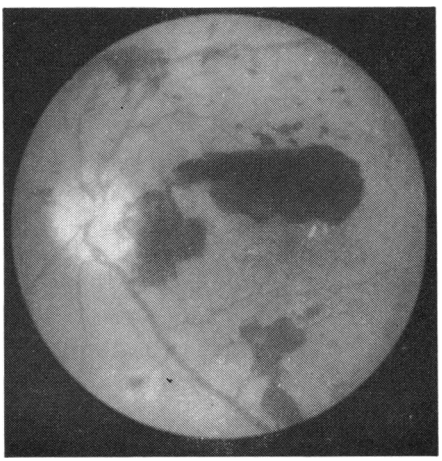


FIGURE 22
Preretinal hemorrhage adjacent to the disk makes the traction lines across the macula more visible.

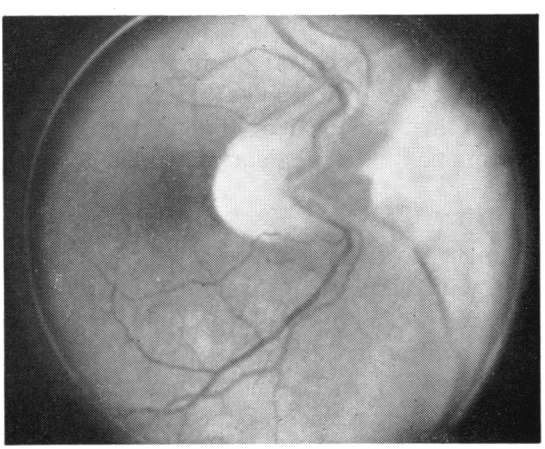


FIGURE 23
Marked nasal traction by fibrotic proliferation. The macula is drawn almost to the disk and the major vessels are also pulled nasally. Although the macula was displaced, the vision in this eye was 20/40.

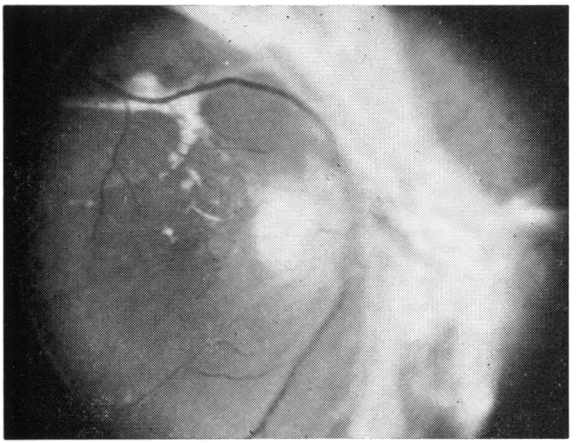


FIGURE 24

An eye with nasal traction by an arc of fibrotic proliferation. The major vessels are pulled nasally as is the macula. Traction lines cross the macula. Vision in this eye was counting fingers at 8 feet.

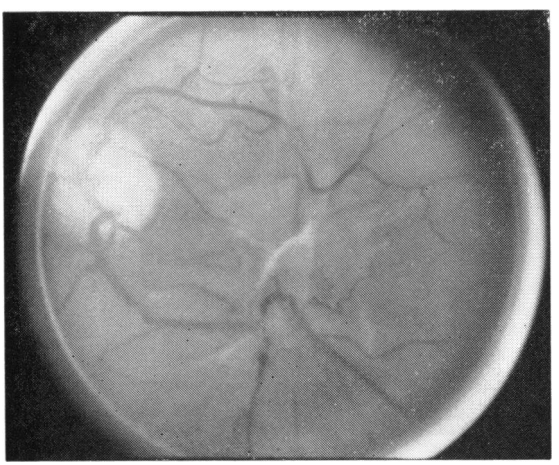


FIGURE 25

Marked preretinal fibrosis. Following photocoagulation nasal to the disk of the left eye, a preretinal fibrosis developed over the macular area and markedly distorted the course of the superior and inferior temporal vessels. The vision was counting fingers at 5 feet.

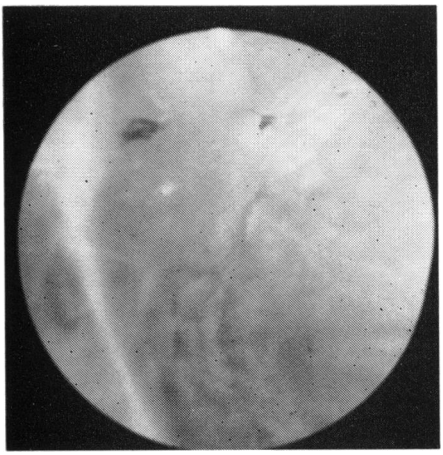


FIGURE 26

The whitish line on the left side of the photograph represents a region of fibrotic proliferation. A slightly grayish region to the right of it is the slope of the traction detachment. At approximately the midvertical portion there is faint demarcation line with the flat retina to the right.

