Diffuse unilateral subacute neuroretinitis[1]

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William Lang was one of the many distinguished clinicians who was instrumental in the development of Moorfields Eye Hospital as a world renowned centre for patient care, physician training and eye research. He had a particular interest in uveitis and its relationship to infections, and I wish to think that he might have been interested in the topic of my presentation.

This communication reports the clinical, fluorescein angiographic and electrophysiologic features of a distinct clinical syndrome in which only one eye of a healthy child or young adult is affected. Features of the syndrome include: (1) insidious, usually severe loss of peripheral and central vision; (2) vitritis; (3) diffuse and focal pigment epithelial derangement with relative sparing of the macula; (4) narrowing of the retinal vessels; (5) optic atrophy; (6) increased retinal circulation time; (7) subnormal electroretinographic findings (Figure 1). For a period of eleven years, in the absence of information concerning the early stages or cause of this disease, we categorized these patients as the 'unilateral retinal wipeout syndrome.' Only during the past two years have we become aware of the features of the early stages of this disease. These include vitritis, mild optic nerve head oedema, multifocal areas of active chorioretinitis and occasionally, iridocyclitis. This disease runs a subacute or chronic course and is usually detected initially during the late stage of its development. Evidence is presented that this disease may be a viral inflammation affecting primarily the retina, pigment epithelium and optic nerve head.

Methods and materials

Twenty-nine patients with this disease have been seen at the Bascom Palmer Eye Institute; 4 patients, aged 7–29 years, with the typical clinical picture of this disease, were excluded from this study because of the unavailability of electrophysiologic tests to confirm the diagnosis. Of the 25 patients included in this study, 9 were seen either at the Bascom Palmer Eye Institute or by their local physicians during the early stages of the disease; 16 patients detected the disease initially during its late stages, either by chance covering of the unaffected eye or during a routine eye examination.

All patients had a complete eye examination, fundus photographs, and electroretinography; 21 patients had fluorescein angiography and electro-oculography. Electro-oculography was done using the technique described by Arden *et al.* (1962). Selected patients each had a general physical examination, neurologic examination, complete blood counts, blood chemical

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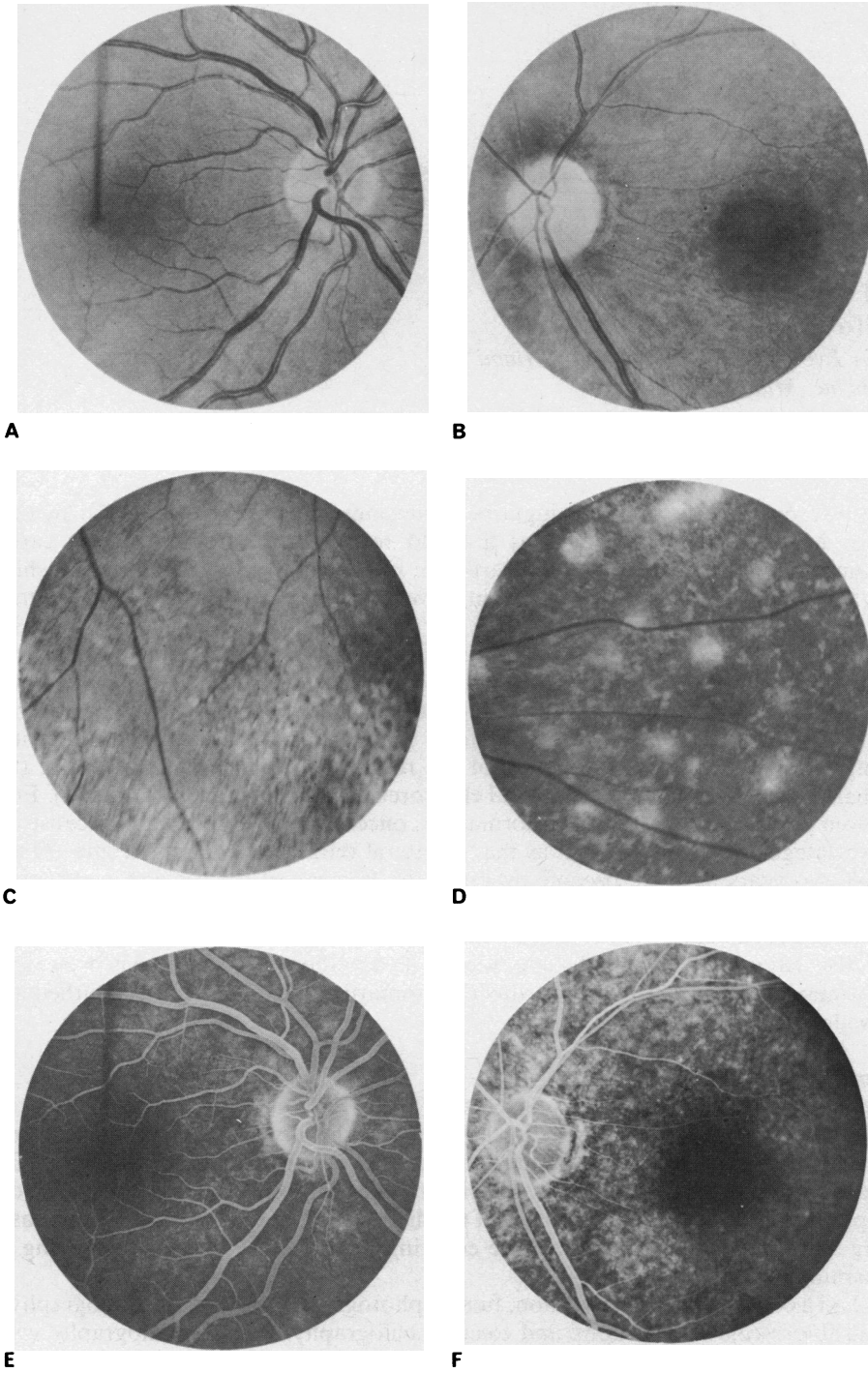


Figure 1. Typical late stage of diffuse unilateral subacute neuroretinitis ('unilateral wipeout syndrome'). A, unaffected eye; B, C & D, affected eye; E, angiogram unaffected eye; F, angiogram affected eye

analyses, X-rays of the skull, optic foramina and chest, EMI scan, lumbar puncture, gonioscopy, ophthalmodynomometry, and electroencephalography. Follow-up information was available in 13 patients, including all of the 9 patients seen during the early stages of the disease. The duration of follow up varied from 4 months to 11 years (average 3 years).

The eye of one patient, who was seen elsewhere and who probably had this disease, was studied in the Eye Pathology Laboratory at the Bascom Palmer Eye Institute. It was fixed in formalin and routine histopathologic sections were prepared from paraffin-imbedded tissue. Formalin-fixed tissue from the temporal portion of the macular area was prepared for electron microscopic study.

Findings

History

The insidious nature of this disease is attested to by the fact that 16 of the 25 patients had the late stages of the disease and usually advanced visual loss when they first became aware of its presence. Of these 16 patients, 12 had had poor vision in the affected eye for periods of time ranging from two to twelve years before their initial examination here; the other 4 patients had only recently detected the poor vision. Only 9 patients became aware of the disease during its early stages, and in 3 of these visual loss was detected on a routine eye examination. Blurred vision was the presenting complaint in 6 out of 9 patients and was accompanied in 4 patients by discomfort and injection of the affected eye.

