MACULAR AND PARAMACULAR DETACHMENT OF THE NEUROSENSORY RETINA ASSOCIATED WITH SYSTEMIC DISEASES*

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INTRODUCTION

SEROUS RETINAL DETACHMENT (SRD) IN THE MACULAR REGION MAY DEVELOP AS A result of trauma, uveitis, optic neuritis, optic pit, and other conditions.[1,2] In addition to these well-recognized disorders, there is a group of patients in whom transient episodes of SRD of the macula develop that are not presently associated with any recognized ocular or systemic disease. This group represents the clinical syndrome known as idiopathic central serous choroidopathy (CSC).[2] The systemic implications of CSC are not known. Many reports have dealt with this without satisfactory evidence that there is a specific association between CSC and a systemic disease.[1,3,4]

This paper is a retrospective review of 168 cases of angiographically proved SRD of the macular region of unknown etiology that were seen at The Cleveland Clinic Foundation between 1971 and 1980. The associated systemic diseases were identified.

Nine patients who had SRD of the posterior pole and subjective visual symptoms that appeared to correlate with an exacerbation of their systemic diseases were included in the category of autoimmune disorders. Im-

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mune complexes have been implicated in the pathogenesis of these diseases. There have been few reports[5-8] of SRD in patients with autoimmune diseases, and only one report implicates immune complexes in the pathogenesis of SRD.[7] In none of the patients with other systemic diseases were we able to demonstrate an association between the systemic disease and SRD.

MATERIALS AND METHODS

The profile of 168 patients with SRD of unknown etiology is as follows: More than 80% of the patients were men, 94% Caucasians, 2.9% blacks, and 2.9% orientals. The age range was from 20 to 60 years; more than two-thirds were between 35 and 50 years old; 7.1% of the patients had bilateral SRD of the macular regions. Thirty-seven percent of the patients had an associated systemic illness. The most common was cardiovascular disease, and most of these patients were being treated for hypertension. The following case reports describe patients with autoimmune diseases who had SRD during an exacerbation of their disease.

CASE REPORTS

RHEUMATOID ARTHRITIS

CASE 1

A 39-year-old white man had a diagnosis of rheumatoid arthritis after development of severe inflammatory synovitis, positive rheumatoid factor, and HLA-B-27 tissue typing. No extraarticular manifestations were reported. He had been treated with prednisone, aspirin, and hydroxychloroquine. A total dose of 21 mg of intravenous nitrogen mustard was given for a severe exacerbation. On January 13, 1972, five days after nitrogen mustard treatment was begun, he was seen in The Cleveland Clinic Foundation Department of Ophthalmology. He complained of blurred vision OD of three weeks' duration. Vision was 20/70 OD and 20/20 OS. He had a central scotoma OD on the Amsler grid. Slit-lamp examination was normal. Fundus examination of the right eye revealed a large SRD of the macula with subretinal precipitates. A fluorescein angiogram revealed a large SRD without evidence of any focal leak. On February 24, 1972, vision was 20/50 OD and 20/20 OS with persistent macular SRD. An active leak was noted on fluorescein funduscopy and laser photocoagulation was performed. Follow-up examination and fluorescein angiography in March 1972 revealed no SRD. While the patient had SRD the arthritis was active. He received intramuscular injections of ACTH, triamcinolone acetonide (Kenalog), methotrexate, and thiotepa during this period. He was last seen in September 1977. His vision was 20/20 OU with mild

retinal pigment epithelium disturbance in the right macula. The arthritis was stable, and hydroxychloroquine had been discontinued.

CASE 2

A 52-year-old white man had a diagnosis of seropositive rheumatoid arthritis since 1965; the disease had been well controlled until exacerbations began monthly in August 1973. He received a course of intravenous nitrogen mustard therapy in December 1973 and was maintained on prednisone, hydroxychloroquine, aspirin, methotrexate, folate, and indomethacin. On February 25, 1974, he was seen with blurred central vision in the right eye of one day's duration. Vision was 20/20 − 3 OD and 20/20 OS. Slit-lamp examination showed mild hydroxychloroquine keratopathy. There were faint posterior subcapsular changes in both lenses. Fundus examination revealed a shallow serous detachment in the macula OD. On March 4, 1974, vision was 20/30 − 2 OD and 20/20 OS with bilateral SRD. A fluorescein angiogram revealed bilateral focal choroidal leakage within the areas of SRD (Fig 1 and 2). On March 26, 1974, vision was 20/70 OD and 20/20 OS. Fluorescein angiography revealed a persistent leak OD and no choroidal leakage OS. In May 1974, vision was 20/60 OD and 20/20 OS with persistent SRD of the right macula.

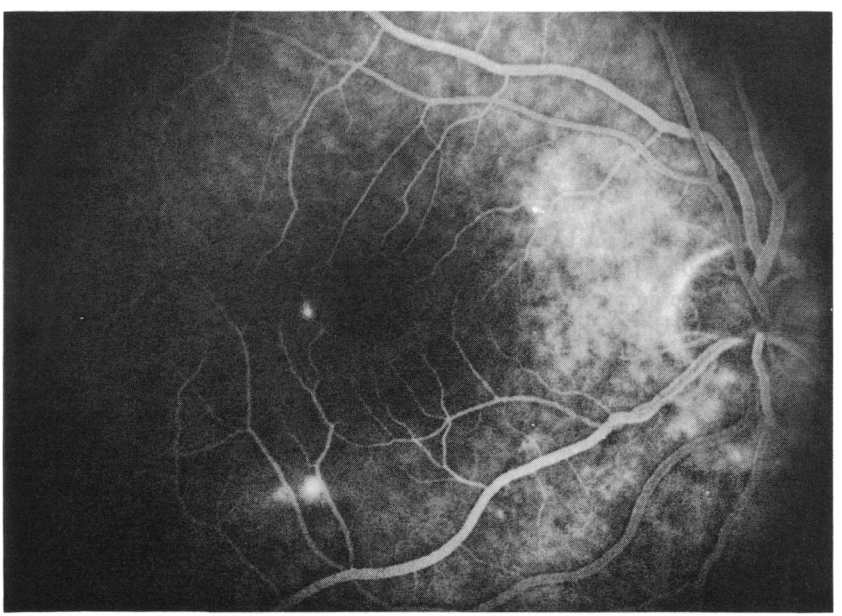


FIGURE 1
Fluorescein angiogram of right eye obtained on March 4, 1974. This late venous phase angiogram documents three focal choroidal leaks and staining within the area of SRD of the right macula. Vision was 20/30.