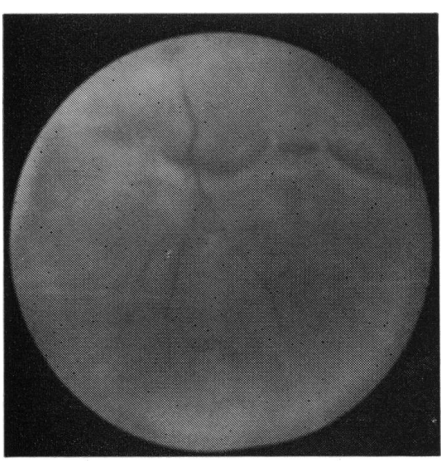


FIGURE 27

The horizontal lesion in the upper portion of the photograph. The tenting of the retina by posterior traction. The detachment lies inferior to the line of traction, as the retina is pulled posteriorly in addition to the inward vector.

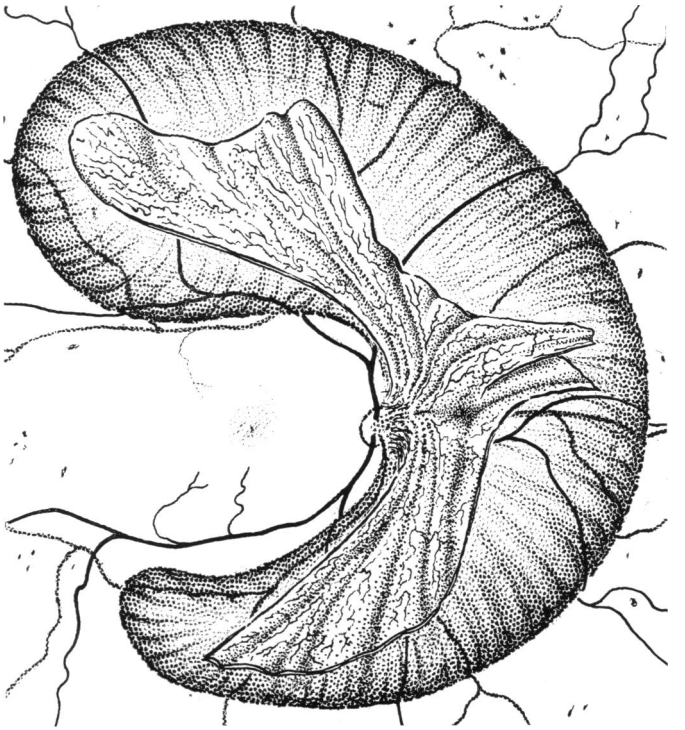


FIGURE 28

A traction detachment associated with an arcing plateau of fibrotic proliferation. A taut shiny retina slopes from the site of traction with the fibrotic tissue to the level of the choroid.

retina forming the segment of the arc intercepted by the chord. The retina was thus pulled posteriorly as well as inward (Figure 27). In the few instances in which this was noted, the detachments remained stable.

Sloping from the site of traction to the choroid, the retina is taut and has a shiny surface (Figure 28). The course of the retinal blood vessels may be altered at the edge of the traction area by the proliferative tissue. The arc of contact between the slope of the elevated retina and the choroid may be convex anteriorly or posteriorly, depending on the site of the forces of traction. Infrequently a solitary avascular strand from the posterior surface of the vitreous face may extend to the retina, tenting up a small segment.

Concentric demarcation lines are often seen, indicating that, although the point of separation between retina and choroid may remain stable for several months, extension of the detachment due to traction is com-

mon. The area of detachment is primarily posterior, infrequently extending more than two-thirds the distance to the equator. There is no shifting of subretinal fluid or mobility of the retina.

RHEGMATOGENOUS DETACHMENT

Rhegmatogenous retinal detachments in diabetics are of two types, those with significant proliferation and those without. In the absence of proliferative retinopathy detached retinas in the diabetic and nondiabetic do not differ significantly. Intraretinal hemorrhages and exudates alone do not alter the surgical prognosis.

In contrast to a traction detachment, a rhegmatogenous detachment has an irregular, dull, undulating, grayish finish. The surface may balloon inward so it is convex toward the center of the globe. The borders of the area of detachment are often indistinct, and usually extend to the ora serrata (Figure 29). If holes are seen they verify the diagnosis.