Twenty patients were white and 5 were black; 15 were male and 10 were female. The patients' ages at the time they were initially examined at the Bascom Palmer Eye Institute ranged from 8–23 years (average 15 years). The age at the time of initial detection of the visual deficit ranged from 5–22 years (average 12.5 years). There was documentation of previously normal visual acuity in 14 out of 25 patients. All patients were in excellent health at the time of onset of visual symptoms. Three patients first noted visual loss and presented with the early stages of the disease within several months following recovery from a moderately severe febrile illness: chicken-pox in 2 patients, and rubeola in one patient. Four patients gave a history of head trauma, usually several years prior to the discovery of poor vision; in only one of these was there a history of direct injury to the eye – the patient was struck in the eye with a ball. He was examined by an ophthalmologist several months later because of a bacterial conjunctivitis; his vision was normal and there was no evidence of trauma to the eye. One patient gave a history of having multiple allergies. The past medical history and the family history in these patients were otherwise unremarkable.

Diagnoses made by referring physicians in patients examined during the early phases of the disease included amblyopia ex anopsia, papilloedema, papillitis, pars planitis, acute posterior multifocal placoid pigment epitheliopathy, multifocal choroidal infarcts, and active chorioretinitis caused by histoplasmosis, toxoplasmosis, and *Toxocara canis*. Diagnoses during the later stages of the disease included the presumed ocular histoplasmosis syndrome, unilateral retinitis pigmentosa, ophthalmic artery occlusion, and post-traumatic neuroretinopathy.

Ocular findings

Only one eye was affected in each of the 25 patients; the right eye in 13 patients and the left eye in 12 patients. The visual acuity in the unaffected eye was 6/6 or better in every patient. At initial examination here, the visual acuity in the affected eye ranged from 6/7.5 to light perception only. It was 6/60 or less in 19 of the 25 patients. There was no significant difference in the refractive error in the affected and unaffected eyes. A positive Marcus Gunn pupillary reaction was present in 13 of the 14 patients in whom it was recorded. The intraocular pressure was normal in all patients.

Early stages: Visual loss and cellular infiltration of the vitreous in the affected eye were the

earliest signs of this disease. Visual acuity in the affected eye ranged from 6/10 to counting fingers on initial examination of the 9 patients who presented during the early stages of the disease. It was 6/60 or less in 7 of these patients. Of the 9 patients, 4 had a mild to moderate ciliary flush, anterior chamber flare and cells, and keratic precipitates; one patient had a small hypopyon; 5 patients had mild oedema of the optic disc; none showed evidence of optic disc pallor when examined initially by their local physician; 3 had mild optic atrophy when first examined here. A fan-shaped pattern of fine superficial retinal striae radiating outward from the optic disc margin into the macular area was present in at least 3 patients (Figure 2B). Widespread changes in the colour of the pigment epithelium and partial loss of the light reflexes from the retinal surface occurred early in the course of the disease. The pigment epithelium appeared dull and less pigmented in the affected eye (Figures 2A, 3A, 4A,B). Fine mottling of the pigment epithelium was usually more apparent in the peripapillary and peripheral parts of the fundus. Five patients had multiple, small (usually less than one disc diameter size), white or yellow-white, deep retinal or chorioretinal lesions with fuzzy borders and irregularly round shape in the paramacular or peripheral areas of the affected eye (Figure 4B,C). These lesions occurred in the macular area in only one patient. They were associated with a localized serous detachment of the retina in one patient (Figure 4C). They were interpreted as active inflammatory lesions and in at least 3 cases were accompanied by multiple, focal, peripheral, atrophic, nonpigmented or partly pigmented, chorioretinal scars. Mild narrowing of the major retinal arteries was present in all 9 patients when they were first examined here (Figures 2B, 4B).

Late stages: The 16 patients who were examined initially during the late stages of the disease showed varying degrees of optic atrophy that was graded as moderate or severe in 13 patients, and retinal artery narrowing that was graded as moderate or severe in 14 patients (Figure 1). Twelve patients had varying degrees of retinal artery sheathing that was most prominent in the peripapillary area (Figure 1B). Five patients had fine, inner-retinal folds radiating from the temporal margin of the optic disc toward the macula. At least 4 patients showed varying degrees of vitreous cells and vitreous strands. There were no comments in the charts of 12 patients concerning the presence or absence of vitreous cells. All patients showed widespread pigmentary changes throughout the fundus. These changes included fine and coarse mottling of the pigment epithelium, focal atrophic nonpigmented and pigmented chorioretinal scars, and large irregular areas of pigment derangement (Figure 1). The pigment changes were most prominent in the peripapillary and the peripheral parts of the fundus. Two patients showed small, grey-white, hypertropic, subretinal scars at the temporal margin of the optic disc. Only one patient had a chorioretinal scar involving the centre of the macula. While some had evidence of migration of pigment into the overlying peripheral retina, none showed large areas of bone spicule pattern of migration similar to that seen in patients with retinitis pigmentosa.

While the retinal artery narrowing always was greater than retinal venous narrowing, both were present in those patients with severe optic atrophy. The degree of retinal vessel narrowing was often unequally distributed in the quadrants. While there was good correlation between the degree of optic atrophy and arterial narrowing and sheathing, there was less correlation between these findings and the degree of loss of visual acuity. One patient with severe optic atrophy had 6/10 visual acuity. Several patients with only mild optic disc pallor had counting-fingers vision. Five patients had localized grey epiretinal membranes surrounded by fine radiating retinal folds either in the midperipheral or posterior fundus. None of the 16 patients showed abnormalities in the anterior segment of the affected eye at the time of initial examination, and none had evidence of cataract.

Natural course: The 9 patients who were examined during the early stages of the disease were followed for periods ranging from three months to ten years. Visual acuity in the affected eye was 6/60 or less in all but one patient when last examined. All patients, except one with the

shortest follow up, have developed varying degrees of optic disc pallor (Figures 2C, 3B, 4F), greater narrowing and, in some cases, sheathing of the retinal arteries and more pronounced fine and coarse mottling of the pigment epithelium with relative sparing of the macula. One patient, who presented initially with counting-fingers vision, showed no evidence of optic disc pallor five months later; when examined twelve months following initial examination, she had developed moderate optic atrophy and narrowing of the retinal vessels. Four patients had only mild to moderate optic atrophy, in spite of having only counting-fingers vision at periods ranging from one to eleven years following the onset of their disease (Figure 2). Active focal retinal or chorioretinal lesions recurred in the same patient for periods at least as long as eight months. They either faded from view leaving no focal change in the pigment epithelium, or were replaced by nonpigmented or partly pigmented chorioretinal scars (Figure 4F). The 4 patients who did not have active lesions on their initial examination subsequently developed additional focal, atrophic, chorioretinal lesions. One patient retained 6/12 visual acuity and showed only minimal optic atrophy and narrowing of the retinal vessels ten years following the onset of symptoms. One patient developed heterochromia of the iris in the affected eye nine years after the onset of visual loss. The iris in the affected eye became lighter in colour. On the last follow-up examination eleven years after the onset of symptoms, he had multiple, grey-white, keratic precipitates and a few cells in the anterior chamber in the affected eye.