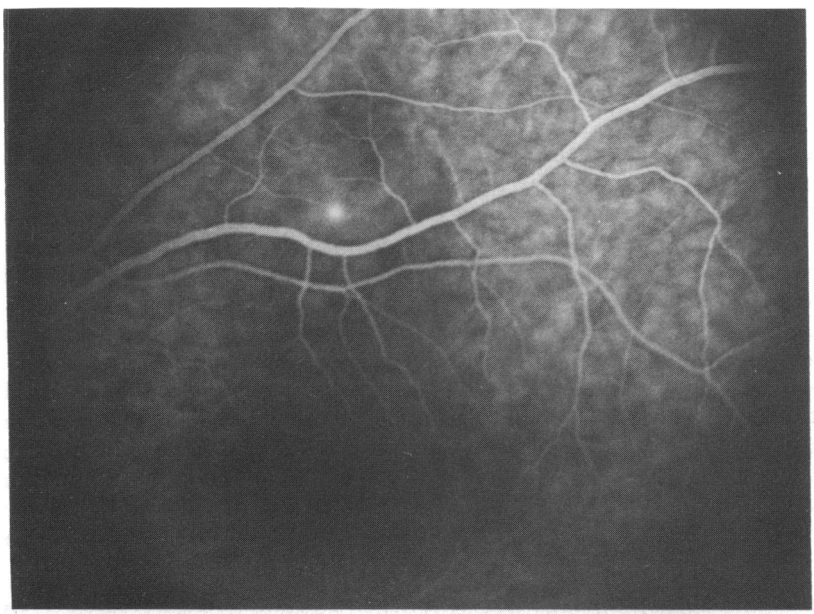


FIGURE 2
Fluorescein angiogram of left eye obtained on March 4, 1974. Late venous phase angiogram documents a focal choroidal leak and staining within area of SRD beneath superotemporal vessels. SRD was approximately 1.5 disc diameters in size and did not extend into macula. Vision 20/20.

Photocoagulation of the areas of leakage in the right eye was performed, and the SRD resolved by June 14, 1974. In February 1980, his vision was 20/20 OU, and there has been no recurrence of SRD.

During the course of SRD, the rheumatoid arthritis was active, and the rheumatoid factor was positive at 1:2,560. Despite intraarticular injections of thiotepa and triamcinolone acetonide, exacerbations continued, and by August of 1975 he was considered effectively disabled with active rheumatoid arthritis. With the addition of azathioprine the disease became relatively inactive by July 1976.

CASE 3

A 37-year-old white woman had rheumatoid arthritis diagnosed in 1968 after development of inflammatory polyarthritis. She has had intermittent exacerbations since 1968. She was treated with prednisone, aspirin, and hydroxychloroquine. Methotrexate was added in 1971. Laboratory studies on February 9, 1972, included a rheumatoid factor positive at 1:640, a weakly positive antinuclear factor, and a negative LE test. She was examined on February 7, 1972, and complained of decreased vision in her left eye for three months. Vision was 20/20

OD and 20/30 OS. Fundus examination revealed SRD involving the left macula. A fluorescein angiogram performed on February 8, 1972, showed a focal choroidal leak approximately 3 mm above the left macula. This patient failed to return for a follow-up examination.

SYSTEMIC LUPUS ERYTHEMATOSUS

CASE 4

A 31-year-old white woman had a diagnosis of systemic lupus erythematosus (SLE) confirmed in 1960 at age 17. The findings included migratory, nondeforming polyarthritis, pleuritis, rash, proteinuria, and a positive LE cell preparation. Initial treatment consisted of a single course of nitrogen mustard and a maintenance dose of prednisone. In October 1973, hypertension and azotemia developed, and membranous glomerulonephritis was diagnosed on renal biopsy. Prednisone (20 mg per day) and azathioprine (75 mg per day) were initiated, and her blood pressure (180-190/110-130 mm Hg) was poorly controlled despite maximal therapy.

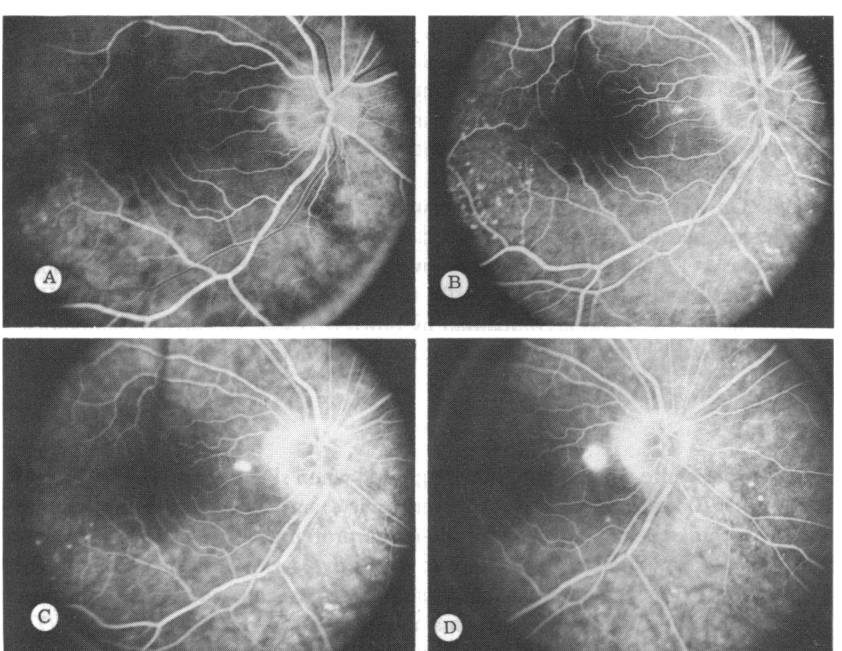


FIGURE 3

Case 4. Sequence of fluorescein angiograms of right eye obtained on December 18, 1973 (A-D). Focal choroidal leak with late staining is seen between temporal edge of the disc and the macula. Leak was within area of overlying serous retinal detachment. Visual acuity 20/30.

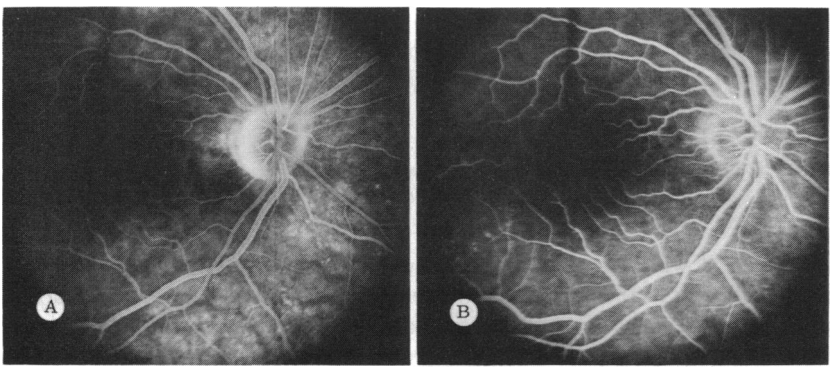


FIGURE 4
Case 4. Fluorescein angiograms of right eye obtained on February 28, 1974. The choroidal leak, which was evident in Figure 3A-D, is no longer present. SRD had resolved and visual acuity was 20/25 OD.

She was examined in the Department of Ophthalmology on December 4, 1973. She complained of blurred vision OU of approximately five to six weeks' duration. Her blood pressure on that day was 184/110 mm Hg, and her vision was 20/30 − 1 OD and 20/20 − 2 OS. Slit-lamp examination was normal. Fundus examination revealed SRD in the right peripapillary area. On December 18, 1973, fluorescein angiography revealed SRD with focal choroidal leakage (Fig 3A-D). On December 23, 1974, vision was 20/30 OD and 20/20 − 2 OS. The SRD was no longer present. On February 28, 1974, vision was 20/25 OU. Fluorescein angiography revealed no choroidal leakage (Fig 4A and B). Other systemic problems, including blood pressure, improved over the 12-week period of observation. Her blood pressure returned to a 120-150/78-100 mm Hg range. Another flare of SLE occurred in 1975 and was accompanied by blurred vision, but no ophthalmologic examination was performed. The patient has been on chronic hemodialysis since 1975.