Rhegmatogenous retinal detachments associated with proliferative diabetic retinopathy often have complicating factors. Visualization of the fundus may be difficult because of poor dilation of the pupil or the presence of cortical lens opacities frequently noted in long-standing diabetics. Also, vitreous hemorrhage may obscure the fundus. An increase in vitreous turbidity in the absence of hemorrhage has been noted occasionally. Retinal breaks may be hidden by overgrowth of proliferative retinopathy or lie within deep crevices between sharp folds of retina. Small round holes may be difficult to differentiate from small round intraretinal hemorrhages. Thorough examination of the posterior pole with the slit lamp and contact lens is imperative. Variable illumination with the slit beam combined with stereopsis and greater magnification makes this the most effective method of verifying suspicious breaks in this region. In addition to the difficulties of visualization, surgery may be complicated by the posterior location of the retinal breaks and by traction on the retina by proliferative tissue that may not allow it to settle. The above factors all make accurate localization of holes more difficult.

As the retinal holes are invariably small, the prognosis depends on the position of the holes and the amount of traction exerted upon the area of the breaks as well as their accurate localization.

Diagnosis of rhegmatogenous detachment does not depend solely on the discovery of a retinal break, but can be made if the characteristics of the detachment are typical of the rhegmatogenous type. The major reasons for deciding against surgery are excessive traction from proliferative tissue, inability to see a break, poor general medical condition, poor visual function, or a combination of the above factors.

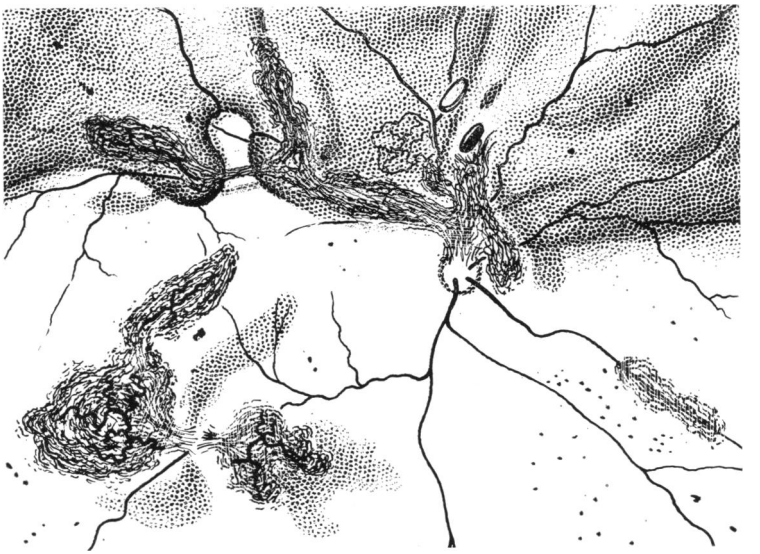


FIGURE 29

Rhegmatogenous detachment associated with fibrotic proliferative retinopathy. A retinal hole is present just superior to the disk. It was located 23 mm posterior to the limbus at operation. The detachment extends to the ora as a ballooning undulating surface.

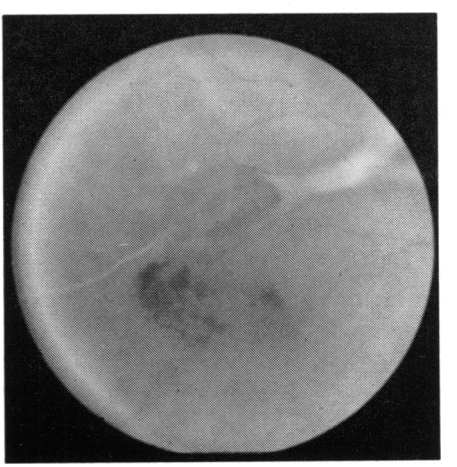


FIGURE 30

An apparent hole at the macula is produced by an avascular fibrotic strand arcing from the mid vitreous. There is a tenting of the retina for 2 to 3 mm above the hole. The degree of traction, the area of detachment, and the visual acuity (20/100) has not changed in 6 months.

Infrequently, holes occur in the elevated retina of a traction detachment, but the area of detachment remains unchanged. Despite the apparent hole, the detachment mimics a traction detachment in all other respects (Figure 30). Six cases have been followed by the author from six months to eight years. In no instance has the detachment taken on the characteristics of a rhegmatogenous detachment. Possibly an internal separation of the retina similar to retinoschisis has occurred. In view of the stability, conservative management is probably indicated.

METHODS AND MATERIAL

Five hundred and seventeen randomly selected cases of diabetic retinopathy with fibrotic proliferation were reviewed. All had an ophthalmic examination that included fundus examination by indirect ophthalmoscopy. Almost all were examined by the author. Since most of the patients were examined to evaluate them for treatment of diabetic retinopathy or retinal detachment, they represented a group with particularly severe manifestations of diabetic retinopathy.