Only 4 out of 16 patients seen during the late stages of the disease have been followed here. Three have shown no further progression of the disease. One patient, who was deemed to have the late stages of the disease when he was seen here in December 1973 after failing a school eye examination, showed further atrophy and narrowing of the retinal vessels when he was last seen in January 1977; at that time, his visual acuity was unchanged. He had five grey-white keratic precipitates and a few cells in the anterior chamber. None of the 25 patients has developed evidence of disease in the unaffected eye.

Fluorescein angiographic findings

Fourteen patients had satisfactory, timed, fluorescein angiographic studies. The dye appeared in the choroid 8–13 seconds following injection into the antecubital vein in 12 patients. In 2 patients with severe optic atrophy, the dye appeared initially in the choroid at 15 and 16 seconds following dye injection. Six additional patients had rapid sequence untimed angiograms. In 12 of 20 patients with satisfactory rapid sequence angiography, the dye arrived in the choroidal circulation of the affected eye ahead of that in the retina; in 7 patients it arrived simultaneously in the retina and choroid; in one patient the dye arrived in the retinal circulation first. Several patients showed patchy areas of delayed filling of the choroidal circulation in the peripapillary area. In most cases there was angiographic evidence of increased retinal circulation time. The dye appeared in the retinal arteries 12–24 seconds following injection in 9 patients. The delay in retinal artery appearance time was greatest in those patients with the greatest degree of optic atrophy and retinal vessel narrowing.

In the affected eye, angiography revealed a widespread pattern of abnormal hyperfluorescence indicative of alterations in the pigment content of the retinal pigment epithelium throughout the fundus (Figures 1E, 2D, 4D). These changes were most marked in the peripheral and peripapillary areas of the fundus. There was relative sparing of the macular area which showed usually only a fine, and less often coarse pattern of mottled hyperfluorescence. During the early stages of the disease the angiographic changes caused by pigment epithelial damage were minimal and they are most easily detected by comparing the findings in the affected and unaffected eyes (Figure 1E,F). The focal grey or yellow-white active lesions, involving the deep retina, pigment epithelium and choroid during the early stages of the disease, appeared hypofluorescent during the early stages of angiography and they stained during the later stages (Figure 4D,E). Two patients with the early stages of the disease showed evidence of leakage of

dye from the optic disc capillaries in the affected eye. One of these also showed leakage of dye from the peripheral retinal vessels.

Electroretinographic and electro-oculographic findings
In 24 out of 25 patients, electroretinography (ERG) showed in the affected eye subnormal findings that were graded as 'moderate to marked' in degree. One patient seen during the early stage of the disease had a normal ERG. He was re-studied three months later and showed a slightly abnormal tracing. Both rod and cone functions were usually affected. The b-wave was more severely affected than the a-wave. No patient had an extinguished ERG. The unaffected eye in every case showed normal ERG findings.

Electro-oculography was done in 21 patients. In the affected eye it was subnormal in 12 patients. While it was within normal limits in 9 patients, the light rise in the affected eye was usually lower than that in the unaffected eye. The light rise was normal in the unaffected eye in 21 patients.

Visual field loss
The areas and density of visual field loss were variable; in some cases, only a small island of peripheral vision remained. Most patients had a large central scotoma and large irregular areas of peripheral field loss.

Other studies
Most patients had medical, and in some cases neurologic, evaluations. The results of these examinations and laboratory studies – including complete blood counts, urinalysis, chest X-rays (9 patients), skull and optic foramina X-rays (13 patients), brain scan (1 patient), lumbar puncture (3 patients), electroencephalogram (2 patients), haemoglobin electrophoresis (5 patients), skin tests or serologic tests for toxoplasmosis, histoplasmosis and tuberculosis (6 patients), and blood chemical analysis (13 patients) – were all within normal limits, except for the presence of an elevated lactate dehydrogenase in 4 patients and an elevated serum glutamic oxaloacetate transaminase in 3 patients. These latter two tests were normal in 7 patients. Gonioscopy and ophthalmodynomometry were done in selected patients and were within normal limits in every case.

Therapy
Most of the 9 patients seen during the early course of the disease were treated for varying periods of time with systemic corticosteroids. A few of these patients showed temporary improvement in visual acuity and vitreous inflammation following institution of corticosteroid therapy. They later developed progressive visual loss which failed to respond to treatment.

Case reports
Case 1
Mr P P, a baseball player aged 18 years, was well until March 1966, when he developed a high fever and skin rash. The diagnosis was rubeola and he was confined to bed for approximately ten days. Four weeks following recovery, he resumed baseball practice and noted blurred vision in the left eye. His local ophthalmologist noted mild swelling of the left optic disc and vitreous inflammatory cells in the left eye. This eye had been normal on many previous eye examinations. Following institution of corticosteroid therapy for a period of six weeks, there was some improvement in his visual acuity. In September 1966 his acuity worsened. A general medical evaluation, that included X-rays of the skull and optic foramina, was negative. He was referred here in October 1966. Visual acuity was 6/5 in the right eye and 6/120 in the left eye. External examination was normal except for a Marcus Gunn pupillary reaction in the left eye. The right eye was normal (Figure 2A). Slit-lamp examination revealed a moderate number of

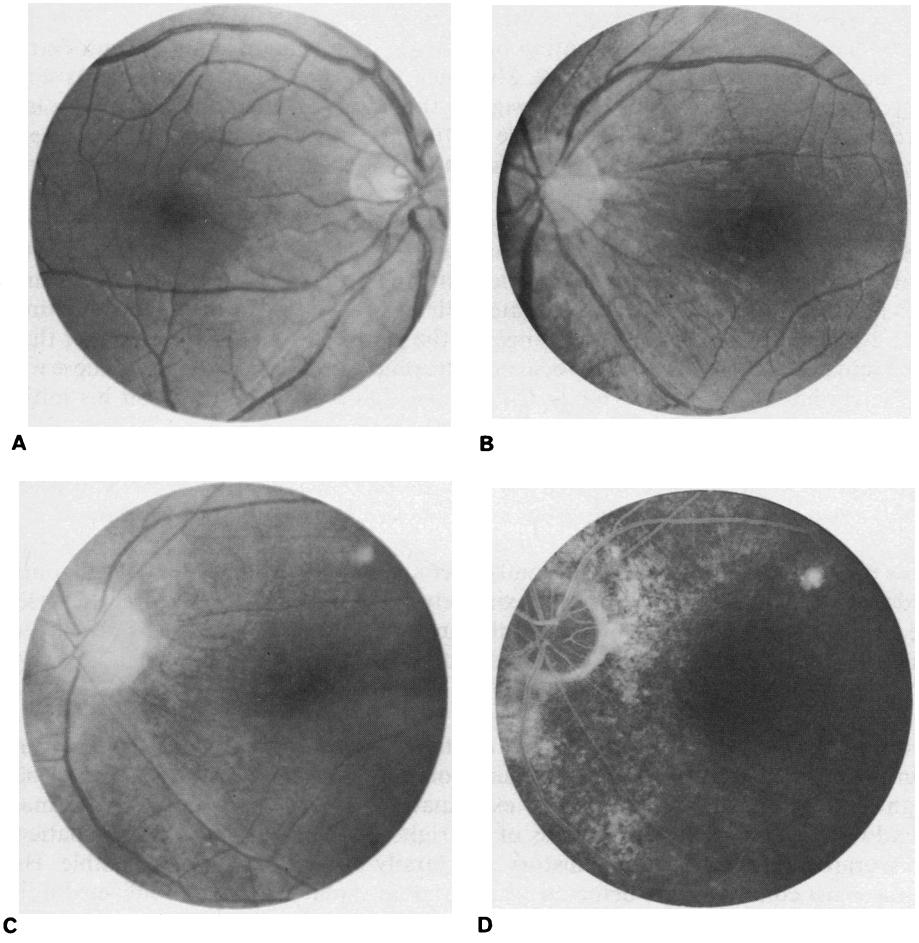


Figure 2. Case 1. A, right eye (September 1966); B, left eye (September 1966); C, left eye (February 1977); D, angiogram left eye (February 1977)