CASE 5

A 29-year-old white woman had SLE diagnosed when she came to The Cleveland Clinic in 1970 with malar rash, sun sensitivity, and polyarthritis. Laboratory findings included leukopenia, nephrotic-range proteinuria, an antinuclear factor positive at serum dilution of 1:160, and a positive LE cell preparation. Renal biiopsy revealed focal glomerulonephritis. She was treated acutely with nitrogen mustard and ACTH and was placed on a maintenance regimen of prednisone (7.5 mg per day), hydroxychloroquine (200 mg per day), and methotrexate (7.5 mg per week). Aseptic necrosis of the right hip in May 1977 required total hip replacement, and a second biopsy of her kidney revealed membranoproliferative glomerulonephritis. Azathioprine (50 mg per day) was initiated. From October 1977 to August 1979 the renal disease rapidly progressed with worsening hypertension

and declining creatinine clearance values. On August 20, 1979, the patient was seen in the Department of Ophthalmology with a complaint of blurred vision OS of approximately ten days. Vision was 20/20−1 OD and 20/40 OS. Slit-lamp examination was normal. Fundus examination revealed a SRD of the left macula with areas of pigment clumping beneath the left superior temporal vascular arcade. Fluorescein angiography performed on the left eye revealed several focal areas of choroidal leakage (Fig 5A-C). Her blood pressures on that day were 224/120 mm Hg supine and 220/124 mm Hg standing. Her blood urea nitrogen (BUN) was 50 mg/dl, and creatinine was 3.7 mg/dl. She was admitted on August 31, 1979, with a flare of SLE and hypertensive crisis that was controlled with 100 mg boluses of diazoxide intravenously and 1 gm IV pulses of methylprednisolone given on two consecutive days. Her blood pressure returned to a normal 120/80 mm Hg. Reexamination on September 11, 1979, revealed no SRD, and no choroidal leaks were seen in repeat fluorescein angiography (Fig 6A-C). In January 1980, the hypertension was again uncontrolled (220/120 mm Hg). On February 4, 1980, vision was 20/20 OD and 20/60−1 OS. Fundus examination revealed a recurrent SRD of the left macula. Fluorescein angiography revealed multiple choroidal leaks within the area of SRD. The patient's blood pressure was normal by the fourth hospital day with the addition of minoxidil. She was given intravenous therapy, 1 gm of methylprednisolone for four consecutive days, but the BUN and creatinine level rose to 69 mg/dl and 7.4 mg/dl respectively. On February 14, 1980, her vision was 20/20 OD and 20/60 OS, but the SRD of the left macula had resolved. The blood pressure remained controlled, but renal failure progressed and hemodialysis was required in September 1980.

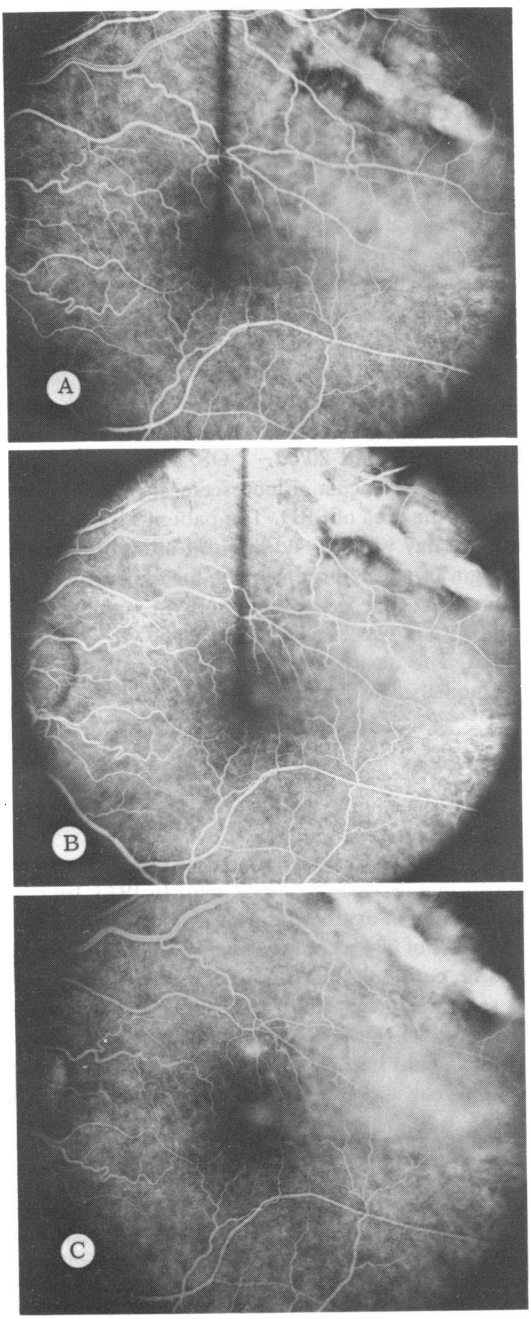
CHRONIC ACTIVE HEPATITIS

CASE 6

In July 1972 a liver biopsy confirmed a diagnosis of chronic active hepatitis with postnecrotic cirrhosis in a 28-year-old white man. In 1973, his examination at The Cleveland Clinic Foundation explored the cause of the liver disease and revealed alpha-1-antitrypsin level of 624 μg/ml (normal, 800-1,300), negative LE preparation, negative HBsAg, ceruloplasmin 20 mg/dl (normal, 20-35), antinuclear factor positive at 1:160 serum dilution, antismooth muscle antibody positive at 1:160 serum dilution, negative antimitochondrial antibody, and serum IgG was 500% above normal. He had mild hepatosplenomegaly, and esophagogastroduodenoscopy revealed esophageal varices. He was treated orally with prednisone and