REVIEW OF DATA

The data in Tables 4 through 8 show how pathologic changes of fibrotic proliferation are related to one another and to visual prognosis. Tables 9 through 13 reveal relationships between fibrotic proliferation and retinal detachment, both traction (non-rhegmatogenous) and rhegmatogenous. Totals of the statistics in the tables vary because of problems in data collection such as lack of fundus visibility, enucleations, variable incidence of ocular changes from diabetes mellitus, and inadequate recording of data.

RELATIONSHIPS OF FIBROTIC PROLIFERATION

Table 4 shows the incidence of the different degrees of proliferative retinopathy in patients who had diabetes for various lengths of time. Fibrotic proliferative retinopathy was rarely the initial change noted in these eyes. It was infrequent until 10 to 20 years after onset of the disease. This was usually several years after intraretinal hemorrhages or exudates had appeared and after neovascularization had become established. The patients in Table 4 may be usefully divided into two groups: those with growth onset proliferation (age 20 or younger) and those with maturity onset proliferation (age 21 and over). Of 91 patients with fibrotic proliferative retinopathy who had diabetes ten years or less, five (6 per cent) had juvenile onset diabetes and 86 (94 per cent) had

TABLE 4. INCIDENCE OF THE DEGREES OF FIBROTIC PROLIFERATION CORRELATED TO THE DURATION OF GROWTH ONSET AND MATURITY ONSET DIABETES

	Less than 10 years			11–20 years			21–30 years			Over 30 years		
	Growth	Maturity	Total	Growth	Maturity	Total	Growth	Maturity	Total	Growth	Maturity	Total
F_1	1	27	28	47	45	92	20	26	46	7	3	10
F_2	2	26	28	50	31	81	29	21	50	26	7	33
F_3	2	27	29	49	49	98	44	29	73	23	12	35
F_4		6	6	17	13	30	7	4	11	2	1	3
Total	5	86	91	163	138	301	100	80	180	58	23	81

Total growth onset 326 eyes
Total maturity onset 327 eyes
Grand total 653 eyes

TABLE 5. CORRELATION BETWEEN NEOVASCULAR AND FIBROTIC PROLIFERATION

	No	N_1	N_2	N_3	N_4	Total
F_1		27	103	48	1	174
F_2	1	16	84	74	3	178
F_3	4	25	73	113	2	217
F_4			12	19	10	41
Total eyes with grading of both neovascular and fibrotic proliferation						610

maturity onset diabetes. This supports the contention that the changes of diabetes had probably been developing for several years in the maturity onset group although no clinically overt diabetes had been noted.[16] Occasionally, diabetes was first diagnosed in the maturity onset group by an ophthalmologist on the basis of a typical fundus picture.

The percentage of patients with maturity onset diabetes compared to growth onset became less with each decade of duration of diabetes. The percentage of maturity onset diabetes was 94, 46, 44, and 28 in the first, second, third, and fourth decades respectively. This decrease may be associated with increased mortality in the maturity onset group due to other aspects of premature aging in diabetics.

As the duration of diabetes increased, the percentage of eyes with minimal fibrotic proliferation (F_1) decreased. In the 91 eyes in patients diabetic ten years or less, 28 (30 per cent) were in the F_1 group, but in those with diabetes over 30 years, only 10 of 81 eyes (12 per cent) were in the F_1 group.

In Table 5 the relative severity of neovascular and fibrotic proliferation is noted. There is a general correlation between the severity of neovascular and fibrotic proliferation. However, some cases may show a marked preponderance of one or the other. In the eyes where neovascular proliferation was most severe, almost half the eyes had been treated with photocoagulation or pituitary ablation. In those eyes with moderate to severe fibrotic proliferation (F_2, F_3, F_4) but only minimal neovascularization (N_1), no eye had either treatment. Thus, the classification system accurately characterized the type of cases requiring treatment as well as the type in which treatment was contraindicated.