cells in the anterior and posterior vitreous. The left optic disc margin was blurred (Figure 2B). Fine superficial retinal striae radiated from the optic disc into the macular area. There were diffuse changes in the retinal pigment epithelium of the left eye; these consisted of a mild dullness of the normal retinal reflex and the normal orange colour of the pigment epithelium in the macular area, as well as patchy areas of more extensive depigmentation and mottling of the pigment epithelium in the peripapillary and peripheral fundus. There were several focal, nonpigmented, atrophic, chorioretinal lesions near the equator. There was minimal narrowing of the retinal vessels in the left eye. Central field examination revealed a large, dense, central scotoma which surrounded the blind spot. Fluorescein angiography in the left eye revealed dye appearing in the choroid at 8 seconds and in the retina at 9 seconds. There was a large zone of delayed filling of the choroid in the peripapillary area temporally. The zone filled within several seconds and was interpreted as probably normal. There was evidence of diffuse mottled depigmentation of the pigment epithelium with relative sparing of the macula. Late photographs revealed no evidence of leakage of dye from the optic disc and retinal capillaries.

The following year his visual loss progressed and remained stable thereafter. In 1970, his local physician recorded his vision as counting fingers. He had optic atrophy and moderate narrowing of the retinal vessels in the left eye. He noted no further signs or symptoms until 1975, when he became aware of a gradual change in the colour of the left iris. He was last examined here on 10 February 1977. The right eye was normal; visual acuity in the left eye was counting fingers in the inferotemporal fields; he had hand movements only in the other three quadrants; the right iris was yellow-green and the left iris was blue; the pupils were round and equal; there was a Marcus Gunn pupillary reaction on the left side; the intraocular pressure was 10 mmHg in both eyes. Slit-lamp examination revealed a few fine, white, keratic precipitates and an occasional cell in the anterior chamber; there were scattered cells and coarse strands in the vitreous; there was moderate optic atrophy and narrowing of the retinal vessels (Figure 2C). The pigment epithelial changes in the peripheral fundus were greater than on previous examination; there were many focal and atrophic scars near the equator; there was a small round atrophic scar just superior to the macula that was not present on his initial examination (Figure 2C,D); the foveal reflex was absent.

The results of electroretinography and electro-oculography in the right eye were normal. The electroretinogram in the left eye was markedly abnormal with the b-wave being affected greater than the a-wave. The electro-oculogram in the left eye was slightly subnormal.

Comment: This patient's disease progressed rapidly over a period of approximately one month and continued to progress more slowly for approximately one year. Eleven years after the onset of his disease he still has evidence of low-grade inflammation and, in addition, has developed the typical picture of Fuchs's heterochromic iridocyclitis.

Case 2

M P, a boy aged 9 years, was well until he was confined to bed for two weeks with severe chickenpox in May 1969. A routine school examination in June 1969 revealed marked visual loss in the right eye and mild deafness. Similar examinations a year previously were normal. His mother had noted occasional mild redness of the right eye for several weeks. The patient denied any discomfort. His past medical history and family history were unremarkable. His local ophthalmologist confirmed the defective vision and an otolaryngologist confirmed mild high-tone deafness. He was referred here on 4 August 1969. Visual acuity in the right eye was counting fingers at 2 ft (0.6 m); there was generalized constriction of the right visual field. Visual acuity in the left eye was 6/5; the examination in the left eye was normal. Slit-lamp examination in the right eye revealed 2+ cells and 1+ flare; there were 3+ cells in the vitreous; the optic disc colour was normal but its margins were blurred; there was slight narrowing of the retinal vessels; there was a white opacity on the optic disc surface; fine superficial retinal striae radiated from the optic disc into the macular area; there was a generalized dullness of the retinal reflex and pigment epithelial colour; there was mild mottling of the pigment epithelium in the periphery; there were several yellow-white chorioretinal lesions that were interpreted as active areas of inflammation in the periphery; the intraocular pressure was 7 and 11 mmHg respectively in the right and left eyes.

Fluorescein angiography in the left eye was normal. In the right eye there was evidence of widespread alterations in the pigment content of the pigment epithelium with the least changes being evident in the macular area. There was leakage of fluorescein from the swollen optic disc, as well as from the retinal vessels peripherally.

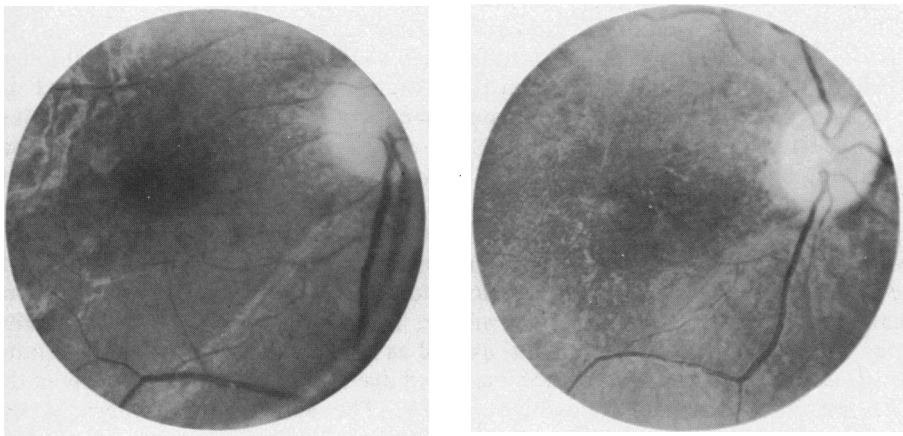
An electroretinogram in the right eye was markedly abnormal with the b-wave reduced relative to the a-wave. The left eye was normal. The electro-oculogram in both eyes was normal. Toxoplasma indirect fluorescent antibody test and eosinophilic count were normal.

The patient was re-examined in March 1975. The visual acuity in both eyes was unchanged; there were a few cells in the vitreous of the right eye; the disc showed 1 to 2+ pallor and

narrowing of the retinal vessels; there were marked irregular changes in the pigment epithelium peripherally similar to those described in Case 1; the left eye was normal.