FIGURE 5

Case 5. Angiograms (A-C) of left eye obtained on August 20, 1979. Multiple focal choroidal leaks with staining evolved in macular and paramacular areas. Diffuse hyperfluorescence temporal to macula indicates some fluorescein leakage into subretinal space. Superior and temporal to macula is an area of RPE disturbance with pigment clumping and some choroidal atrophy. This sequence documents the presence of multiple sites of choroidal fluorescein leakage within the area of SRD. Systemic blood pressure was 224/120 mm Hg at this time.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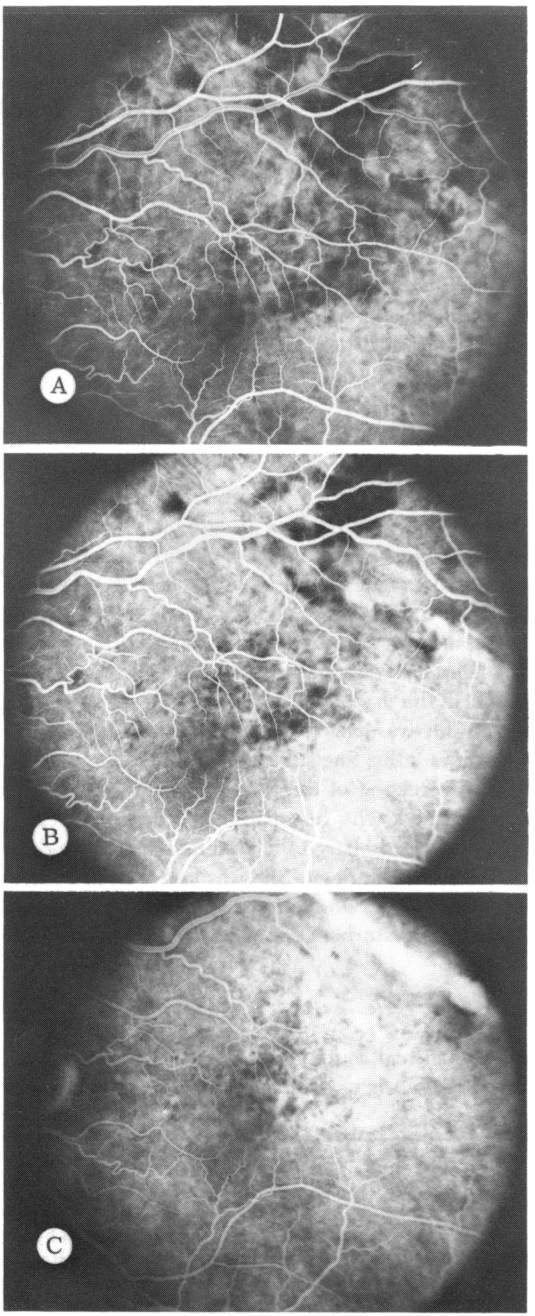
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azathioprine. An exacerbation of the disease occurred in 1974, and it was necessary to increase the dosage of steroid. In September 1976 the patient's antinuclear factor increased to 1:800 serum dilution, and IgG remained elevated. His LE preparation was 2+. The patient complained of episodic blurred vision in the right eye from 1974 to 1976. Ophthalmologic examination on December 14, 1976, revealed visual acuities of 20/25 + 1 OD and 20/20 − 1 OS. His fundus examination revealed a localized SRD in the right macular region. Fluorescein angiography revealed no leaks. A small hyperfluorescent area seen on the angiogram within the area of SRD corresponded to retinal pigment epithelial changes in the fundus color pictures. The patient was not reexamined in the Ophthalmology Department. He died six months later with refractory hepatic encephalopathy. Autopsy showed severe hepatic cirrhosis.

INFLAMMATORY BOWEL DISEASES

CASE 7

A 20-year-old white woman with Crohn's disease had been maintained on prednisone since age 16. She had an exacerbation of Crohn's disease manifest by nausea, diarrhea, cramping, and weight loss in late March 1978. On April 12, 1978, she complained of blurred vision in her right eye of one months' duration. A subjective paracentral scotoma was recorded in the right eye with vision of 20/25 OD and 20/20 OS. Slit-lamp examination was normal, and examination of the fundus revealed a small SRD in the macula OD. Fluorescein angiography revealed a faint choroidal leak within the avascular fovea. The eye findings remained unchanged during the subsequent months. She suffered flares of inflammatory bowel disease. On August 2, 1978, a resection of the terminal ileum with end-to-side ileocolic anastomosis was performed. The histopathologic findings were consistent with Crohn's disease. Following discharge the systemic symptoms decreased, and the prednisone was gradually withdrawn. She was last seen in September 1979, and vision was 20/20 OD and 20/15 OS. Fundus examination of the right eye showed retinal pigment epithelial disturbance in the macula without SRD.

CASE 8

A 49-year-old white man had acute gastrointestinal symptoms in June 1976 and had a biopsy-proved diagnosis of ulcerative colitis. He was symptomatic for the

FIGURE 6

Case 5. Fluorescein angiograms of left eye obtained on September 11, 1979, following normalization of blood pressure to 120/80 mm Hg (A-C). Photographs are of same area as recorded in Figure 5A-C. There is evidence of multiple focal areas of hyperfluorescence due to RPE disturbance and pigment clumping. No active leaks or late staining are noted. This series of angiograms documents the cessation of choroidal leakage, which correlates with the resolution of SRD.

next two years and was treated with sulfasalazine and prednisone (25 mg per day). On December 5, 1978, he was examined in the Ophthalmology Department. He complained of blurred vision OS of two weeks' duration. Vision was 20/20 − 2 OD and 20/30 + 2 OS. Slit-lamp examination was normal. Fundus examination revealed retinal pigment epithelial disturbance in the right macula and two SRD OS, one in the macula and another in the peripapillary area. Fluorescein angiography OS revealed several focal choroidal leaks. On January 11, 1979, vision was 20/20 OD and 20/60 OS, and SRD OS were unchanged (Fig 7A-D). Despite focal photocoagulation treatment to the areas of paramacular choroidal leakage, the macular SRD persisted, and a new area of leakage was identified on May 29, 1979. During this period of observation, the ulcerative colitis remained active. Colonoscopy was repeated in April 1979, and a repeat biopsy was interpreted as active ulcerative colitis. The SRD resolved in August 1979. On September 2, 1980, vision was 20/20 OU, and there was no evidence of SRD OS. The ulcerative colitis had stabilized.

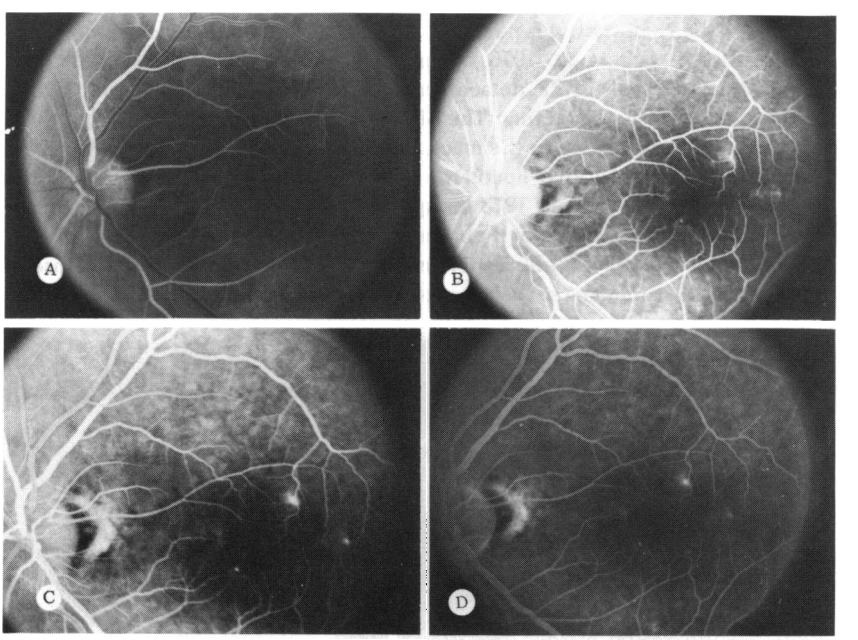


FIGURE 7

Case 8. Sequence of fluorescein angiograms (A-D) of left eye obtained on January 11, 1979. Angiograms document three foci of choroidal paramacular leaks and late staining within one area of SRD. There is a focus of hyperfluorescence and apparent late staining that develops at the temporal edge of the disc within a separate area of parapapillary SRD. Macular SRD involved avascular fovea, and visual acuity was 20/60.

