

THE OCULAR MANIFESTATIONS OF SICKLE-CELL DISEASE: A PREVALENCE AND NATURAL HISTORY STUDY*

BY *John G. Clarkson*, MD

INTRODUCTION

THE SICKLE HEMOGLOBINOPATHIES RESULT FROM AN ABNORMALITY IN the beta chain of the hemoglobin molecule. The chief manifestations are chronic hemolytic anemia and vaso-occlusive crises that produce severe pain as well as long-term and widespread organ damage. There are several clinically important hemoglobin variants that constitute the sickle syndromes.

About 8% of black Americans are heterozygous for hemoglobin S and have sickle cell trait. These individuals usually have about 35% to 40% hemoglobin S and 55% to 60% hemoglobin A; they do not have increased morbidity or mortality.¹

Approximately 0.15% of black children in the United States have homozygous hemoglobin S (SS disease).¹ They suffer from a severe hemolytic anemia with hematocrit values between 18% and 30%. Symptoms do not usually develop until after the age of 6 months, when fetal hemoglobin (hemoglobin F) has been replaced by hemoglobin S. Delayed growth and development and increased susceptibility to infection are the primary constitutional manifestations. Their prevalence among adults is much lower because patients with sickle cell anemia have a decreased life expectancy. The increased morbidity and mortality in homozygous sickle cell disease is due primarily to recurrent vaso-occlusive episodes. The most common clinical event is the so-called *painful crisis*.² These events usually appear suddenly and affect various parts of the body, particularly the abdomen, chest, and joints. Painful crises are frequently preceded by a viral or bacterial infection but may occur in association with a change in

*From the Department of Ophthalmology, Bascom Palmer Eye Institute, University of Miami School of Medicine, Miami. This study was supported in part by Comprehensive Sickle Cell Center grant H-580654—1979-88 from the National Heart, Lung and Blood Institute of the National Institutes of Health, Bethesda.

temperature, most often due to cold. Reduced oxygen concentration results in a change in shape of the red blood cells containing hemoglobin S from a biconcave disc into an elongated crescent shape or "sickle"-shaped cell. As the red blood cell sickles, it becomes rigid and may obstruct capillary flow. Such capillary obstruction can lead to further tissue hypoxia and increased tendency for the red cells to sickle. Almost any organ can be affected by the vaso-occlusive phenomenon, but it most frequently affects the lungs, kidneys, liver, skeleton, and skin.¹

There are several double heterozygous states included in the sickle syndromes. The two most common are sickle cell-hemoglobin C (SC) disease and sickle beta-thalassemia (sickle β -thalassemia). In SC disease, about 50% of the hemoglobin is hemoglobin S and the remaining 50% is hemoglobin C. The gene frequency for hemoglobin C is only about one fourth of that for hemoglobin S. However, the prevalence of SC disease among adults is almost as high as that of SS disease because of the increased mortality associated with SS disease and the relatively normal life expectancy for persons with SC disease.¹ The presence of hemoglobin C reduces the risk of sickling as compared with SS disease. However, persons with SC disease usually have a mild to moderate hemolytic anemia and may occasionally have painful crises or organ infarcts. Sickle β -thalassemia is commonly encountered in people from Mediterranean countries and from Central Africa. These individuals show from 60% to 90% hemoglobin S and from 10% to 30% hemoglobin F. In some forms of sickle β -thalassemia, hemoglobin A represents 10% to 30%.¹

The diagnosis of one of the sickle hemoglobinopathies depends upon the demonstration of sickling of red cells under reduced oxygen conditions. In the sickle prep test, sickled cells may be seen microscopically after the addition of an oxygen consuming reagent such as metabisulfite. However, this test does not distinguish between sickle trait, SS disease, SC disease, or sickle thalassemia. Hemoglobin electrophoresis is necessary to establish a definitive diagnosis.^{1,3}

The sickle syndromes have the highest incidence in black Africans and African-Americans but are also found in people from Mediterranean countries (Greece, Italy, Israel) as well as Saudi Arabia and India. Africans have known of the disease for generations, and it has been traced back as far as 1670 in Ghana.² It was first reported in the United States in 1910 by Herrick.⁴ In 1949, Neel⁵ demonstrated that sickle cell anemia was transmitted as a recessive gene, and the same year Pauling and associates³ noted that sickle hemoglobin and normal hemoglobin demonstrated a different electrophoretic mobility.