Table 6 shows the correlation of the different stages of vitreous change as classified by Van Heuven[48] to the various degrees of proliferative retinopathy. Data from only 151 eyes were recorded because only eyes examined with slit lamp and contact lens were reported. In the categories where vitreoretinal traction was absent or of a minimal degree,

TABLE 6. SEVERITY OF PROLIFERATIVE RETINOPATHY CORRELATED TO DEGREE OF VITREOUS CHANGE

	Group I		Group II		Group III
	No vitroeretinal adhesion and no vitreous shrinkage	Vitreoretinal adhesion with no vitreous shrinkage	Flat vitreoretinal adhesion; vitreous shrinkage	Elevated vitreo-retinal adhesion and vitreous shrinkage	No vitreoretinal adhesion with vitreous shrinkage
F_1	14	13	4	10	9
F_2	4	5	4	29	5
F_3		2	2	44	
F_4				6	
Total	18	20	10	89	14

proliferative retinopathy was grade 1 or 2 except in a few instances. In contrast, the eyes with grades 3 and 4 fibrotic proliferative retinopathy were associated with vitreoretinal adhesion and vitreous shrinkage in 52 of 54 eyes (96 per cent). This latter group did significantly less well following treatment with photocoagulation than those with no vitreoretinal adhesion.[49]

Eyes with peripheral proliferation were associated with the lesser degrees of fibrosis, whereas those with fibrotic tissue from the disk or a combination of the disk and periphery were more likely to have extensive fibrotic proliferation, as shown in Table 7. Eyes having peripheral proliferative tissue (15 degrees or more from the disk) were noted to have a different prognosis than those with proliferative tissue coming from the disk region.[18] Eyes with peripheral lesions were better candidates for treatment with photocoagulation. In a series of 100 eyes treated by the author, the success rate of photocoagulation of peripheral proliferative retinopathy was approximately 60 per cent for eyes with grade 2 or 3 proliferation; but when the proliferative retinopathy was at the disk, less than 10 per cent of the cases in which the proliferation was grade 2 or 3 were successful. Thus, in the F_1 stage, changes in 91 of 156 eyes (58 per cent) were peripherally located and the patients good candidates for photocoagulation, but in the F_2 and F_3 stages this decreased to 21 per cent and 12 per cent respectively.

The most devastating type of proliferation, in both rapidity of progression and severity of end stage, is that which develops from a fibrovascular sheet that enlarges diffusely about the disk and then extends temporally over the macula. This form is present in some degree in most eyes blinded by proliferative retinopathy. Arcs of flat fibrovascular tissue above and below the posterior pole also indicate a poor prognosis. In some cases, however, a mass of fibrovascular tissue, usually from the disk, may extend perpendicularly into the vitreous cavity and exert no apparent traction on the retina (Figure 12). Retinal detachment is infrequent in these cases.

The form of fibrotic proliferation least likely to progress is that which forms the fine, avascular, "sucker foot" that tents the retina toward a shrunken vitreous gel (Figure 18). The traction detachments thus produced are usually small, round, and located peripheral to the posterior pole. The proliferative tissue that grows along the surface of the retina may produce signs of traction parallel to the retinal surface, but will not produce retinal elevation.

Table 8 shows that fibrovascular tissue is more likely to progress to more severe degrees of fibrosis than avascular proliferation. Of 34 eyes

with proliferation of only the avascular fibrotic type, six (18 per cent) progressed into a higher grade. The eyes with fibrovascular proliferation progressed to a more advanced grade of classification in 32 of 131 eyes (24 per cent). Although the relative percentages for progression of each type are similar, the greatest difference is in the percentage of eyes that progressed two grades or more in the classification. Eleven of 131 eyes (8 per cent) having fibrovascular proliferation progressed more than one grade compared to only one of 34 eyes (3 per cent) in the avascular group.

TRACTION PHENOMENA

Non-rhegmatogenous detachment was much more frequent than rhegmatogenous. Data from 517 cases of diabetic retinopathy are used in the following discussion of the correlations between several aspects of proliferative retinopathy and traction detachment. Detached retinas were recorded in 376 eyes, 279 detachments were non-rhegmatogenous, 74 were rhegmatogenous, and in 23 the type was not determined (Table 9). Table 10 shows the more severe degrees of proliferative retinopathy that are associated with the more extensive traction. Of 174 eyes with grade 1 proliferation, 12 (7 per cent) had traction detachment. When the severity of proliferative retinopathy increased, the incidence and extent of the traction detachments increased as well. Twenty-eight of 41 eyes (68 per cent) with grade 4 of fibrotic proliferation had traction detachments. Thirteen (31 per cent) of these were grade 4 detachments. A slightly higher percentage of eyes with grade 3 proliferation had traction detachments (74 per cent) than those with grade 4, but only 8 per cent had grade 4 traction detachments.

In traction detachment, a major factor in determining visual acuity was the status of the macula. If not subject to traction, vision could be 20/20 but, if distorted or elevated, a vision of counting of fingers was common. The data showed that the extent and incidence of macular involvement depended on the following factors: size of the traction detachment, the extent of proliferative retinopathy and its type.