DERMATOMYOSITIS

CASE 9

A 49-year-old Japanese man had a diagnosis of dermatomyositis after the development of proximal muscle weakness, facial swelling, and a heliotrope rash about the eyes. Confirmatory evidence was obtained in the results of laboratory studies on March 1, 1976, which included markedly elevated creatine phosphokinase (CPK) 2,330 mU/ml, lactic dehydrogenase (LDH) 345 mU/ml, serum glutamic oxaloacetic transaminase (SGOT) 144 mU/ml, and aldolase 22.5 units/ml. The LE test and rheumatoid factor were negative. Severe perivasculitis and inflammatory myopathy were diagnosed on the muscle biopsy and electromyography. Initial treatment consisted of 15 mg of intravenous nitrogen mustard, methotrexate (12.5 mg per week), folic acid (9 mg per week), and prednisone (80 mg per day).

He was examined in the Ophthalmology Department on April 30, 1976, with a complaint of blurred vision OD of seven weeks' duration. Vision was 20/30 + 2 OD and 20/30 − 2 OS. Slit-lamp examination was normal, and the fundus examination revealed a retinal pigment epithelial (RPE) detachment in the right macular region. There was RPE disturbance in the macular region OS. Fluorescein angiography of the right posterior pole was compatible with an RPE detachment (Fig 8A and B). On August 30, 1976, vision was 20/50 OD and 20/25 OS. Fundus examination revealed a RPE detachment in the right macular area with a large SRD of the neurosensory retina. The SRD persisted in the right eye (Fig 9A-C), and a new SRD developed in the macula OS in November 1976 (Fig 10A and B). The visual acuities and SRD fluctuated with exacerbations and remissions of the systemic disease. In January 1978 his systemic symptoms improved with coincident resolution of SRD, and by February 1978, the prednisone had been discontinued. In December 1980 he underwent a left nephroureterectomy because of transitional cell carcinoma of the left ureter. He has not had a recurrence of SRD.

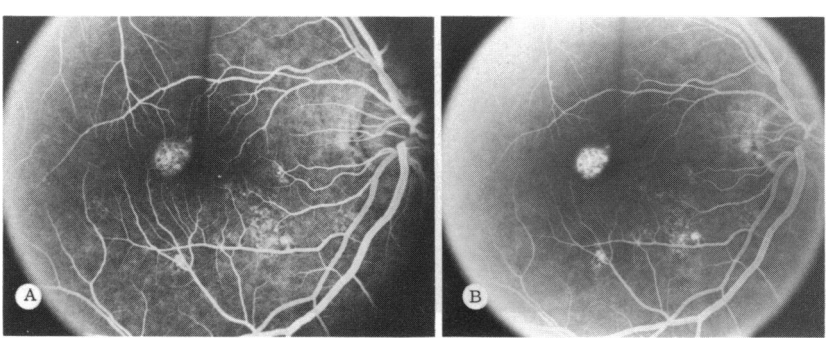
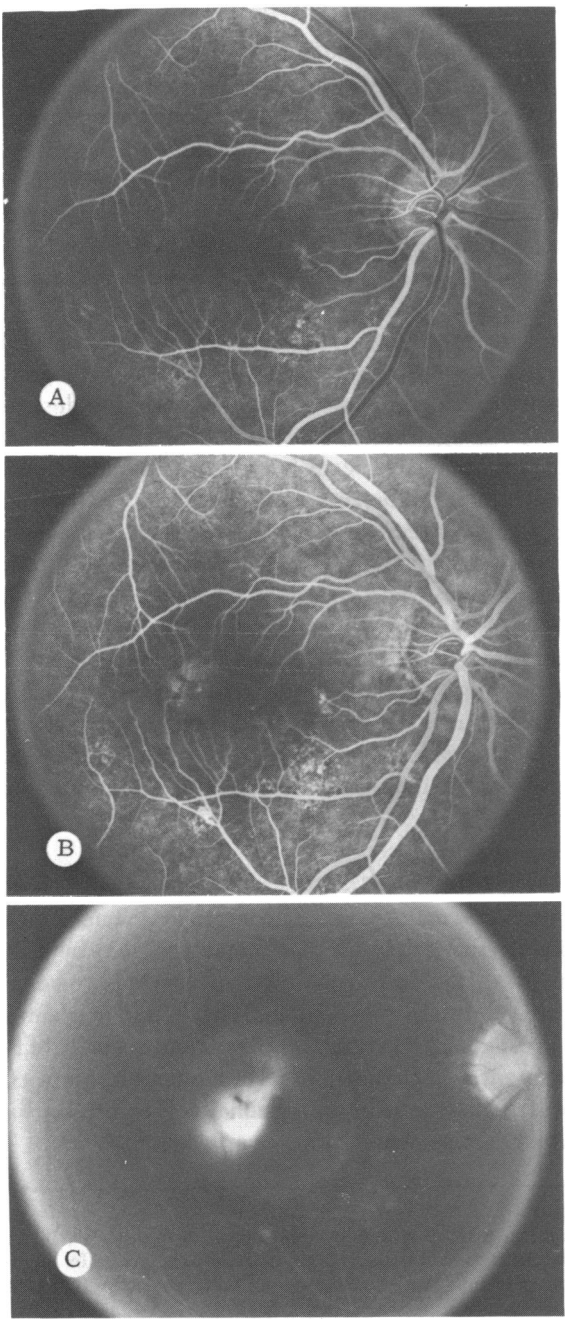


FIGURE 8

Case 9. Fluorescein angiograms of right eye obtained on April 30, 1976. A: Late venous phase. B: Five minutes after fluorescein injection. These document gradual accumulation of fluorescein within a discrete area of the superotemporal macula. Pattern of homogeneous intense fluorescence is consistent with a RPE detachment. Visual acuity 20/30 OD.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DISCUSSION

We have reported nine cases of SRD of the neurosensory retina in the macular region in patients with autoimmune diseases. The cause of the SRD can be linked hypothetically to a phenomenon common to all these diseases, the presence of circulating immune complexes. Immune complexes have an established role in the pathogenesis of SLE,[9] rheumatoid arthritis,[10] and chronic active hepatitis.[11,12] The sera of patients with regional ileitis,[13] ulcerative colitis,[13] and dermatomyositis[14] have been shown to contain immune complexes that have been implicated in the production of secondary systemic manifestations.