Abnormalities in the ocular fundus in sickle cell anemia were first

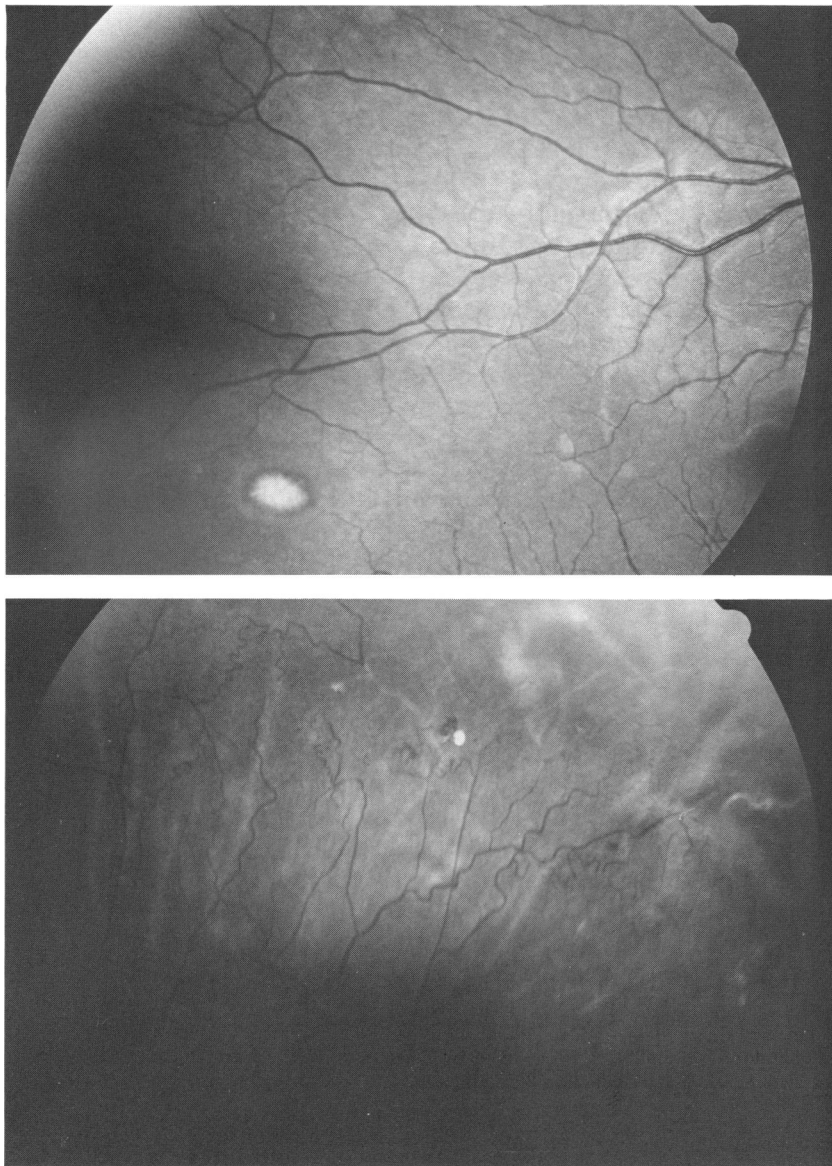
described in 1930 by Cook,⁶ who noted fresh hemorrhages in the retina in a patient who died of subarachnoid hemorrhage. In 1952, Edington and Sarkies⁷ reported two patients with sickle cell anemia who had retinal aneurysms and vitreous hemorrhage. In 1966, Welch and Goldberg⁸ reported the ocular findings in 55 patients with SS disease, 34 patients with sickle trait, and 22 cases of SC disease, and compared these findings with those in 38 patients with normal hemoglobin. These investigators were the first to note background changes such as the "black sunburst spot," "refractive and lipid deposits," and "peripheral arterial obliteration." They described the proliferative retinopathy as the "sea fan sign," because it resembled *Gorgonia falbeloum*, known as a sea fan, which they found primarily in patients with hemoglobin SC disease. Fluorescein angiography confirmed peripheral vaso-occlusive disease. They found no significant fundus abnormality in the patients with sickle trait, and although they observed evidence of proliferative disease in patients with SS disease, they noted more severe proliferative disease in patients with hemoglobin SC disease.

In 1971, Goldberg⁹ proposed a classification of proliferative sickle retinopathy (Table I). Peripheral arteriolar occlusion is classified as stage I. Hemorrhages may occur when aggregated sickled erythrocytes abruptly occlude an arteriole, resulting in a "blowout" of the vessel wall and intraretinal hemorrhage. This hemorrhage usually remains confined within the sensory retina, but it can extend beneath the internal limiting membrane or into the outer retina and possibly the subretinal space, where it can produce changes in the retinal pigment epithelium.¹⁰ Initially the hemorrhage has a typical bright-red appearance. As the blood begins to reabsorb, it takes on a peach or salmon color, known as the "salmon patch." Following further reabsorption of the blood, cholesterol deposits may appear; these have been described as "glistening bodies" (Fig 1). The disturbance at the level of the retinal pigment epithelium results in hyperpigmentation (which Welch and Goldberg⁸ called the

TABLE I: CLASSIFICATION OF PROLIFERATIVE
SICKLE RETINOPATHY*

Stage I	Peripheral arterial occlusion
Stage II	Peripheral arteriovenous anastomoses
Stage III	Neovascular and fibrous proliferations
Stage IV	Vitreous hemorrhage
Stage V	Retinal detachment

*From Goldberg.⁹

**FIGURE 1**

Stage I proliferative sickle retinopathy. A: Partially resorbed intraretinal hemorrhage temporal to macula in right eye of 17-year-old black male with sickle cell-hemoglobin S disease. B: Iridescent spot in superior midperiphery in left eye of 27-year-old black male with sickle cell-hemoglobin S disease.

“black sunburst spot”). Although these changes typically occur in the midperiphery, they may occur more posteriorly in the fundus as well.

Stage II is represented by peripheral arteriovenous anastomoses, which occur subsequent to the peripheral occlusion. Fluorescein angiography confirms the presence of retinal capillary nonperfusion peripheral to the arteriovenous anastomoses. It is at this site that stage III, proliferative neovascularization, develops. Goldberg⁹ defined stage IV as vitreous hemorrhage usually due to proliferative retinopathy, and stage V as any retinal detachment.

Other ocular changes may occur in the sickle hemoglobinopathies.¹¹⁻¹⁷ Paton¹⁸ described a unique segmentation of conjunctival vessels occurring primarily in patients with homozygous sickle-cell disease, which he called the “conjunctival sign.” This segmentation of capillary flow is often minimal, and it is best observed on the inferior bulbar conjunctiva. Similar segmentation of the blood column has been observed on the optic nerve head of patients with one of the sickle hemoglobinopathies and is called the “disc sign.”¹⁹ Iris infarcts may also occur. Additional fundus findings have been described, including epiretinal membrane formation, angioid streaks, macular hole, ischemic optic neuropathy, central and branch retinal artery occlusion, and central retinal vein occlusion.^{11-17,19}

The prevalence of the ocular findings in patients with SS disease, SC disease and sickle thalassemia disease has been reported by several investigators. However, only Condon and Serjeant^{16,17,20} reviewed a group of patients unselected on the basis of ocular complications. The natural history of the eye findings, particularly peripheral retinal vascular disease, and the development of proliferative sickle retinopathy has been reported by Goldberg,⁹ Condon and Serjeant,²⁰ and Raichand and associates.²¹ In these studies it was anticipated that proliferative lesions would not regress. Condon and Serjeant²⁰ were the first to notice that spontaneous regression of proliferative lesions could occur. They²⁰ and others²² subsequently confirmed that regression due to autoinfarction does occur in a large number of proliferative lesions. Welch and Goldberg⁸ first proposed that photocoagulation in patients with proliferative retinopathy, particularly in hemoglobin SC disease, might be indicated to reduce the risk of vitreous hemorrhage and/or retinal detachment. The demonstrated benefit of laser photocoagulation for proliferative retinopathy due to diabetes, branch vein occlusion, and cryotherapy for stage III retinopathy of prematurity would appear to indicate that some form of treatment should be considered for eyes with proliferative sickle retinopathy.²³⁻²⁵ However, Goldbaum and associates²⁶ observed retinal detachment in two of nine patients receiving cryotherapy for proliferative sickle retinopathy

using a multiple freeze-thaw technique. Also, in over 90% of eyes, choroidal neovascularization developed when photocoagulation treatment was applied to the feeder vessel in a clinical trial reported by Condon and Serjeant.²⁷ The significant complications after cryotherapy and long-term complications of photocoagulation cast doubt on the effectiveness of these treatments and stress the importance of understanding the natural history of proliferative sickle retinopathy. Previous natural history studies were limited by patient selection and length of follow-up. More recent reports have specifically evaluated the long-term visual effects of proliferative retinopathy in untreated and treated sickle cell patients.²⁸⁻³⁰