Case 3

M R, a boy aged 12 years, was examined here on 18 February 1977. When he was 7 years old, poor vision in the right eye was discovered on a school examination; one year previously the vision had been normal. Several months prior to discovery of the poor vision the patient had a severe episode of chickenpox. The local ophthalmologist recorded visual acuity in the right eye of counting fingers at 2 ft (0.6 m) and in the left eye of 6/6. Multiple, focal, white, chorioretinal lesions and mild swelling of the optic disc were noted (Figure 3A). The clinical diagnosis was



A B

Figure 3. Case 3. A, right eye (March 1972); B, right eye (February 1977)

probable active histoplasmic chorioretinitis. The patient was hospitalized and all studies, including blood counts, complement fixation tests for histoplasmin, coccidiomycosis and blastomycosis, lumbar puncture, skull X-ray, optic foramina X-rays, brain scan and electroencephalogram, were negative. The discharge diagnosis was probable resolving papillitis in the right eye. He was seen one month later in consultation at the Massachusetts Eye and Ear Infirmary. Multiple, focal, yellow-white lesions, interpreted as choroidal infarcts, were described in the posterior pole and periphery of the eye; the reflex in the macula was described as abnormal; there were many pigmentary changes in the peripheral fundus of the right eye; the left eye was normal. An electroretinogram in the right eye was abnormal; it was normal in the left eye. The patient noted no further change in his visual status after March 1972. Mild deafness was diagnosed several years later.

In February 1977, examination here revealed that the visual acuity in the right eye was 6/120 and in the left eye was 6/6; there was a Marcus Gunn pupillary reaction in the right eye; the left eye was normal. Slit-lamp examination of the anterior segment of the right eye was normal; there were a few cells in the vitreous; there was 2 to 3+ pallor of the optic disc and narrowing of the retinal vessels (Figure 3B); the pigment epithelial changes in the right eye were identical to those described in Cases 1 and 2. There were several areas of focal epiretinal membrane formation in the posterior pole and peripherally. The focal white chorioretinal lesions noted in 1972 were either no longer evident or had been replaced by focal atrophic lesions (Figure 3B). An electroretinogram in the right eye showed markedly abnormal rod and cone responses; the

b-wave was affected more than the a-wave. The electroretinogram in the left eye was normal. The electro-oculogram was normal in both eyes.

Case 4

A M, a boy aged 14 years, was in good health when he noted blurred vision in the right eye in April 1974. He had previously used this eye to aim his gun. He was examined by two ophthalmologists who diagnosed vitritis and active multifocal choroiditis in his right eye. His left eye was normal. A general physical examination, blood counts and blood chemical profile were normal. His past medical history and family history were unremarkable. He received sub-Tenon's injections of corticosteroids and the visual acuity improved from 6/24 to 6/12. He noted further loss of vision in the right eye, however, and was referred here on 23 December 1974. Visual acuity in the right eye was 6/20 and in the left eye was 6/6; the left eye was normal (Figure 4A). Slit-lamp examination of the right eye revealed scattered cells in the vitreous; the optic disc was slightly pale and the retinal arteries were slightly narrowed (Figure 4B). The pigment epithelium was diffusely abnormal; in the posterior pole the retinal reflex and the colour of the pigment epithelium was dull. In the paramacular and midperiphery of the fundus, there were multiple irregularly round, grey and yellow-white lesions affecting the deep retina, pigment epithelium, and choroid (Figure 4B,C). These lesions showed various stages of resolution. The outer margins of the less active lesions appeared finely pigmented. There was a small two-disc diameter area of serous detachment of the retina in the region of several of these lesions temporal to the macula (Figure 4C). These lesions were similar in appearance to lesions present in the same area of the fundus in photographs taken in May 1974; some of the lesions present at that time, however, were no longer visible. There were numerous focal inactive atrophic lesions in the periphery of the fundus, as well as in the midperiphery of the fundus nasal to the optic disc. Fluorescein angiography revealed dye appearing simultaneously in the choroid and retina at 11 seconds following injection. The active lesions appeared hypofluorescent during the early phases of the study but stained during the later phases (Figure 4D,E). There was angiographic evidence of widespread mottled and patchy depigmentation of the pigment epithelium. There was no leakage of dye from the optic disc and retinal capillaries. Electroretinographic and electro-oculographic findings were identical to that described in Case 3.

On 22 February 1977, visual acuity in the right eye was counting fingers and in the left eye was 6/6. Funduscopic examination of the right eye revealed 3+ optic atrophy, marked narrowing of the retinal vessels, widespread irregular areas of pigment epithelial mottling, and focal atrophic changes in the pigment epithelium throughout the peripheral fundus. The yellow-white lesions noted previously appeared atrophic and were partly replaced by mottled pigment. Several atrophic lesions were present in the macula where no lesions were visible originally (Figure 4F). There was increased atrophy of the pigment epithelium along the temporal margin of the optic disc. A repeat fluorescein angiogram showed evidence of increased retinal circulation time and an increase in the degree of mottled depigmentation of the pigment epithelium in the right eye. The left eye was normal. The central macular area, however, was still relatively spared. Electroretinographic findings in both eyes were unchanged.

Case 5

B F, a girl aged 14 years, had 20/20 vision in both eyes on a school screening examination in November 1974. In February 1975, severely diminished vision was discovered in the left eye on a routine eye examination. Both fundi were normal. She was hospitalized for 11 days. Multiple ocular and neurologic studies including lumbar puncture, brain scan, skull X-rays, electroencephalography, and ultrasonography were normal. A diagnosis of optic neuritis was made and systemic corticosteroids were given. Her past medical history and family history