As fibrovascular proliferation was grade 3 or 4, more often than the avascular type, it was associated more frequently with the large traction detachments that involved the macula and produced a loss of central vision. Of 32 eyes with traction detachments due to avascular fibrosis, only four (13 per cent) had grade 3 detachments and none had grade 4, whereas 86 of 142 eyes (61 per cent) with traction detachments due to fibrovascular proliferation had grade 3 or grade 4 detachments (Table 11). In the 32 eyes with traction detachment due to avascular fibrotic

TABLE 7. CORRELATION OF SITE OF PROLIFERATIVE RETINOPATHY WITH THE SEVERITY OF FIBROTIC PROLIFERATION

	Disk	Peripheral (over 15° from disk)	Combined (both disk and peripheral)	Total
F_1	52 (33%)	91 (58%)	14 (9%)	157 (100%)
F_2	56 (33%)	36 (21%)	77 (46%)	169 (100%)
F_3	65 (28%)	29 (12%)	138 (60%)	233 (100%)
F_4	13 (32%)		27 (68%)	40 (100%)
Grand total				599

TABLE 8. COMPARISON OF PROGRESSION OF FIBROVASCULAR PROLIFERATION AND AVASCULAR PROLIFERATION

	Fibrovascular	Avascular
Number of eyes classified and followed for 6 months or longer	131 (100%)	34 (100%)
Progression of one classification grade	21 (16%)	5 (15%)
Progression of two classification grades	9 (7%)	1 (3%)
Progression of three classication grades	2 (1%)	
Total	32 (24%)	6 (18%)

TABLE 9. INCIDENCE OF THE GRADES OF TRACTION DETACHMENT AND RHEGMATOGENOUS DETACHMENT OF THE RETINA

Traction detachments	
Grade I	71
Grade II	72
Grade III	93
Grade IV	36
Size undetermined	7
Total	279
Rhegmatogenous detachments	74
Detachment seen but type not determined	23
Combined total	376

TABLE 10. CORRELATION BETWEEN DEGREE OF PROLIFERATIVE RETINOPATHY AND EXTENT OF TRACTION DETACHMENT OF THE RETINA

Grade of proliferation	Number of eyes in grade	Eyes in each grade of traction detachment				Total
		I	II	III	IV	
1	174	9 (5%)	1 (1%)	2 (1%)		12 (7%)
2	178	26 (15%)	23 (13%)	18 (10%)	5 (3%)	72 (41%)
3	217	35 (16%)	42 (20%)	65 (30%)	18 (8%)	160 (74%)
4	41	1 (2%)	6 (14%)	8 (20%)	13 (31%)	28 (68%)
Total	610	71	72	93	36	
Grand total						272

TABLE 11. CORRELATION BETWEEN TYPE OF FIBROTIC PROLIFERATION AND EXTENT OF TRACTION DETACHMENT OF THE RETINA

	Grade of traction detachment				
	I	II	III	IV	Total
Fibrovascular proliferation	28 (19%)	28 (19%)	54 (38%)	32 (24%)	142 (100%)
Avascular proliferation	22 (69%)	6 (19%)	4 (12%)		32 (100%)
Combined	22 (26%)	30 (37%)	30 (37%)		82 (100%)

TABLE 12. CORRELATION OF EACH TYPE OF FIBROTIC PROLIFERATION WITH THE SIZE OF THE TRACTION DETACHMENT AND MACULAR INVOLVEMENT

	Extent of traction detachment											
	I			II			III			IV		
Status of macula	F	A	C	F	A	C	F	A	C	F	A	C
No detachment	22	19	15	7	6	19	7	1	8	1		
Questionable detachment	4	2	7	17		7	7	1	13			
Detachment	2	1		4		4	40	2	9	31		

F = fibrovascular
A = avascular
C = combined

TABLE 13. PROGRESSION OF THE EXTENT OF TRACTION DETACHMENT OF THE RETINA DUE TO FIBROVASCULAR AND AVASCULAR PROLIFERATION

Degree of progression	Fibrovascular	Avascular
One classification grade	19 (13%)	6 (18%)
Two classification grades	15 (11%)	3 (9%)
Three classification grades	10 (7%)	
Four classification grades	3 (2%)	
No progression	95 (67%)	23 (73%)
Total number of eyes with extent of traction detachment classified	142	32

proliferation, only 3 (9 per cent) involved the macula, but 77 of 142 eyes (54 per cent) with traction detachment due to fibrovascular proliferation had produced distortion or elevation (Table 12). Thus, fibrovascular proliferation led to a loss of central vision in a greater proportion of cases than avascular proliferation.