To gain a better understanding of the natural history of proliferative sickle retinopathy, a group of sickle cell patients were contacted to report for a complete eye examination. Patients were selected only on the basis of having one of the sickle hemoglobinopathies. A subset of this original group, including all previously untreated patients who demonstrated evidence of proliferative retinopathy (stage III or greater) at the initial evaluation, was followed prospectively for an average of 6.7 years to determine the long-term natural history.

METHODS AND MATERIALS

In 1979, 200 patients followed at the Sickle Cell Center, Miami, FL, were randomly selected to have eye examinations. Eighteen patients under 5 years of age were excluded from this study. Of the remaining 182 patients, 150 reported for the examinations. Table II summarizes the demographics and prevalence of the subgroups of sickle-cell disease in these patients. Twenty-four of the 27 patients with stage III proliferative sickle retinopathy (neovascular proliferative disease based on the Goldberg classification⁹) from the prevalence study returned for periodic follow-up examinations between 1979 and 1989. Fundus findings were documented with large retinal drawings and fundus photographs. Twenty-three of the 24 patients (38 of 39 eyes) with stage III proliferative retinopathy were

TABLE II: DEMOGRAPHICS OF 150 SICKLE CELL PATIENTS IN PREVALENCE STUDY

	HEMOGLOBIN TYPE			TOTAL
	SS	SC	S THAL	
No. of patients	109	29	12	150
Median age (yr)	20	24	20	20
Age range (yr)	5-66	7-58	6-52	5-66
Sex (male/female)	51/58	18/11	4/8	73/77

SS, sickle S disease; SC, sickle C disease; S thal, sickle thalassemia disease.

followed for a minimum of 2 years (mean, 75 months; range, 31 to 118 months). One patient with sickle thalassemia who had mild proliferative retinopathy in one eye was lost to follow-up. Three patients were excluded from the natural history study because they had received some form of prophylactic treatment, either laser photocoagulation or cryotherapy, in both eyes before the initial examination. One eye of each of two patients from this group required surgical intervention during the course of the study. A pars plana vitrectomy was performed on a patient with a dense, nonclearing vitreous hemorrhage; in another eye a retinal detachment associated with a macular hole was repaired through vitreous surgery. Data collection for natural history on these patients was terminated when surgical intervention occurred.

In addition to the patients with proliferative disease, a group of 76 patients from the prevalence study, unselected on the basis of ocular findings, with either normal findings on examination or early peripheral vascular occlusive disease returned for periodic follow-up examinations. Sixty-two of the 76 patients (82%) had a minimum of 2 years' follow-up (average, 83 months; range, 28 to 123 months). One patient died before adequate follow-up was obtained. Thirteen were lost to follow-up. Therefore, a total of 85 patients were examined in the natural history portion of the study and were followed for a mean of 80 months (range, 28 to 123 months) (Table III).

The type of hemoglobin was determined by the Sickle Cell Center with use of cellulose acetate electrophoresis. Results were verified by the Centers for Disease Control, Atlanta, with use of both cellulose acetate and citrate agar electrophoresis and were confirmed by family studies and clinical data. The ocular examination at each visit included best corrected visual acuity, slit-lamp examination of the anterior segment, and fundus examination with a binocular indirect ophthalmoscope. The Hruby and fundus contact lenses were used to further evaluate macular and optic nerve changes, and the Goldmann 3-mirror contact lens and, in later examinations, the Volk 90-diopter lens were used to supplement examination of the peripheral retina. Color photographs and fluorescein angiograms were obtained in cases with suspected macular disease and/or proliferative sickle retinopathy. Stage III disease was defined by ophthalmoscopically visible neovascular or fibrous lesions. The hemoglobin type was not made known to the examiner until the conclusion of the study. All patients in the follow-up study were examined annually, and most were examined every 6 months.

TABLE III: PATIENTS FOLLOWED IN NATURAL HISTORY STUDY (n = 85)

	STAGE III RETINOPATHY AT INITIAL EXAMINATION			NORMAL EYES OR STAGE I OR II RETINOPATHY AT INITIAL EXAMINATION			TOTAL	COMBINED
	SS	SC	S THAL	SS	SC	S THAL		
No. of patients	11	11	1	23	48	12	2	85
Median age (yr)	30	29	41	33	25	22	31	26
Age range (yr)	23-63	11-56		11-63	6-59	9-47	23-39	6-63
Average follow-up (mo)	69	77	107	76	81	88	93	80
Range of follow-up (mo)	31-114	37-118	107	31-118	28-114	41-123	92-94	28-123

SS, sickle S disease; SC, sickle C disease; S thal, sickle thalassaemia disease.

RESULTS

PREVALENCE STUDY

The abnormal ocular findings from the prevalence study are summarized in Table IV. The anterior segment findings were limited to the conjunctival sign,¹⁸ which was noted in 59% of patients, and iris atrophy, noted in one patient (0.7%). The conjunctival sign was seen significantly more often in patients with SS disease (70%) than in patients with SC (34%) or sickle thalassemia (17%) disease ($P < 0.001$ using the chi-square test).

The disc sign, as described by Condon and Serjeant,¹⁵ was noted in 12% of patients with SS disease and was not observed in patients with the other two hemoglobinopathies. No neovascularization of the disc was observed.

Macular changes were noted in relatively small numbers. The most significant findings included macular hole (1.3%), epiretinal membrane (2%), and macular pucker (1.3%). Angioid streaks were present in two patients with SS disease.