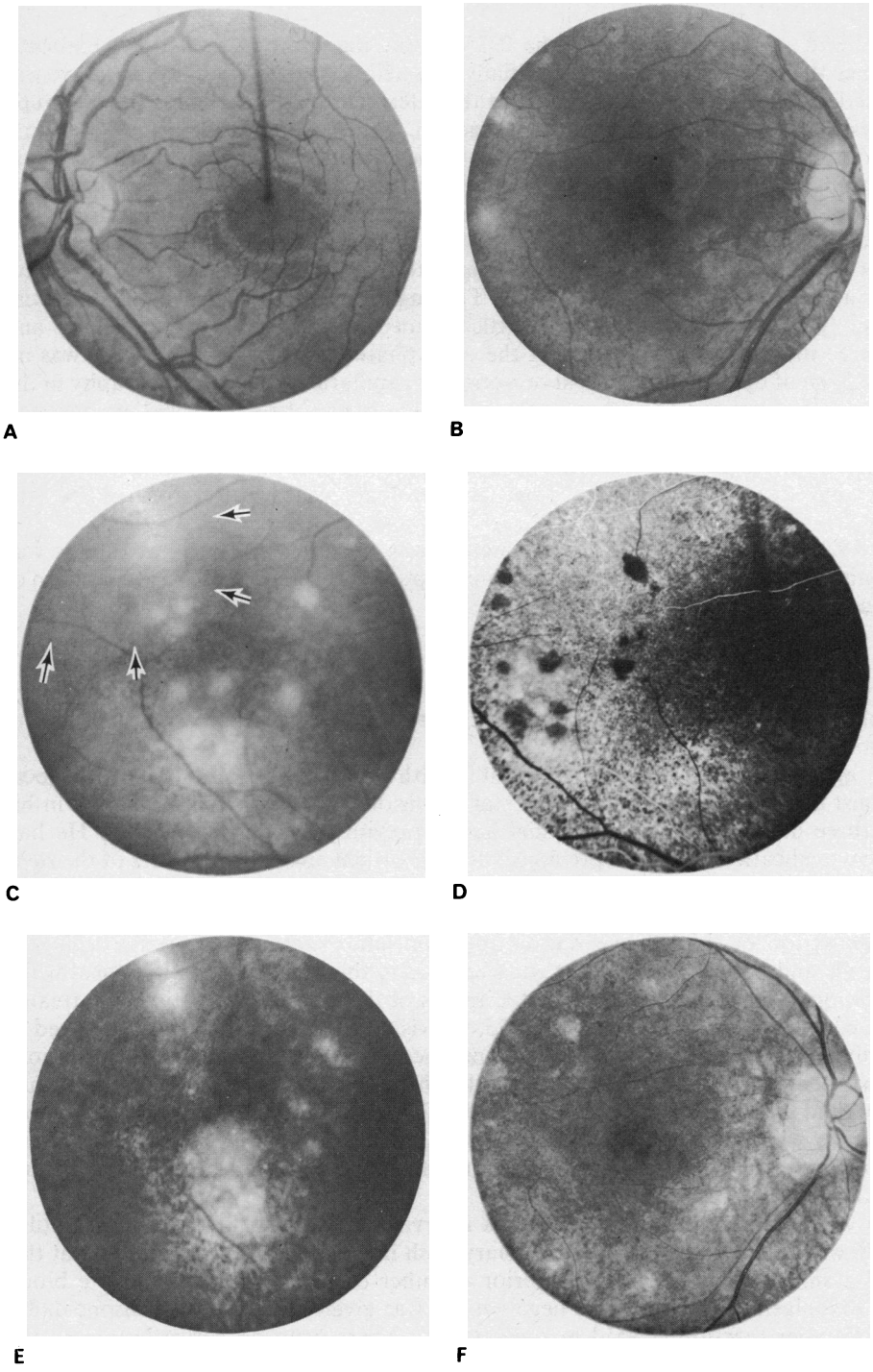


Figure 4. Case 4. A, left eye (December 1974); B, right eye (December 1974); C, right eye (December 1974) with arrows indicating area of serous retinal detachment; D, early angiogram right eye (December 1974); E, late angiogram right eye (December 1974); F, right eye (February 1977)

were negative. She was seen here on 25 June 1975, stating the vision in the left eye had been unchanged since the subnormal vision was initially detected. Visual acuity in the right eye was 6/6 and in the left eye was hand movements in the inferotemporal field only; the left pupil reacted sluggishly; there was a Marcus Gunn reaction. The right eye was normal. Slit-lamp examination of the left eye revealed numerous cells in the vitreous; the optic disc was of normal colour and configuration; the retinal arteries were slightly attenuated. There were diffuse changes in the retinal pigment epithelium similar to those described in the previous case except that peripheral coarse pigmentary and atrophic lesions were not evident.

Fluorescein angiography revealed dye appearing in the choroidal vessels at 11 seconds and retinal vessels at 14 seconds following injection. The angiogram was unremarkable otherwise except for the presence of abnormally mottled hyperfluorescence in the macular and perimacular area in the left eye only during the early phases of angiography. There was no evidence of leakage of dye from the retinal or optic disc capillaries. Electroretinography in the left eye showed abnormal rod and cone function with the b-wave being affected greater than the a-wave. The right eye was normal. Electro-oculography in the left eye was definitely abnormal and in the right eye was normal. Serologic studies for toxoplasmosis, coccidiomycosis, and histoplasmosis were negative. Serologic examination for rubella was positive.

In August 1975 and March 1977, visual function was unchanged. The right fundus was normal. Examination of the left fundus revealed mild optic atrophy and marked attenuation of all of the retinal vessels.

Case 6

This patient was not examined here, but his eye was recently received in our eye pathology laboratory for routine processing. I wish to present the results of the preliminary histologic and electron microscopic findings.

Mr T H, aged 17 years, was in excellent health when seen initially by his local ophthalmologist on 23 July 1975, because of blurred vision, redness and photophobia in his right eye of three days' duration. The visual acuity previously had been normal. He had received topical medications six years previously for a transient episode of redness of the right eye; his vision at that time was normal. His past medical history and family history were otherwise unremarkable. Visual acuity in the right eye was counting fingers and in the left eye was 6/5. Examination of the left eye was normal. Slit-lamp examination of the right eye revealed 3+ cells and flare in the anterior chamber and in the vitreous. Multiple focal white fluffy retinal lesions were described in the midperiphery of the fundus. The patient was treated with systemic corticosteroids. On 1 August 1975, the vision in the right eye had improved to 6/120. In addition to the multifocal active lesions, there were multiple punched-out lesions noted in the periphery. A diagnosis of probable active histoplasmosis was made. By 15 August 1975 the vision had improved to 6/60. Many of the active lesions had faded. On 20 September 1975, visual acuity was reduced to counting fingers at 3 ft (0.9 m). There was no change in the appearance of the fundus. The vitreous cellular reaction was graded as 1+. There was no explanation at that time for his decreased vision.

The patient was followed at two to three week intervals without significant change until 2 February 1976 when he developed pain and ciliary flush in the right eye. Examination at this time revealed a small hypopyon in the anterior chamber of the right eye; complete blood counts and a toxoplasmin dye titre were negative. He was given 100 mg of prednisone daily; the anterior chamber reaction cleared in several days. There were no active lesions in the fundus at that time. He returned on 1 June 1976 with a second episode of pain, ciliary flush, and a small hypopyon. This responded promptly to sub-Tenon's injections of corticosteroids. The patient was referred to the Medical College of Georgia, as well as to other consultants. His visual acuity remained at counting fingers only. The view of the right fundus was partly

obstructed by the continued vitreous inflammatory reaction. Focal grey retinal lesions were again described in the midperiphery of the fundus of the right eye. An electroretinogram in the right eye was extinguished; it was normal in the left eye. Ultrasonography revealed no evidence of an intraocular tumour or retinal detachment; X-rays of the orbit were negative; purified protein derivative tuberculin, histoplasmin, and toxoplasmin skin tests were negative; complete blood counts, blood chemical analysis, and LE prep were negative. He continued to receive sub-Tenon's injections of corticosteroids. The vitreous reaction cleared.

On 1 July 1976, pallor of the optic disc, sheathing of the major retinal vessels, and depigmentation along the temporal margin of the optic disc were described. No active lesions were visible in the fundus at that time. On 25 October 1976 the patient had recurrence of pain and redness associated with a small hypopyon. The vision was light perception only. For the first time in the course of his disease, the intraocular pressure was elevated (56 mm Hg). He had a 15% hyphema and multiple keratic precipitates. The fundus could not be visualized. The following day the hyphema was gone; gonioscopy failed to reveal the source of the hyphema. Within several days the intraocular pressure was normal. The patient continued to have pain and light perception only. The eye was enucleated on 3 November 1976 and was fixed in formalin.

Gross examination: The right eye, which measured $24 \times 24 \times 26$ mm, was sectioned vertically. The inside of the eye appeared normal.