The incidence of extension of traction detachment is similar for both fibrovascular and avascular proliferation, being 33 per cent with fibrovascular proliferation and 27 per cent with the avascular type. However, of 142 eyes with fibrovascular proliferation, 28 (20 per cent) had progression of traction detachment of more than one grade of classification, but of the 32 eyes with avascular proliferation only 3 (9 per cent) had extension of traction detachment of more than one classification grade. None of these latter three had increased more than two grades, but 13 of the 28 eyes in the fibrovascular group had advanced three or four classification grades (Table 13). These data indicate that the fibrovascular proliferative tissue had a more progressive course than avascular proliferation.

Of 279 eyes with traction detachment, a spontaneous decrease in extent occurred in 15 eyes (5 per cent). This was usually associated with a decrease in the angiopathic aspects of the proliferative retinopathy, the eye having reached the "burned out" stage. In some instances the vision improved with the spontaneous reattachment, but in others there was no improvement.

Surgical techniques have been advocated by Okun and Fung and by Schepens, to relax the taut membranes which pull the retina into the vitreous cavity. Each uses a different basic principle. Okun and Fung (1968)[50] described a method for relaxing the membranes of fibrotic proliferation within the eye. A silicone band was placed around the equator of the globe and tightened to decrease the eye's equatorial diameter. By decreasing the radius of the globe in this plane they felt the distance was also decreased between the posterior and anterior attachments of the proliferative membranes. With the decreased tension on the proliferative tissue, the traction detachment would decrease. They operated when proliferative membranes extended to the region of the equator or the ora serrata from the posterior pole in an eye in which the macula was being threatened by a progressive extension of a traction detachment. They drained subretinal fluid whenever possible. In eyes in which retinal holes were visible, they placed an explant beneath them after treating them with cryopexy. Of 50 eyes treated, 63 per cent of eyes with breaks and 66 per cent of eyes with no breaks maintained finger counting vision or better. One factor of importance not stressed was

whether the characteristics of the detachments without holes suggested a rhegmatogenous or non-rhegmatogenous etiology.

Schepens' technique is to shorten the globe, decreasing the internal diameters in an anterior-posterior direction rather than in the frontal plane at the equator.[51,52] It is an adaptation from the scleral shortening technique of Lindner.[53] A full thickness scleral resection 3-mm wide with tapered ends is made from 180 to 270 degrees around the globe at its equator. No attempt is made to put the scleral resection bed beneath the traction detachment. The permanent shortening of the antero-posterior diameter of the globe results in a relaxation of the membranes that extend to both the equatorial and ora regions, allowing the retina to settle. He stresses that this technique would be successful only in the traction type detachment and not the rhegmatogenous type that might be associated with traction from proliferative retinopathy. Data regarding long-term results have not been reported.

RHEGMATOGENOUS DETACHMENT

Thirteen cases are reported that had surgery performed by the author for rhegmatogenous retinal detachment accompanied by proliferative retinopathy. Five patients were juvenile onset diabetics, and eight maturity onset. All the former had been diabetic more than twenty years. The vision of the fellow eye was counting of fingers or less in six patients. The proliferative retinopathy was grade 1 in two eyes, grade 2 in eight eyes, and grade 3 in three eyes. Proliferation peripheral to the posterior pole was present in all 13 cases, although in five eyes proliferation at the disk was also present. Retinal holes were seen in ten eyes. They were small and round in 7, and less than one disk diameter in the other 3. The holes were 16-mm or less from the limbus in 4 eyes, and 17-mm or more from the limbus in 6 eyes. When the breaks were equatorial, the standard scleral buckling technique using a silicone implant and encircling silicone band, with drainage of subretinal fluid was performed. With holes located far posteriorly, more traction was present. For these cases a thick silicone implant was used. It was necessary to indent the choroid deeply, to maintain contact with the retina elevated by traction from fibrotic proliferation.

Eleven of the 13 patients have been followed six months or longer; the longest follow-up was four years. Nine of the 11 retinas were reattached. The two failures occurred in eyes where no breaks were visible.

During surgery, certain precautions were necessary to minimize the risk of intraocular hemorrhage. To avoid choroidal vessels, the perforation sites were examined under magnification with a condensing lens

while the assistant transilluminated the wall of the globe by directing the beam from the ophthalmoscope through the pupil to the area being inspected. The chances for bleeding during perforation were also decreased by lightly applying diathermy to the knuckle of choroid, using one-third of the energy applied to the scleral resection bed. Hypotony associated with drainage of large amounts of subretinal fluid might have led to spontaneous hemorrhage from abnormal vessels into the vitreous cavity. Thus, to minimize the extent and duration of hypotony, intraocular tension was maintained by external pressure. When necessary, sutures were tightened as rapidly as possible over the implants, and intravitreous injection of saline was given promptly if the eye remained soft after the sutures were tied over the implants.