There was generalized vascular tortuosity of the major retinal vessels in 11% of patients. It occurred significantly more often ($P < 0.05$) in homozygous SS patients (14%) than in SC patients (3.4%) or sickle thalassemia

TABLE IV: OCULAR LESIONS IN PATIENTS IN PREVALENCE STUDY

OCULAR LESION	HEMOGLOBIN TYPE			TOTAL (150 PTS) NO. (%)
	SS (109 PTS) NO. (%)	SC (29 PTS) NO. (%)	S THAL (12 PTS) NO. (%)	
"Conjunctival sign"	75 (70%)	10 (34%)	2 (17%)	87 (59%)
Iris atrophy	0	1 (3.4%)	0	1 (0.7%)
Optic disc sign	13 (12%)	0	0	13 (8.7%)
Angioid streaks	2 (1.8%)	0	0	2 (1.3%)
Vascular tortuosity of major vessels	15 (14%)	1 (3.4%)	0	16 (11%)
Macular lesions				
Macular hole	2 (1.8%)	0	0	2 (1.3%)
Macular pucker	1 (1.0%)	1 (3.4%)	0	2 (1.3%)
Epiretinal membrane	3 (2.8%)	0	0	3 (2%)
Nonproliferative sickle retinopathy				
Hemorrhage ("salmon patch")	3 (2.8%)	5 (17%)	1 (8.3%)	9 (6%)
Iridescent spot	4 (3.7%)	8 (28%)	0	12 (8%)
"Black sunburst spot"	32 (29%)	18 (62%)	2 (17%)	52 (35%)
Proliferative sickle retinopathy				
Stage III (neovascularization)	12 (11%)	13 (45%)	2 (17%)	27 (18%)
Stage IV (vitreous hemorrhage)	2 (1.8%)	6 (21%)	0	8 (5.3%)
Stage V (retinal detachment)	0	3 (10%)	0	3 (2%)

SS, sickle S disease; SC, sickle C disease; S thal, sickle thalassemia disease.

patients (0%). Localized vascular tortuosity was noted in an additional 2% of patients.

Nonproliferative sickle retinopathy changes (retinal hemorrhage, iridescent spots, and black sunburst spots) were found in patients with each of the different hemoglobinopathies and in conjunction with all stages of proliferative sickle retinopathy. Retinal hemorrhages and their sequelae, iridescent spots, were present more often in SC patients (17% and 28%, respectively) than in SS patients (2.8% and 3.7%) and sickle thalassemia patients (8.3% and 0%). Black sunburst spots were also found more frequently in SC patients than in SS or sickle thalassemia patients. The increased incidence of the findings in SC patients was statistically significant for iridescent spots ($P < 0.001$) and black sunbursts ($P < 0.002$). Only black sunburst spots were significantly associated with patients who had stage III proliferative retinopathy ($P < 0.02$ using the chi-square test).

The prevalence of proliferative sickle retinopathy is also listed in Table IV. Proliferative changes (stage III) occurred in 18% of all patients. This included 45% of patients with SC disease, 11% of SS patients, and 17% of sickle thalassemia patients. Vitreous hemorrhage (stage IV) occurred in 21% of SC patients and in 1.8% of SS patients. Retinal detachment (stage V) occurred in 10% of SC patients. None of the 12 sickle thalassemia patients manifested vitreous hemorrhage or retinal detachment. There was an increased incidence of proliferative retinopathy in patients over the age of 40 in all three hemoglobinopathies (86% in SC, 39% in SS, and 100% in sickle thalassemia).

Visual acuity of less than 20/30 occurred in five eyes of the 27 patients with proliferative retinopathy. Three patients with SC disease had a retinal detachment caused by proliferative sickle retinopathy. Two of these had no light perception following unsuccessful repair. Two patients with SS disease had decreased central vision caused by a macular hole in one case and by a macular epiretinal membrane following cryotherapy for stage III disease in the other.

Four of the 123 patients with normal findings on peripheral examination or stage I or II disease had visual acuity of less than 20/30. Decreased vision was attributed to a cerebral vascular accident, traumatic cataract, and optic atrophy in three patients. The fourth patient had SS disease, a unilateral pigmented macular chorioretinal scar resembling a black sunburst, and a past history of blunt ocular injury.

NATURAL HISTORY STUDY

Eighty-five patients from the prevalence study were followed for an average of 6.7 years. This group consisted of the 23 patients with untreat-

ed stage III proliferative retinopathy and 62 patients with either normal findings on peripheral examination or stage I or II proliferative retinopathy. Changes in the prevalence of ocular fundus findings, not including the proliferative neovascular changes that occurred during follow-up, are summarized in Table V.

Angioid Streaks

Two patients (1.3%) manifested angioid streaks at the time of the initial examination. Angioid streaks developed in five additional patients over the course of the study, giving a final incidence of 7.2%. The majority of patients (4 of 6) with angioid streaks were over age 50. The difference in incidence in patients over age 50, compared with those under age 50, was statistically significant ($P < 0.01$ using Fisher's exact test). None of these eyes manifested clinical evidence of choroidal neovascularization.

Macular Changes

The macular changes noted either initially or during follow-up are listed in Table V. The percentage of patients with epiretinal membranes increased from 1.2% (1) to 4.7% (4), although only one patient had visual acuity of less than 20/30. This was an SS patient in whom a macular pucker developed during follow-up. A macular hole developed in one patient.

TABLE V: CHANGE IN PREVALENCE OF NONPROLIFERATIVE OCULAR FUNDUS LESIONS DURING NATURAL HISTORY FOLLOW-UP IN 85 PATIENTS

OCULAR LESION	NO. OF PATIENTS	INITIAL PREVALENCE	FINAL PREVALENCE
Angioid streaks		1 (1%)	6 (7%)
Macular hole		1 (1%)	2 (2%)
Epiretinal membrane		1 (1%)	4 (5%)
Retinal hemorrhage			
SS	59	2 (3%)	2 (3%)
SC	23	5 (22%)	3 (13%)
S thal	3	0	0
Total	85	7 (8%)	5 (6%)
Iridescent spot			
SS	59	2 (3%)	5 (8%)
SC	23	8 (35%)	5 (22%)
S thal	3	0	0
Total	85	10 (12%)	10 (12%)
"Black sunburst spot"			
SS	59	20 (34%)	26 (44%)
SC	23	14 (60%)	19 (82%)
S thal	3	1	1
Total	85	35 (41%)	46 (54%)

SS, sickle S disease; SC, sickle C disease; S thal, sickle thalassemia disease.