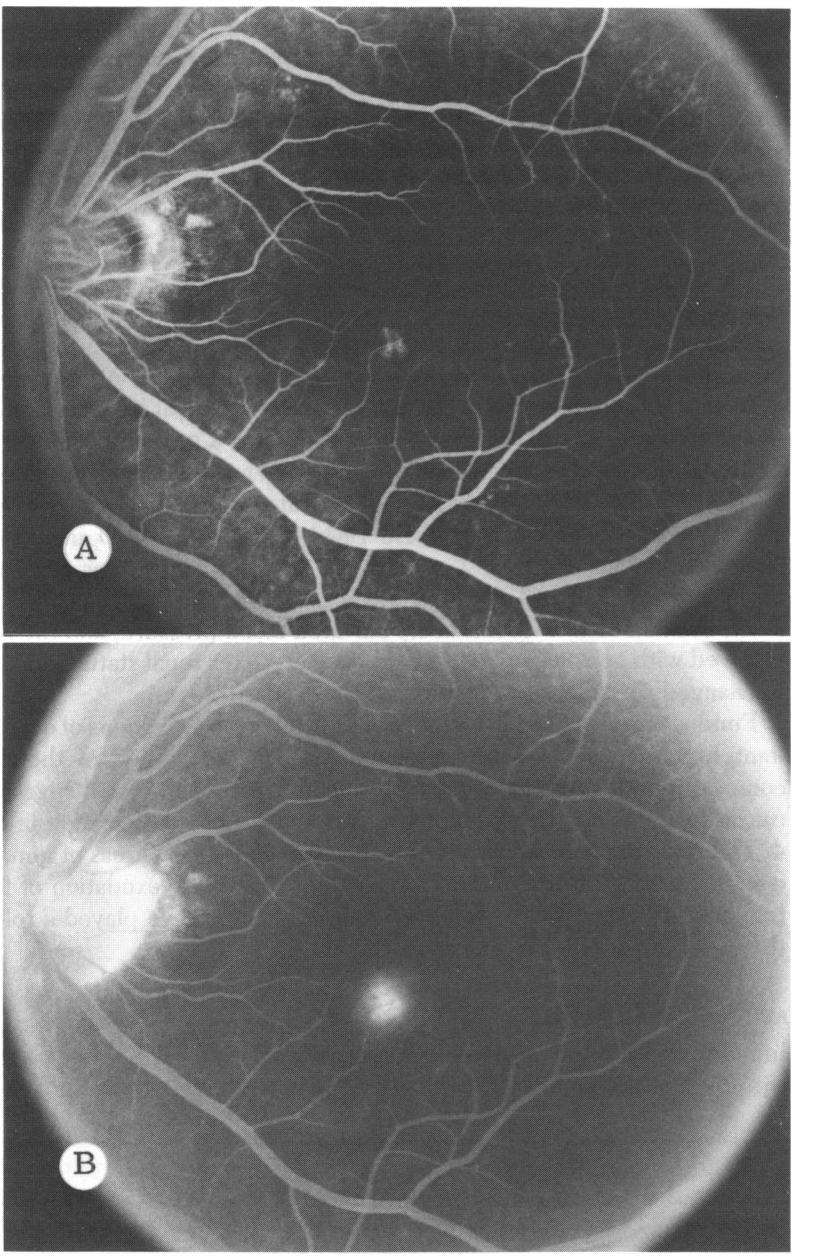
The formation of antigen-antibody complexes (immune complexes) is a crucial component in the normal defense against pathogens and other foreign substances. Physiologic immune responses are designed to eliminate or neutralize antigens and, therefore, protect the host. Under some circumstances, immune complexes become pathogenic, causing injury to the host. Circulating immune complexes, especially as they increase to an appropriate size, may lodge in vascular walls. Immune complexes may induce inappropriate activation or inactivation of either humoral or cellular immunologic factors. The activation of complement by the immune complex produces chemotactic factors that attract polymorphonuclear leukocytes and macrophages. These phagocytic cells phagocytize the antigen-antibody complex, now attached to complement fragments, resulting in the extracellular release of hydrolytic and lysosomal enzymes that produce local inflammation and tissue injury. The clinical expression of the resulting disease depends on the site where immune complexes are deposited.[15,16]

SYSTEMIC LUPUS ERYTHEMATOSUS (SLE)

Systemic lupus erythematosus (SLE) comprises a syndrome that has the potential to involve many organs and is distinguished by many immunologic abnormalities. Low serum complement levels have been recognized as characteristic of this disease since 1951,[17] and a clear relationship between the presence of immune complexes and severity of renal disease has been documented.[9] Deposits of immunoglobulins and complement, which are located between the endothelial cell layer and the basement membrane, are characteristic of lupus nephritis.[18,19]

FIGURE 9

Case 9. Fluorescein angiograms of right eye obtained on November 30, 1976 demonstrating focus of choroidal leakage in superotemporal macular area (A-C). In Figure 9C there is diffusion of fluorescein into subretinal space outlining area of SRD. Visual acuity had declined to 20/200.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Immune complexes have been identified in the choriocapillaris in a patient with SLE who had SRD of the macula.[7] In that report, fluorescein angiography had documented choroidal leaks as the cause of the SRD. Immunoglobulins, complement, and properdin deposits were found throughout the choroid. The patient's blood pressure was under control, and the authors concluded that the immune complexes had caused damage to the choroidal vessels resulting in SRD.[7]

In patients with SLE, factors that might influence the development of SRD would include hypertension and renal disease.[20,21] Severe hypertension associated with renal disease may produce both ischemic infarcts in the choroid and SRD.[22-24] De Venecia et al[25] have recently produced experimentally focal choroidal infarcts (ie, Elschnig spots) and focal SRD by clamping the renal artery and causing acute, severe hypertension. A clinical example of similar ocular signs is seen in toxemia of pregnancy.

In case 4 there were bilateral signs of focal choroidal leakage, and her blood pressure was 180/110 mm Hg. Case 5 had a geographic pattern of multiple choroidal leaks in one eye and an elevated blood pressure of 224/120 mm Hg. Both patients had glomerulonephritis secondary to SLE and elevated blood pressure.[5] Case 4 had resolution of SRD and a slight improvement in blood pressure control. In case 5 there was a peculiar association of SRD and elevated blood pressure. On two separate occasions, she had SRD with markedly elevated blood pressure, and the SRD resolved with normalization of blood pressure. Her renal status remained unchanged throughout the course of the ocular disease.

Fundus changes in SLE are not necessarily mere reflections of concomitant hypertension or glomerulonephritis. The resolution of the SRD coincident with the normalization of blood pressure in case 5 suggests a causal relationship. However, there was not a similar association in case 4. The systemic manifestations of SLE can include focal areas of immune complex damage to the choriocapillaris with resulting exudation of fluid into the subretinal space. Immune complexes may have played a role in the onset of the SRD in one or both patients.

RHEUMATOID ARTHRITIS

Immune complexes are present in serum and synovial fluid of patients with rheumatoid arthritis. They have been implicated in the pathogenesis

FIGURE 10

Case 9. Fluorescein angiograms of left eye obtained on November 30, 1976. A: Choroidal leakage and B: Late staining in the inferior paramacular area OS within area of overlying SRD. Visual acuity 20/40.

of synovitis, nodule formation, vasculitis, and, rarely, the hyperviscosity syndrome which may occur in this disease. Deposits of immunoglobulins and complement are found in neutrophils in synovial fluid (RA cells) and deposited in synovial membranes. Rheumatoid factor is present in serum, synovial fluid, and synovial membrane eluates.