None of the 13 eyes operated upon had an intravitreous hemorrhage. One had a choroidal detachment, but it did not require sclerotomy and drainage. The late complications were as follows: 3 eyes developed traction detachments in areas outside the scleral buckle; 1 eye had an anterior segment ischemia; 1 eye developed a cataract; and 1 eye developed an infection 1½ years after surgery. There was a late vitreous hemorrhage in one patient who also had a traction detachment.

The surgical cure rate of rhegmatogenous detachment in diabetics with proliferative retinopathy was encouraging despite the complicating factors of posterior holes and traction in the areas of the retinal tears.

CONCLUSIONS

On the basis of clinical examinations and review of the pertinent literature, it became evident that there were two types of naturally occurring fibrotic proliferation. The more common type was fibrovascular proliferation, which began in most instances as neovascularization, but slowly transformed into a fibrotic scar with fewer vascular features. The other type had no apparent vascular component and so was described as avascular proliferative tissue. It could be divided into three categories:

1. Extensions from fibrovascular tissue;
2. Vitreoretinal bridges; and
3. Preretinal fibrosis or condensation.

Others have alluded to these tissue types in their descriptions of membranes in the diabetic eye.[19,20,23,24,47]

The two types differ not only in their appearance but also in their clinical course. The eyes with fibrovascular proliferation progressed more frequently to the severe grades of proliferative retinopathy (Table 8). Thus they were associated with the extensive grades of traction

detachment that involved the macula more often than eyes having primarily avascular proliferative tissues. (Tables 12 and 13)

Two types of retinal detachment associated with proliferative retinopathy, traction and rhegmatogenous, were observed. Of 653 eyes in which fibrotic proliferation could be classified, 279 (43 per cent) had traction detachment, a large percentage. Traction detachments have a more progressive course when caused by fibrovascular proliferation rather than the avascular type (Table 13). This suggests that the proximity of the vascular network to the cortical vitreous might possibly accelerate its shrinkage. In some instances, the fibrovascular tissue itself contracts. The avascular fibrotic membrane, however, seems to be a more passively affected tissue, responding in a secondary manner to the more actively metabolizing fibrovascular tissue. This is suggested by the presence of fibrovascular tissue in all markedly advanced grades of retinopathy and traction detachment.

SPECULATION

Fibrotic proliferative tissue may originate from two sources. One is the mesenchymal cells derived from the retinal vasculature; and the other is the cortical layer of the vitreous gel.

One might conjecture that the same stimulus that brings about endothelial budding and subsequent neovascularization might also lead to the reversion of endothelial cells to vasoformative mesenchyme. The fact that the mesenchymal cells may also develop into fibroblasts and form fibrous tissue allows one to use this explanation for the whole spectrum of progression of fibrovascular tissue as described by Dobree. Initially, the mesenchymal cells might form an outgrowth of fully formed vessels with a minimum of fibrosis. Then, when some as yet unidentified environmental factor changes, this same basic mesenchymal cell type could begin to form fibroblasts producing the fibrosis that has been so well documented clinically. It could also explain the frequency with which one finds vitreoretinal adhesions over the areas of flat neovascularization. The vascular tissue on the surface of the retina would be one aspect of the mesenchymal tissue development. A thin sheet of overlying fibrous tissue which would adhere to the posterior wall of the vitreous cortex and form the adhesion might originate in the fibroblastic aspect of the mesenchymal tissue.

Szirmai and Balazs[54] have shown that the hyalocytes of the vitreous cortex, cells with metabolic activity, occur more frequently adjacent to the retinal vessels. Their metabolic activity may be subtly altered in the diabetic and after many years may contribute to vitreous changes.

Other factors accelerating change in the vitreous cortex might be its proximity to the retina, with its active but abnormal metabolism, or to abnormal vascular tissue on the retinal surface. The vitreous body is not a complex tissue. It may respond in only two ways: (1) collapse of the vitreous gel, as documented in an unusually large number of young diabetics as compared with normals of the same age;[24] (2) condensation and shrinkage of the cortical layer, as noted by several authors.[20,23,24]

The above concepts are presented as an attempt to explain the clinical picture seen in fibrotic proliferative retinopathy, including the adhesion between fibrovascular tissue, the shrinking face of the vitreous gel, and secondary traction phenomena.

SUMMARY

Fibrotic proliferation and retinal detachment associated with diabetic retinopathy were discussed. Two types of fibrotic proliferation were described, fibrovascular and avascular. The clinical relationship of several aspects of proliferative retinopathy were explored.

Relationships between traction retinal detachment and proliferative retinopathy were discussed. A series of rhegmatogenous detachments that had proliferative retinopathy was reported.

Speculation was offered regarding the pathogenesis of the two types of fibrotic proliferative retinopathy.

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