This patient had stage III proliferative retinopathy with normal vision at the time of entry into the study. Five years later a vitelliform macular lesion associated with cuticular drusen was noted on fluorescein angiography. Over a 2-year period the yellow lesion resolved, leaving mild pigmentary changes and a visual acuity of 20/50. This patient returned 1 year later with a macular hole and a secondary retinal detachment. The detachment was successfully repaired, and the patient has maintained 20/200 vision for 1 year.

Nonproliferative Sickle Retinopathy

The initial and final percentages of nonproliferative changes (retinal hemorrhages, iridescent spots, and black sunbursts) are listed in Table V. The percentage of patients with retinal hemorrhages and iridescent spots remained basically unchanged during follow-up. None of the nonproliferative changes was significantly associated with age or proliferative retinopathy. However, these findings were detected more frequently in patients with SC disease. The number of patients with black sunburst spots increased from 35 to 46. Nearly every patient with SC (19 of 23) had at least one black sunburst spot in one or both eyes, but less than half (44%) of patients with SS disease had black sunburst spots at the end of the study. The black sunburst spots were seen more frequently in the superotemporal quadrant (46%), followed by the inferotemporal (25%), superonasal (17%), and inferonasal (13%) quadrants.

Proliferative Sickle Retinopathy

The change in prevalence of proliferative sickle retinopathy in the different hemoglobin types is summarized in Table VI. Since all untreated patients with stage III disease or worse were included in the natural history study, the initial incidence of proliferative disease was determined from the prevalence study. During follow-up, stage III lesions developed

TABLE VI: CHANGE IN PREVALENCE OF PROLIFERATIVE SICKLE RETINOPATHY (STAGE III OR HIGHER) DURING FOLLOW-UP IN 82 PATIENTS*

GENOTYPE		INITIAL EXAMINATION	DEVELOPED STAGE III, IV, OR V	FINAL
SS	59 Patients	11 (19%)	7	18 (31%)
	117 Eyes	17 (15%)	9	26 (22%)
SC	23 Patients	11 (48%)	6	17 (74%)
	45 Eyes	19 (42%)	10	29 (64%)

*Patients with sickle thalassemia included in natural history study are not included. None of those patients had new proliferative lesions develop during follow-up.

SS, sickle S disease; SC, sickle C disease.

in an additional 19 eyes of 13 patients (9 eyes of SS patients and 10 eyes of SC patients). The mean follow-up was 6.7 years for the entire group. The difference in the frequencies of proliferative disease in the SC and SS patients is statistically significant for both the initial incidence and the de novo development ($P < 0.0001$ and $P < 0.01$, respectively, using the chi-square test).

The 38 eyes of 23 patients who presented with untreated proliferative sickle retinopathy are considered as a separate group. The initial and final stages of this group are presented in Table VII. The development of a vitreous hemorrhage (stage IV) was observed in 36% (5 of 14) of the eyes of SC patients, 7% (1 of 15) of the eyes of SS patients, and none of the eyes of patients with sickle thalassemia. Two of the four SC patients who entered the study with evidence of old vitreous hemorrhage (stage IV) had recurrent hemorrhages to bring the total to 7 of 19 (37%) of the SC patients with proliferative retinopathy who had at least one vitreous hemorrhage during follow-up; this is significantly higher than for SS patients ($P = 0.025$ by Fisher's exact test). However, five of these hemorrhages were subclinical with little or no decrease in visual acuity.

TABLE VII: STAGE PROGRESSION IN PATIENTS PRESENTING WITH PROLIFERATIVE SICKLE RETINOPATHY

GENOTYPE	STAGE III		STAGE IV		STAGE V	
	INITIAL	FINAL	INITIAL	FINAL	INITIAL	FINAL
SS (17 eyes)	15	13	2	3	0	1
SC (19 eyes)	14	8	4	9	1	2
S thal (2 eyes)	2	2	0	0	0	0
Total (38 eyes)	31	23	6	12	1	3

SS, sickle S disease; SC, sickle C disease, S thal, sickle thalassemia disease.

Progression of proliferative disease (denoted by an increase in the number or size of existing neovascular lesions) and regression (the development of atrophic or autoinfarcted lesions) are presented in Table VIII. The SC patient who entered the study with a total-traction retinal detachment was excluded from this table. No change was observed in 59% of the eyes in SS disease and 26% of the eyes with SC disease (mean follow-up, 69 and 77 months, respectively). Older patients appeared to be more stable, with a mean age of 47 years in the stable patients compared with 39 years in patients who showed progression. Although regression of individual lesions was noted more often in SC patients, the percentage of regression drops to 17% in SC patients when eyes that demonstrated evidence of both progression and regression are excluded. Neovasculari-

TABLE VIII: NATURAL HISTORY OF PROLIFERATIVE SICKLE RETINOPATHY

	GENOTYPE	
	SS	SC
No. of eyes (patients)	17 (11)	19 (11)
Mean follow-up (mo)	69	77
Stable	59%	26%
Regression (partial/ complete)	18%	42%
Progression	35%	58%
Vitreous hemorrhage	6%	37%*
Retinal detachment	6%	6%
Vision loss	6%†	16%‡

*Five of seven vitreous hemorrhages were subclinical or transient.

†Patient also had diabetes mellitus, hypertension, and a history of syphilis.

‡Two patients were successfully treated with vitrectomy; the third had a vitreous hemorrhage that cleared spontaneously within 1 year.

SS, sickle S disease; SC, sickle C disease.

zation was located most commonly in the superotemporal quadrant (37%), followed by the inferotemporal (35%), superonasal (17%), and inferonasal (13%) quadrants.