Microscopic examination: The cornea and anterior chamber depth were normal. The angle was open and in some areas there were melanin-laden macrophages in the trabecular meshwork. There was mild lymphocytic and plasma cell infiltration of the iris and ciliary body. The lens was normal. There were a few red blood cells and many scattered macrophages, some of which contained melanin pigment in the vitreous cavity. There were many clumps of inflammatory

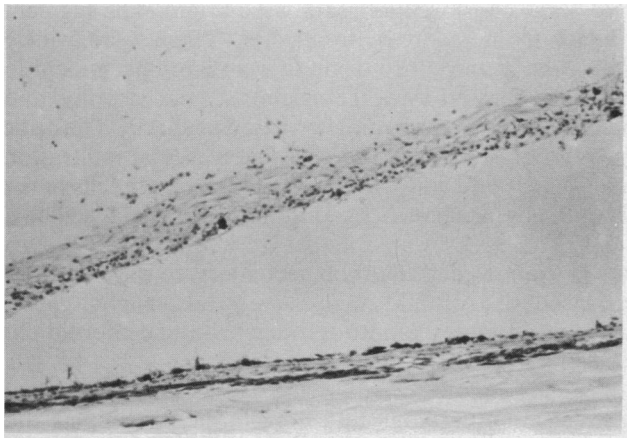


Figure 5. Case 6, peripheral retina showing extensive degeneration, gliosis, inflammatory cell infiltration and pigment-laden macrophages. Note inflammatory cells in the vitreous and the irregular depigmentation of the pigment epithelium. ($\times 85$)

cells along the inner retinal surface (Figure 5). The midperipheral and peripheral retina showed extensive degeneration, gliosis, inflammatory cell infiltration, loss of ganglion and receptor cell layers, intraretinal migration of melanin pigment and thickening of the retinal vessel walls (Figure 5). Inferonasally, there was a small focal area of interretinal haemorrhage. Posteriorly, there was gliosis and lymphocytic and plasma cell infiltration of the retina. This was most prominent in the inner retinal layers. There was striking lymphocytic and plasma cell

infiltration of the retinal vessel walls and perivascular tissue (Figure 6); this was particularly prominent in the peripapillary and macular region. There were multiple focal, atrophic, and gliotic scars, some involving the outer half and others the full thickness of the retina. There was partial loss of the ganglion cell layer and receptor elements posteriorly; this was least evident in the macular area where the retinal architecture was well preserved. There was minimal evidence of cyst formation in the outer plexiform layer. Scattered within the ganglion cell layer posterior

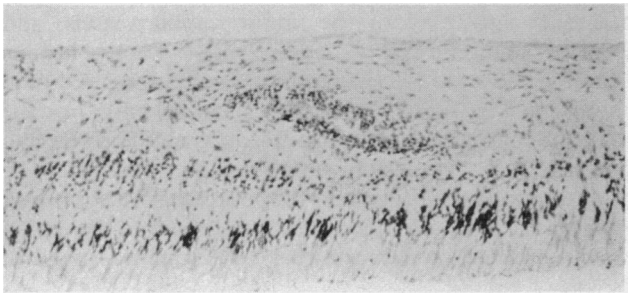


Figure 6. Case 6, posterior retina, nasal to optic disc. Note perivascular inflammatory cell infiltration. (× 85)

to the equator, there were large cells with pale eosinophilic cytoplasm and large, well-defined, irregular rounded, homogeneous, purple nuclei. Some of these cells appeared to contain intranuclear and intracytoplasmic inclusions. A few of these cells were also present in the bipolar layer. The retinal receptor elements were intact throughout the posterior pole of the eye. The pigment epithelium in the peripheral fundus was generally thinned and irregularly depigmented and hyperpigmented (Figure 5). It was, however, intact even underlying focal areas of retinal atrophy and gliosis. No focal chorioretinal scars were found. The pigment epithelium appeared within normal limits in most areas posteriorly. There were widely scattered small foci of lymphocytic infiltration in the choroid; these were more prominent in the peripheral choroid. The optic nerve head showed evidence of gliosis, mild atrophy, and lymphocytic and plasma cell infiltration of the blood vessels and perivascular spaces. The optic nerve posterior to the lamina cribrosa was mildly atrophic. There was perivascular infiltration of lymphocytes around the central retinal vessels and a few scattered inflammatory cells in the meninges surrounding the anterior part of the optic nerve. Special stains for bacteria, acid fast bacilli, fungi and iron were negative.

The histopathologic diagnoses were: (1) retinal degeneration secondary to chronic nongranulomatous retinitis and retinal perivasculitis; (2) mild optic nerve head atrophy, gliosis and perivasculitis; (3) vitritis; (4) mild chronic nongranulomatous iridocyclitis and choroiditis; (5) possible intranuclear and intracytoplasmic viral inclusions in the retina.

Preliminary electron microscopic examination of formalin-fixed tissue failed to reveal evidence of a viral infection. Following enucleation, serologic tests done for herpes simplex and herpes zoster were negative. The cytomegalovirus titre of 1:128 suggested infection at some undetermined time with cytomegalovirus.

Comment: The recurrent complications developing in the anterior segment of this eye during the several months prior to enucleation are difficult to explain in view of the minimal histopathologic changes found anteriorly. There was minimal evidence of uveal inflammation or postinflammatory damage to the uveal tract. Equally puzzling is the lack of correlation between the patient's low visual function and the minimal loss of neural elements at the posterior pole or in the optic nerve. The loss of visual function in this patient has to be explained partly on a pathophysiologic, and not solely on a morphologic, basis. The loss of

neural elements in the peripheral retina is probably adequate to account for a subnormal, but not an extinguished, electroretinogram. The changes in the pigment epithelium peripherally are compatible with the pigmentary changes found in the periphery of the other 25 patients. Failure to find histologic evidence of focal areas of choroidal atrophy underlying focal areas of peripheral retinal atrophy in this patient suggests that the atrophic lesions seen in this patient were primarily lesions affecting the pigment epithelium and retina. This is not the case in the presumed ocular histoplasmosis syndrome where the peripheral punched-out lesions seen clinically have been demonstrated histopathologically to be focal atrophic chorioretinal scars surrounded by choroidal lymphocytic infiltration (Gass 1976). Failure to detect definite histopathologic abnormalities in the pigment epithelium in the macular area is also compatible with the mild colour change and pigment derangement seen clinically in these patients. Failure to find more than moderate loss of the peripheral ganglion cells and minimal evidence of optic atrophy histologically in the presence of severe visual loss is perhaps in keeping with the minimal optic atrophy and severe visual loss seen in some of these patients, e.g. Cases 1, 2 and 5, during the later, as well as early stages of the disease. While the severity and frequency of recurrent bouts of iridocyclitis in this patient are atypical, the clinical history and anatomic findings suggest that this patient had the same disease as the 25 patients presented in this report. Further histopathologic and electron microscopic studies are in progress and the results will be the subject of a future communication.

Discussion

We have chosen to call this clinical syndrome 'diffuse unilateral subacute neuroretinitis' (DUSN), because evidence to date suggests that inflammation affecting primarily the retina, retinal blood vessels, pigment epithelium and optic nerve head, is the cause of progressive visual loss occurring over a period of several months or more. The patient is usually asymptomatic until visual loss is discovered on a routine eye examination. A few patients, usually because of signs or symptoms of iridocyclitis, present during the early course of the disease. Inflammatory cell infiltration of the vitreous, mild optic disc swelling, slight narrowing of the retinal arterial tree, and mild changes in the retinal reflex and colour of the pigment epithelium are the earliest signs of DUSN. All these signs may escape detection unless careful biomicroscopic and fluorescein angiographic comparison of the two eyes is done. At this stage the disease may be misdiagnosed as amblyopia ex anopsia, retrobulbar neuritis or visual loss caused by a lesion affecting the posterior optic pathways. Electroretinography in the affected eye is usually subnormal and is valuable in making the correct diagnosis.