Nonrhegmatogenous retinal detachments are unusual manifestations of rheumatoid arthritis and have only been reported in association with choroidal nodules and scleritis.[5,6,26,27] In one report, bilateral choroidal masses associated with bullous retinal detachments developed in a patient with active rheumatoid arthritis and marked systemic vasculitis.[5] The eye lesions had developed simultaneously with an eruption of cutaneous rheumatoid nodules. The choroidal masses and cutaneous rheumatoid nodules disappeared after large doses of prednisolone and cyclophosphamide were administered. In cases 1, 2, and 3 with rheumatoid arthritis, SRD developed during an exacerbation of their systemic disease. None of these patients had any evidence of choroidal nodules or scleritis. A possible explanation is that circulating immune complexes lodged in the choroidal vasculature and produced the SRD.

CHRONIC ACTIVE HEPATITIS

Chronic active hepatitis is defined as a chronic inflammatory reaction in the liver as demonstrated by liver function tests. The specific pathologic findings at biopsy include chronic lymphocytic infiltration of the periportal region with bridging necrosis between involved portal triads.[12] Several immunoglobulin abnormalities are present in the serum of patients with chronic active hepatitis and in many asymptomatic family members. Antinuclear factor is present in one-half to one-third of the patients. About two-thirds of the patients with chronic active hepatitis have a positive smooth muscle antibody test. Measurement of serum immunoglobulin levels shows a polyclonal elevation.[11] These tests were positive in case 6. Injury of liver cells in chronic active hepatitis appears to be due to persistent immunologic activity.[28] Antibody-dependent cellular toxicity and immune complex-mediated cytotoxicity has been demonstrated in this disease.[28]

Systemic manifestations of chronic active hepatitis are similar to other autoimmune diseases. They include acute, recurrent, nondeforming, migrating polyarthritis of large joints, skin lesions, pulmonary parenchymal and pleuritic changes, endocrine changes, glomerulonephritis, and ulcerative colitis.[12]

Case 6, with chronic active hepatitis in its active stage, had only one eye examination and died six months later. This patient had SRD of the

right macula with some faint choroidal hyperfluorescence in the early phases of the angiogram but no definite late staining. This was interpreted as a resolving leak. One can only speculate about the pathogenesis of the SRD in this patient. However, this report does document another case of a SRD occurring coincidentally during the active stage of an autoimmune disease.

INFLAMMATORY BOWEL DISEASES

Inflammatory bowel diseases, ulcerative colitis, and Crohn's disease, have no proved etiology. However, the systemic manifestations and laboratory findings suggest an immunologic mechanism.[29-31] Patients with ulcerative colitis and Crohn's disease have circulating antigen antibody complexes in the sera[13] and have lymphocytes that show toxicity toward colonic epithelial cells.[31]

SRD developed in both of our patients with inflammatory bowel disease during active stages of gastrointestinal disease while they were on a regimen of systemic steroids. Case 7 with Crohn's disease had resolution of SRD only after resection of the involved small bowel. Knox and Bayless[32] reported a case of bilateral SRD in a patient with Crohn's disease who had resolution of the detachments following drainage of a psoas abscess associated with an intestinal fistula. Case 8 with ulcerative colitis had resolution of the SRD following medical therapy that stabilized the gastrointestinal disease. Photocoagulation had been performed eight months earlier. Not only did the photocoagulation fail to arrest the choroidal leaks, but new ones developed. These findings document the coincidental occurrence of SRD during the active systemic phase of inflammatory bowel disease and the coincidental remission of the SRD with successful treatment and control of the inflammatory bowel disease.

POLYMYOSITIS (DERMATOMYOSITIS)

Polymyositis is an inflammatory myopathy of unknown cause to which the term dermatomyositis is applied in the presence of the characteristic skin rash.[33] Our patient had all the classic findings of this disease. This disease is usually included in the collagen vascular category because both humoral and cellular immune mechanisms are implicated in its pathogenesis. Humoral factors have been studied extensively, and antigen-antibody complexes have been found to occur in some patients with dermatomyositis.[14,33] In case 9, the course of the SRD fluctuated and reflected the

course of the systemic disease. When the dose of prednisone was lowered, there was a coincidental increase in the severity of systemic and ocular symptoms. Progression of ocular findings included development of a more severe choroidal leak with an enlarging SRD OD and the appearance of a new choroidal leak and SRD OS. This SRD resolved only after remission of the systemic disease.

What are the factors that may have influenced the development of SRD in these patients? Hypertension appeared to be a definite factor in one patient with SLE. Although immunosuppressive therapy was commonly utilized, it was not used in all patients. The initiation of immunosuppressant therapy was temporally related to the onset of the SRD in treatment of only two patients. In addition, 300 patients per year with autoimmune disease are treated with these same immunosuppressant regimens at The Cleveland Clinic Foundation. The authors are unaware of any other cases of SRD associated with immunosuppressant therapy. One hypothesis that might explain the development of SRD in patients with autoimmune disease would be the deposition of circulating immune complexes in the choroidal vasculature.

Immune complexes formed elsewhere may be trapped in the choriocapillaris and activate the complement system. This phenomenon occurs in the kidney where immune complexes are deposited in the basement membrane of the glomerular capillaries, activate the complement system, and lead to tissue injury and increased vascular permeability.[19] If immune complexes lodge in the choriocapillaries, damage to these vessels and the adjacent RPE cells could produce SRD.

In this report the patients had diseases characterized by immune complexes. However, in most of these diseases only a small percentage of the patients will show circulating immune complexes. The ability to identify immune complexes is limited by the presently available assays.[10,13,15,16]

We do not have pathologic proof that immune complexes are involved in the SRD in our patients. It would be necessary to study immunoglobulin deposits in the choriocapillaris by immunofluorescence to prove our hypothesis. With the advent of corticosteroids and immunosuppressant medication, patients rarely have a disease severe enough to cause death. An animal model to demonstrate the entity we suggested would be necessary to confirm a relationship between choroidal immune complexes and SRD. However, the finding that immunoglobulins, complement, and properdin were deposited in the choroidal capillaries of a patient with active SLE[7] is strong supportive evidence that immune-complex disease may manifest itself in the eye with resultant choroidal vessel damage and leakage.

SUMMARY

We have reviewed 168 cases of angiographically proved SRD of the macular region of unknown etiology that were seen at The Cleveland Clinic Foundation. Thirty-seven percent of these patients had documented coincident systemic diseases. Of that group, patients with autoimmune disease appeared to have ocular symptoms during the active phase of the systemic illness. Nine cases are reported characterizing the coincidence of exacerbation of systemic disease with recurrent serous detachment of the neurosensory retina. It is our hypothesis that in patients with autoimmune disease, the choroiditis is secondary to the damage caused by immune complexes. Thus, in these patients, SRD was a manifestation of the systemic illness.

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DISCUSSION

Dr David L. Knox. I would like to thank Doctor Gutman and his co-authors for sending me the typescript and photographs for this paper in time for me to prepare this discussion. I have had so much time to prepare the discussion that I have almost ended up not knowing what to say.

From the base of 168 patients seen with central serous retinopathy in the years 1971 to 1980, the authors identified that 37% of their patients had coincident systemic disease and they present the details of nine particular patients, three with rheumatoid arthritis, two with lupus erythematosis, one with hepatitis, one with dermatomyositis, and two with inflammatory bowel disease. The latter two, I wish to consider separately.