Vision Loss

Three eyes of three patients presenting with evidence of proliferative disease had visual acuity of less than 20/30 at presentation. Vision loss occurred in five eyes of five patients during follow-up. Thirty-one months after entering the study, one patient had a decline in visual acuity to 20/200 along with development of an epiretinal membrane with macula traction, peripheral-traction retinal detachment, and vitreous hemorrhage. However, this patient also had adult-onset diabetes mellitus and hypertension and had previously undergone treatment for syphilis. Three patients with SC disease experienced visual loss in four eyes. One patient had a macular hole and 20/200 visual acuity with secondary retinal detachment. Further details of this patient are presented in the section "Macular Changes." Two patients lost vision in one eye owing to vitreous hemorrhage in one and central retinal artery occlusion in the other. The first patient underwent a pars plana vitrectomy for the dense, nonclearing vitreous hemorrhage, with a return of 20/20 visual acuity 1 year after vitrectomy. The acuity subsequently dropped to 20/50 from progressive nuclear cataract by the second year. The follow-up periods prior to the

reported vision loss for the three patients were 118, 49, and 27 months, respectively. One other patient with SC disease had transient vision loss secondary to vitreous hemorrhage, but vision returned to 20/20 within 2 weeks and remained normal for an additional 36 months of follow-up.

In the 19 eyes in which proliferative retinopathy developed *de novo*, only one patient had associated visual acuity loss. An 11-year-old patient with SC disease presented with nonproliferative disease in his right eye and stage III disease in his left eye. One year after he entered the study, stage III disease developed in the right eye. A retinal detachment developed in the right eye 4½ years later. The patient underwent an unsuccessful attempt at retinal reattachment with a scleral buckling procedure and lost all light perception. This was the youngest patient in the study in whom proliferative sickle retinopathy developed and the only patient with permanent central vision loss directly attributed to proliferative sickle retinopathy. His untreated left eye maintained 20/20 acuity after 9 years of follow-up.

DISCUSSION

ANGIOID STREAKS

The association between angioid streaks and sickle cell disease has been well documented.³¹⁻³⁵ The incidence of angioid streaks in an unselected population of sickle cell patients has been estimated to be 1% to 2%, although a definite age relationship has been observed.^{34,35} Condon and Serjeant³⁴ reported that 22% of 60 homozygous patients over 40 years of age had angioid streaks, compared with only 2% of 150 younger Jamaican patients. The present study confirms those findings. Angioid streaks were observed initially in two patients (1.3%) and developed in five patients, aged 25 to 68, during follow-up (Fig 2). Streaks were found in both SS and SC patients, and the overall incidence was 7.2% for all patients and 27% for patients over the age of 50. No relationship was found between angioid streaks and the type of hemoglobinopathy or the severity of sickle retinopathy. No associated vision loss caused by complications of angioid streaks occurred in these patients; this is consistent with the benign clinical course of angioid streaks in sickle patients described in previous studies.^{34,35}

PROLIFERATIVE SICKLE RETINOPATHY

Retinal neovascularization was observed more frequently in the temporal quadrants than in the nasal quadrants. This relationship has been noted in

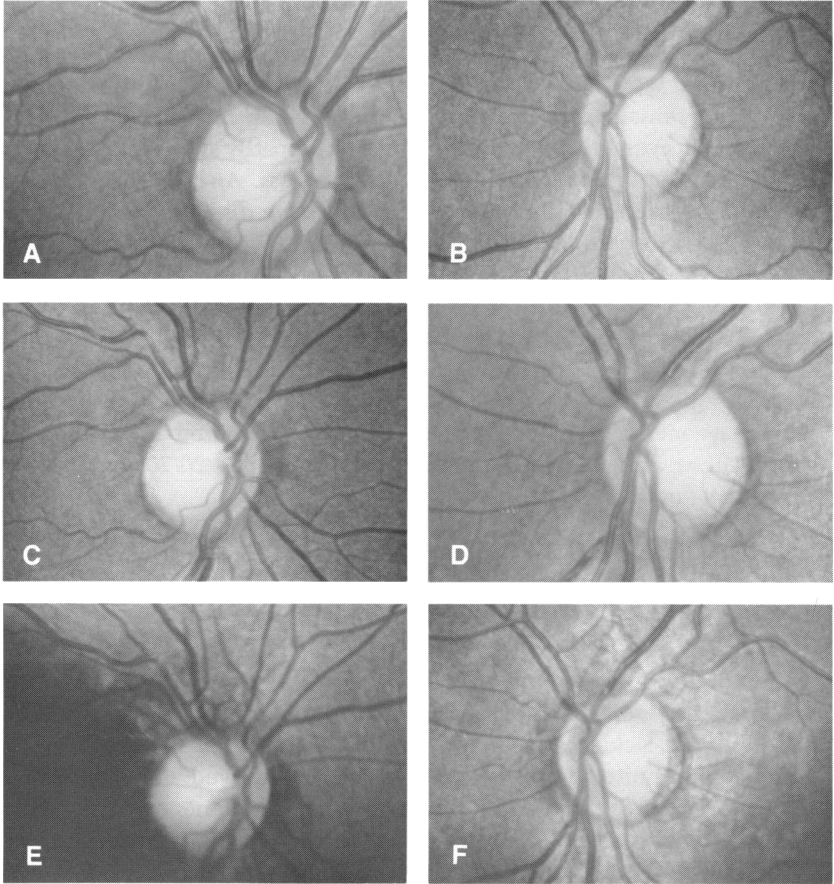


FIGURE 2

Homozygous hemoglobin S disease in 17-year-old black male. A: Right eye at first examination, January 1981. Visual acuity was 20/20 in both eyes, and there was no evidence of any fundus abnormality. B: Left eye, January 1981. C: Right eye, September 1982. Early angioid streak is visible at 12 o'clock position, just superior to disc. D: Left eye, September 1982, continues to appear normal. E: Right eye, January 1989. F: Left eye, January 1989. Both eyes had 20/20 vision. Evidence of peripheral vascular occlusion with arteriovenous anastomoses and peripheral "sunburst spots" is seen. Peripapillary angioid streaks were present in both eyes.

the past, with the superotemporal quadrant considered the most common location for early neovascular proliferation. This was true for SC patients in the present study, but not for 55 patients in whom the inferotemporal quadrant was more frequently involved. This predilection for the temporal quadrants early in the development of stage III proliferative sickle retinopathy was quite dramatic. Over 93% (54 of 58 eyes) had at least some, if not all, of the neovascularization located temporally when retinal neovascularization was first observed.