The finding of multiple grey or yellow-white retinal or chorioretinal lesions, usually in the mid or far periphery of the fundus, is another sign of early development of this disease. These lesions are probably focal active areas of retinal and choroidal inflammation and they probably are the precursors of focal, flat, atrophic scars that frequently accompany the active lesions, and that are found in most patients with later stages of the disease. The active lesions of DUSN may be mistaken for other causes of focal retinitis, e.g. toxoplasmosis, monoliasis or chorioretinitis, caused by histoplasmosis, sarcoidosis or other granulomatous diseases. While the multiple, focal, atrophic lesions may simulate those seen in the presumed ocular histoplasmosis syndrome, in patients with DUSN they are always associated with irregular diffuse changes in the pigment epithelium separating the lesions. Because the lesions of DUSN involve the deep retinal layers and the pigment epithelium, they may simulate the active, flat, grey-white, placoid lesions of acute posterior multifocal pigment epitheliopathy (Gass 1968) or serpiginous choroiditis (Hamilton & Bird 1974, Chisholm, Gass & Hutton 1976). All of the above simulating lesions typically cause marked loss of vision only when the lesion involves the central macular area. The active lesions in DUSN are typically smaller and cause less retinal necrosis and haemorrhage than those seen in cytomegalic inclusion disease and subacute sclerosing panencephalitis.

Information concerning the natural course of this disease is incomplete. Visual loss may be marked during the early stages of the disease in the presence of minimal funduscopic changes. Although visual function may improve temporarily after systemic corticosteroid therapy, the prognosis for permanent improvement in vision is poor. Optic atrophy may not develop for a period of six months or longer after onset of visual loss; it varies in degree and may be minimal in some patients with marked loss of visual function. The duration of the active disease and the rate of its progression appear to be variable. Remissions and exacerbations may occur and visual loss may progress one to two years following the onset of symptoms. To date, none of the 25 patients has developed evidence of the disease in the second eye. Bilateral involvement probably does occur occasionally. Patients with second eye involvement occurring simultaneously with or soon after that in the first eye might be difficult to distinguish from patients with a rapidly progressing tapetoretinal dystrophy.

After developing optic atrophy and retinal arterial narrowing and sheathing, patients with DUSN may be misdiagnosed as having unilateral retinitis pigmentosa, post-traumatic chorioretinopathy and optic neuropathy, occlusive vascular disease affecting the ophthalmic artery, or toxic retinopathy and optic neuropathy.

In DUSN, features that are atypical for retinitis pigmentosa include: absence of a positive family history; presence of subnormal, but not extinguished, ERG; absence of bone corpuscular pattern of pigment migration; severe degree of optic atrophy and marked retinal vascular narrowing and sheathing that occurs in some patients; absence of posterior subcapsular cataract; marked decrease in visual acuity in the absence of evidence in the macula of advanced changes in the pigment epithelium or cystic changes; and failure of patients to show progression of the disease beyond one to two years.

The absence of a positive family history and failure of the disease to progress are recognized features of unilateral retinitis pigmentosa (Francois & Verriest 1952, Kolb & Galloway 1964, Carr & Siegal 1973). We believe that many cases previously reported as unilateral retinitis pigmentosa had DUSN.

While blunt trauma may produce optic atrophy and occasionally large areas of chorioretinal atrophy, it infrequently causes both in the same eye in the absence of a clear-cut history of trauma and visual loss. Only 4 of 25 patients with DUSN gave a history of trauma, and in each case visual loss was detected months or years later. There was no other evidence (anterior chamber angle recession, cataract or choroidal rupture) to suggest ocular trauma in these patients.

The funduscopic findings in DUSN cannot be explained on the basis of occlusive vascular disease affecting either the retinal or choroidal circulation alone. Occlusion of the ophthalmic artery, caused by inflammatory diseases such as cranial arteritis or by compression during anaesthesia for neurosurgical operations (Hollenhorst *et al.* 1954), may cause a funduscopic picture which resembles that in DUSN. The spontaneous occurrence of ophthalmic artery occlusion in otherwise healthy children or young adults is unlikely. The relative sparing of the pigment epithelium in the macular area characteristic of DUSN is difficult to explain on a choroidal vascular basis. We found no definite fluorescein angiographic evidence that the choroidal circulation was affected by this disease. While we found a delay in the retinal artery appearance time in 9 of 14 patients, this usually occurred in patients with more severe optic atrophy and retinal-vessel narrowing and it may, therefore, be the result rather than the cause of retinal damage. There was no history or clinical findings of an intraocular foreign body in any of the patients with DUSN. None of the patients gave a history of ingestion of a retinotoxic substance.

The findings of vitreous cellular infiltration, focal grey-white retinal lesions progressing to atrophic scars, and the occasional signs of iridocyclitis during the early stage of DUSN suggest an inflammatory basis for the disease. The confinement of the disease to one eye of a healthy individual does not exclude the possibility of an infectious aetiology, viz., herpes simplex or

herpes zoster. In only 3 of 25 patients was a systemic illness (rubeola and chickenpox) temporally related to the discovery of visual loss. None gave a history of herpetic ocular infection. Only limited serologic studies for viral infection in these patients have been done and they have not demonstrated a cause for the disease.

While Case 6 had unusually severe signs and symptoms of iridocyclitis, the clinical and anatomical changes observed in the eye are consistent with DUSN. They suggest that the primary locus of the disease is in the retina and, to a lesser extent, the optic nerve head. The vitreous and the uveal tract may be only secondarily involved. The failure of some patients to develop optic atrophy in the presence of profound visual field loss suggest that the destruction of the ganglion cells and nerve fibre layer does not alone account for the visual loss. Failure of the patients to develop marked changes in the pigment epithelium in the macular area further suggests that destruction of the rods and cones is also not a major cause of loss of central vision. As was demonstrated in Case 6, the explanation for the visual loss in these patients cannot be fully explained on morphologic changes present in the retina or optic nerve.

The development of the clinical picture of Fuchs's heterochromic iridocyclitis in the affected eye of one patient with DUSN nine years after the onset of visual loss, raises the question of a possible common aetiologic factor in the two diseases.

The value of systemic corticosteroid therapy is unknown. It probably should be employed in high doses in the management of the early stages of the disease. If no improvement in visual field occurs after several weeks of therapy, the therapy probably should be tapered and discontinued. If a therapeutic response occurs, it may be necessary to keep the patient on long-term therapy, since there is evidence that field loss can continue to progress for at least a year or more.

Acknowledgment: Electron microscopy was done by Dr Harry Quigley.

Addendum

Since submitting this paper for publication, we have studied 12 additional patients with DUSN and have observed a viable subretinal nematode, probably Toxocara canis, moving in the subretinal space of the affected eye of 2 patients during the early stage of the disease. Evidence that migration of a single nematode in the subretinal space for months or even years is responsible for the clinical syndrome of DUSN was reported in October 1977 at the American Academy of Opthalmology and Otolaryngology.

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