At the time that Doctor Gutman was preparing his paper, a medical student, Mr Mitchel Gilbert, at our Institution was analyzing the patients seen by our Retinal Vascular Center. Looking at the numbers in the two series shows that

there are considerable similarities. Mr Gilbert analyzed 196 patients. Age range and average age were similar to those described by Doctor Gutman and both series have approximately 80% males. In contrast to Doctor Gutman's series with 37% having systemic disease, Mr Gilbert's series however, has only six patients, (3%) who described any kind of systemic disease as defined at the time of history taking. It is at this point that I began having trouble with Doctor Gutman's paper.

It is my experience that patients with central serous retinopathy do not have the systemic diseases that have been defined by Doctor Gutman. Thirty-seven percent is awfully high. It may very well be that the selection processes of Doctor Gutman's practice may depend upon the fact that many of the patients that he has seen were basically patients of the Cleveland Clinic for severe medical problems. When they develop an eye problem they are referred within the Cleveland Clinic to the Ophthalmology Service. The difference in my experience, the difference tabulated by Mr. Gilbert from the Wilmer Retinal Vascular Center, and the experience at the Cleveland Clinic, however, may represent the fact that for this disease we gave less attention to the past medical history. I have found that many patients deny any medical problem until you ask specific questions.

The next point I would like to make is that patients seen at the Cleveland Clinic are very similar in many ways to the patients seen at the Johns Hopkins Medical Institutions. They are likely to be acutely ill, or have serious ocular or medical problems. This fact is emphasized by the authors of this paper in that the nine patients described were acutely ill from their basic inflammatory disease. As evidence of this severity, of the nine patients presented, seven were being treated with one or more of the anti-inflammatory cytotoxic agents. The two patients with inflammatory bowel disease were not receiving cytotoxic agents. All nine patients were being treated with systemic prednisone.

In my personal experience, and the experience of many ophthalmologists with whom I have talked and discussed this on a one to one basis, central serous retinopathy is commonly associated with stress: work, family, or social pressures have peaked in the period immediately preceeding the sudden onset of reduced acuity, micropsia, or distortion. Stress as an aspect of this syndrome was emphasized in an early name, "angiospastic retinopathy" described by Doctor Frank Walsh in the late 1930s. The mechanisms by which stress causes this syndrome are not known to me, but I believe it is a real component. The fact that Doctor Gutman's patients were seriously ill, were being seen at a referral center, and being given complicated, toxic medications, makes me wonder if his patients' ocular problems were related to stress more than to his proposal of circulating antigen-antibody complexes.

I personally do not have experience with central serous retinopathy occurring in patients with rheumatoid arthritis, lupus erythematosis, hepatitis, or dermatomyositis. The frequency of those diseases in the general population is so high that if they were the basic mechanism responsible for the ocular problem described by Doctor Gutman, more of us would have seen this earlier. It may be, however, that we have seen it and considered that it was coincident and not a significant or etiologic association.

Because of the frequency of the use of cytotoxic anti-inflammatory agents in these patients, we must consider that those agents themselves may have played a role in the central serous retinopathy reported here.

I would like to discuss separately the patients with inflammatory bowel disease, and particularly the 20-year-old woman with Crohn's disease. I think that this is a separate situation which I have experienced. I would like to show photographs of several patients. (slides)

The first of these is a 32-year-old woman who developed blurred vision in both eyes at the same time as her symptoms of Crohn's disease increased. Photographs and fluorescein angiograms show multi focal leaks suggestive of choroiditis. Management of her Crohn's disease with systemic corticosteroids and diet have improved both her gut and eye symptoms.

The second patient was a 35-year-old white male, who had blurred vision from slight serous detachment of the sensory retina. No focus of active Crohn's disease could be found, though he had had a past history of the disorder. Each time his systemic corticosteroids were reduced his vision decreased. Each time the corticosteroids were increased his vision improved.

The final patient, 48 years of age, had Crohn's disease for 20 years. She had been operated on twice and a narrowed ileum had obstructed eight times in the past year. Increasing systemic corticosteroids relieved her obstruction. While on a cruise ship in the Caribbean, one night at dinner, she realized that her intestinal obstruction had recurred. She excused herself from the table, went to her cabin, and took 40 mg of prednisone. The next morning her obstruction symptoms were relieved, but she had blurred vision. When I saw her with 20/30 acuity, she had classic central serous retinopathy which required five months to subside. I was never able to decide if her eye problem was the result of active Crohn's disease, or the stress of having intestinal obstruction, in the Caribbean, on a cruise ship, without a surgeon.

Doctor Gutman has asked us to consider the role of antigen-antibody complexes in his patients. He has given us evidence that their diseases have an increased amount of antigen-antibody complexes. The case from the literature, which he has quoted, demonstrated antigen-antibody complexes diffusely in retinal vessels and ciliary epithelium. The quoted report did not demonstrate a concentration of antigen-antibody complexes in the areas of the detached retina, or disturbed pigment epithelium. I believe his ideas have merit, but I believe that we need more evidence.

I also believe that this series needs to be analyzed for a variety of factors such as the referral mechanism, the possible role of cytotoxic anti-inflammatory agents, and their effect on ocular processes and the role of stress in his nine patients. It may very well be that the combination of their disease and their drugs produced the central serous retinopathy.

Dr Arnall Patz. I want to congratulate the authors and answer one question that Doctor Knox raised. I think that the referral pattern to the retinovascular program

at Wilmer is probably 90% plus from regional ophthalmologists, and only a relatively small percentage of patients originate from the Department of Internal Medicine or the Department of Rheumatology. This source of referrals might indeed explain the difference which Doctor Knox has alluded to in his discussion. Possibly in a few years our figures will change, as we are just starting to have a closer relationship with the Department of Rheumatology in several areas.

DR FRONCIE A. GUTMAN. First, I would like to thank Doctor Knox for a very fair discussion. We have reported nine cases of serous retinal detachment occurring coincidentally in patients with systemic autoimmune disease. Our patient population is somewhat biased since we access 400 new inflammatory bowel disease patients each year at the Cleveland Clinic Foundation. We also concentrate a huge group of patients with severe autoimmune disease. These patients have gone through every available type of conservative management and are referred to the Cleveland Clinic Foundation because their systemic disease is not controlled. This unusual concentration of patients has permitted us to make the observations that we have reported. In addition, cytotoxic agents are commonly used in the therapy of these patients and may influence the manifestations of their disease. We are initiating a study to evaluate the role of cytotoxic agents. Fluorescein angiography studies will be performed before and after initiating therapy to see if we can recognize any changes in choroidal permeability.

At the present time, we do not have any hard data which confirms that the serous retinal detachments in these patients are a direct consequence of the systemic autoimmune disease. These patients were identified retrospectively from our photography files. However, we have pointed out that immune complexes have been identified in the choroid in a patient with systemic lupus erythematosis and a serous retinal detachment. We are continuing to explore the relationship by performing laboratory tests on new patients with serous retinal detachment and autoimmune disease to see if there is any evidence of circulating immune complexes.