Other investigators^{8,15,16} have documented that proliferative retinopathy is more common in patients with SC disease than in patients with SS disease. Condon and Serjeant¹⁶ examined 76 SS and 70 SC randomly selected patients and found a prevalence of 32.8% for SC patients (later revised to 37%²⁷) and only 2.6% for SS patients. The present study demonstrates a greater frequency of proliferative retinopathy for both SC disease (45%) and SS disease (11%). Condon and Serjeant found that the incidence of proliferative disease increases with age, with the maximum incidence between ages 15 and 29. The median age of the patients in this study (26 years) is probably older than that in the studies by Condon and Serjeant, in which 58 of 76 patients with SS disease¹⁵ and 47 of 70 patients with SC disease¹⁶ were all under age 30. Although patients with SS disease in the Jamaican study¹⁵ were referred from a sickle clinic, those with SC disease in Jamaica¹⁶ were solicited through letters and home visitation. Also, the patients who were referred from the Sickle Cell Center in the present study may have had more severe systemic disease than the Jamaican patients.

The increased severity of proliferative disease in SC patients as compared with SS patients has been observed previously,^{8,20,27} and the difference is striking in this natural history study. In SC patients there was a significant increase in frequency of de novo development of neovascularization (Table VII) (26% in SC compared to 12% in SS), an increase in number and size of proliferative lesions (58% in SC compared with 35% of SS eyes), and a progression to higher stages of the disease (Table VIII). Vitreous hemorrhage developed or recurred in 37% of the eyes of patients with stage III or IV proliferative sickle retinopathy at the beginning of the study, compared, with only 6% of the eyes of SS patients. However, in spite of the increasing development of neovascular lesions and/or vitreous hemorrhage in these eyes, visual function remained surprisingly stable. Many eyes demonstrated gradual regression of neovascularization with little or no change in central vision, although some evidence of "activity," such as minimal vitreous bleeding or angiographic evidence of leakage of fluorescein may have been present (Figs 3 and 4).

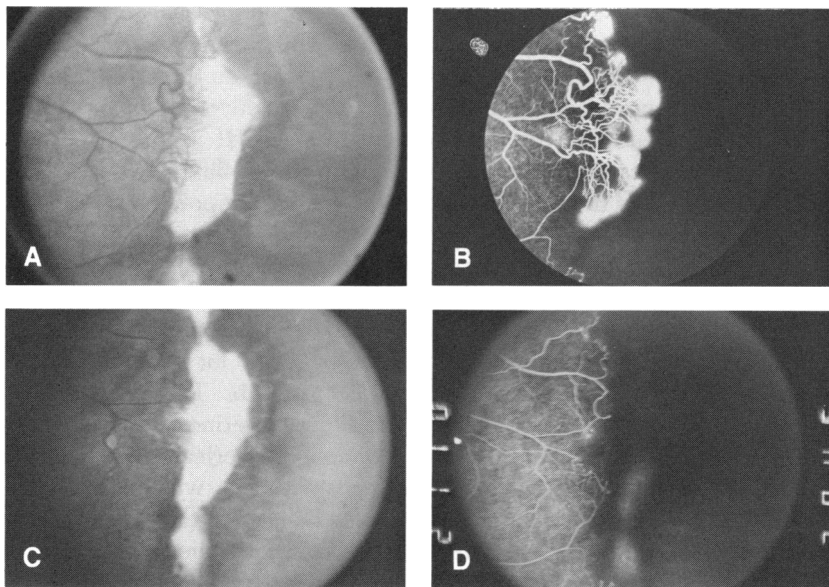


FIGURE 3

Homozygous hemoglobin S disease in 25-year-old male who presented with stage III proliferative retinopathy and 20/20 visual acuity in both eyes. Autoinfarction of proliferative lesion in left eye is evident. Patient maintained 20/20 visual acuity in both eyes with more than 10 years of follow-up. A: Color fundus photograph of proliferative lesion in temporal periphery, left eye. B: Fluorescein angiogram of same area, showing marked vascular activity at time of initial visit. C: Color fundus photograph of same lesion 5 years later. D: Fluorescein angiogram of same area, demonstrating nearly complete autoinfarction of proliferative lesion.

TREATMENT

Treatment has been advocated on the basis of the impression that the natural history of stage III proliferative sickle retinopathy will lead to loss of vision. Various treatment modalities have been utilized and have shown some degree of success; these include diathermy,³⁶ cryotherapy,^{37,38} treatment of feeder vessels with xenon and argon laser photocoagulation,^{30,38-40} and indirect argon laser treatment to the nonperfused peripheral retina.⁴¹⁻⁴⁴ Some form of argon laser treatment has been widely recommended; cryotherapy has been limited to those cases with cloudy media. The direct treatment of feeder vessels, although successful in causing regression of neovascularization, has been questioned because of the development of choroidal neovascularization or chorioretinal neovascularization in 94% of eyes followed for a mean of 11.2 years.²⁸ Vitreous hemorrhage, vitreoretinal traction, and retinal detachment have also

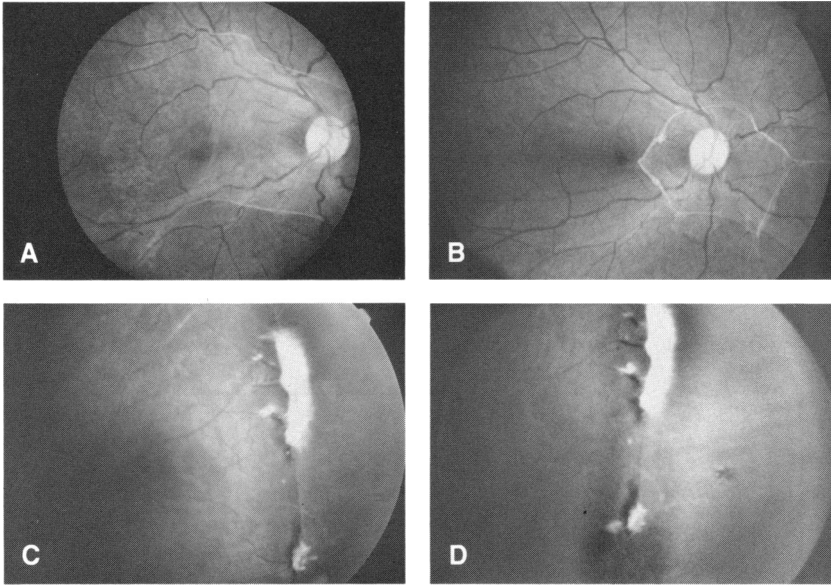


FIGURE 4

Sickle cell-hemoglobin C disease in 21-year-old black male. A: Fundus photograph taken in May 1983 shows prominent epiretinal membrane covering disc and most of macular area, right eye. Visual acuity was 20/30. B: Fundus photograph taken 34 months later (March 1986) confirms spontaneous retraction of epiretinal membrane, no change in visual acuity. C: Fundus photograph of nasal periphery taken in May 1983 shows evidence of proliferative retinopathy, primarily fibrous in nature. Smaller frond shows definite vascular component. D: Fundus photograph of same area taken in March 1986 documents no significant change in peripheral fibrovascular lesions. Note pigmented sunburst spot.

been noted as complications of this form of treatment.^{27,28} The long-term follow-up of 29 of the original 44 patients (20 with SC, 4 with SS, and 5 with sickle β -thalassemia) from the randomized clinical trial of feeder vessel photocoagulation revealed the treated group had a high rate of complications (32%); these included 2 eyes with retinal detachment, 1 with retinal tear, and 5 with choroidal neovascularization.⁴⁵ However, none of these complications appeared to have a long-term adverse outcome. The control group experienced an increased number of transient vitreous hemorrhages, but there was no significant difference in the final visual acuity between the treated and control eyes.

A comparison of the results of this natural history study of patients with proliferative sickle retinopathy (Table VIII) with two studies^{42,43} recommending prophylactic scatter laser treatment (Table IX) reveals no indication for prophylactic treatment in patients with SS disease. Though the

TABLE IX: RESULTS OF TWO STUDIES OF PROPHYLACTIC SCATTER LASER TREATMENT OF PROLIFERATIVE SICKLE RETINOPATHY

	KIMMEL ET AL 1986 ⁴³	REDNAM ET AL 1982 ⁴²
No. of eyes (patients)	70 (44)	21 (19)
Mean follow-up (mo)	39	11
Stable	19%	22%
Complete regression	33%	62%
Partial regression	46%	16%
Progression	2%	0
Vitreous hemorrhage	7%	0
Vision loss (20/200 or worse)	3%	5%

numbers are small, only one eye of one patient in this study had moderate visual acuity loss, and this was perhaps only indirectly related to proliferative sickle retinopathy; this patient had macular pucker and peripheral traction retinal detachment in association with proliferative sickle retinopathy but also had adult-onset diabetes mellitus and hypertension. For patients with SC disease, it might appear that prophylactic scatter laser photocoagulation is indicated because of this high rate of vitreous hemorrhage (37%) and vision loss (16%). However, in 5 of the 7 eyes, the vitreous hemorrhage was subclinical or transient, with visual acuity decreased for only a few days or weeks or not at all. It should be noted that previous peripheral scatter and focal treatment studies have included patients with SS disease, sickle thalassemia, and sickle cell trait; only about 50% of the patients treated were affected by hemoglobin SC disease.^{42,43} In addition, the mean follow-up periods were 39 months⁴³ and 11 months,⁴² compared with 77 months in this natural history study. All three patients in this study had loss of central vision after more than 3 years of follow-up. If the visual acuity results in this natural history study were adjusted to include the patients successfully treated with vitrectomy or with observation (self-clearing vitreous hemorrhage), the development of persistent visual loss due to proliferative retinopathy in SC patients occurred in none of 18 eyes that began the study with proliferative disease and in 1 of 26 (3.8%) of all eyes with proliferative disease with an average follow-up of 6.4 years.

Farber and associates⁴⁴ reported the results of scatter photocoagulation using peripheral argon laser treatment in 1991. This study demonstrated that scatter photocoagulation therapy reduced the incidence of visual loss due to vitreous hemorrhage of at least 3 months' duration in patients with

proliferative sickle retinopathy. However, this study did not show definite evidence that the incidence of retinal detachment, the primary cause of blindness in patients with proliferative sickle retinopathy, was reduced through peripheral scatter photocoagulation. There were no complications reported from the peripheral scatter photocoagulation. The average length of follow-up was 47 months for treated eyes. Although these investigators had reported previously that the extent of stage III retinopathy was probably an important risk factor for vision-threatening complications, only 11 of the treated eyes had 60° or greater (2 clock hours or more) of fibrovascular proliferation. Therefore, 88 of the 99 treated eyes had less than 2 clock hours of neovascularization.

Farber and associates⁴⁴ recommend peripheral scatter laser treatment on the basis of a reduction of "ocular events" in the treated eyes. However, if permanent reduction in vision is considered, five control eyes and three treated eyes lost vision due to proliferative sickle retinopathy during follow-up. This is similar to the loss of vision found in this natural history study (Table VIII), and the difference between treated and untreated eyes is not significant.

SUMMARY

Prophylactic photocoagulation may have a role in the treatment of proliferative sickle retinopathy in selected patients with SC disease, but none of the studies reported to date have established that such treatment of these eyes improves the long-term visual outcome as compared with the natural history as documented in this study. The similar visual outcomes in the eyes reviewed in this natural history study as compared with those that have been treated with photocoagulation should not be unexpected, because there is greater predilection for spontaneous involution or autoinfarction of the neovascular tissue in SC disease as opposed to the neovascularization that develops in other retinal vascular disease.

A controlled, multicenter clinical trial designed to study those eyes at greatest risk should be considered. Such a trial should specify patient age (15 to 30 years), hemoglobin type (SC disease), and a minimum threshold of active proliferative disease (60° or greater). Such criteria have been suggested by others.^{29,40} By comparing the outcome of eligible eyes randomly assigned to treatment or observation and followed for an extended period, it will be possible to learn whether laser photocoagulation offers a better prognosis than the natural history of proliferative sickle retinopathy. There is no question that in some eyes with proliferative sickle retinopathy, nonclearing vitreous hemorrhage and/or retinal de-

tachment will develop. Clear definition of the risk factors leading to these advanced stages, however, is lacking, and the value of treatment is uncertain.

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