Hyperviscosity Syndrome: Natural History in a Patient with Sjögren's Syndrome

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Serum protein abnormalities can be responsible for elevations of serum viscosity. When clinical disease results, this condition is termed hyperviscosity syndrome. Immunoglobulin complexes are a prominent cause of this syndrome. The acute illness in a patient with Sjögren's syndrome, IgG-IgG complexes, and serum hyperviscosity was described in a previous report.[1] After subsequent five-year follow-up, it has become apparent that the acute hyperviscosity syndrome in this patient was but one phase of a prolonged, perhaps life-long, illness. This five-year follow-up, which included observation of the effects of steroid therapy on the underlying disease process, is the subject of this report.

Materials and Methods. Serum relative viscosity was determined by the method of Fahey, Barth, and Solomon,[2] using freshly obtained serum at 37 C in an Oswald viscometer (Induchem Glass Co., Vineland, N. J.) of 5 ml capacity. Total protein concentration of serum was determined by the biuret technique. Serum protein electrophoresis was done on cellulose acetate strips in the Beckman Microzone Cell, Model R 101 (Beckman Instruments, Inc., Fullerton, Ca.). These measurements along with the serum electrophoresis were used to calculate the gamma globulin in grams per hundred milliliters. Rheumatoid factor titers were determined by the sensitized human cell test as previously described.[3]

Sedimentation patterns of serum proteins were determined with a Beckman Spinco Model E analytical ultracentrifuge equipped with electronic speed control, rotor temperature indicator control, and schlieren optics. Sera were diluted 1:4 with PBS (0.13M sodium chloride, 0.02M sodium phosphate, pH 7.4) and dialyzed against PBS overnight. Runs were performed with standard and wedge double sector cells at 20 C and 60,000 rpm and photographs were taken at 32 and 64 minutes after operating speed was reached.

Case Report. The patient, a 56-year-old black woman, has been seen repeatedly at the Medical College of Virginia Hospitals during the past 49 years (Table 1). She presented first in 1927 because of abdominal pain and vaginitis which were apparently attributable to gonorrhea. In 1934, she was treated for secondary syphilis manifested by rash, condylomata, and a 4+ Wasserman reaction, although previously the Wasserman test had been negative; she has remained sero-fast. Alopecia developed in 1956 and chest pains, myalgias, and arthralgias were her main complaints in 1963. These unexplained pains recurred in 1964 and in 1965. In 1966, after a four-month period of chest pain, an infiltrate in the left lower lobe of the lung was detected by x-ray; the white blood count was then 3500/mm^3. The pneumonic process, thought to be a viral pneumonia, subsided uneventfully.

The patient was referred to the Arthritis Clinic in 1967 because of a five-month history of morning

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stiffness and persistent hand, shoulder, ankle, and foot pain. There was obvious synovial thickening; a rheumatoid factor test (sensitized human cell test) was positive with a titer of 1:640, an antinuclear antibody (ANA) test was weakly positive, and lupus erythematosus cell tests were negative. A diagnosis of definite rheumatoid arthritis by American Rheumatism Association criteria was made. In 1968, Sjögren's syndrome evolved with dryness of the eyes and mouth, parotid gland enlargement, progression of arthritis, and a positive Schirmer's test. At that time, the serum total protein was 8.0 gm% with 19.7% gamma globulin.

Vertigo and recurrent nosebleed first occurred in 1969 when the total serum protein was 11.2 gm%. Hyperviscosity was first suspected and detected in May, 1970, when headaches, blurred vision, further nosebleeds, exertional dyspnea, and paroxysmal nocturnal dyspnea occurred. The course of the acute hyperviscosity syndrome associated with polyclonal gammopathy, IgG-IgG complexes, and extraordinary titers of rheumatoid factors was presented in the earlier report.[1] Since 1971, the hyperviscosity syndrome has not recurred, but the clinical problems of underlying connective tissue disease, recurrent infections, and steroid-induced complications including aseptic necrosis of the femoral heads have remained.

Table 1
Medical Problems Prior to Hyperviscosity Syndrome at 51 Years of Age

Age	Date	Medical Problems
8	1927	Abdominal pain, etiology unknown
13	1932	Tonsillitis
15	1934	Secondary lues (syphilis)
25	1944	Acute right cervical lymphadenitis
28	1947	Right salpingo-oophorectomy, appendectomy
29–33	1948–53	Acute dacryocystitis
35–37	1954–56	Alopecia, recurrent back pain, epigastric pain
41	1960	Enlarged right parotid, chronic cervicitis
42	1961	Pleurisy, hysterectomy, left salpingo-oophorectomy
44	1963	Hypertension, chronic bronchitis, arthralgias
45	1964	Total alopecia, periophthalmic pigmentation, arthralgias
46	1965	Pyelonephritis
47	1966	Viral pneumonia
48	1967	Submucous resection for right nasal obstruction, seropositive rheumatoid arthritis
49	1968	Dry mouth, swelling of left parotid, malar rash (Sjögren's syndrome)
50	1969	Sjögren's syndrome, urinary tract infection, pleurisy, nosebleeds
51	1970	Hyperviscosity syndrome, cirrhosis, alopecia

Results. Throughout the five-year period from 1970 to 1975, there has been a remarkable correlation between gamma globulin levels, rheumatoid factor titers, serum viscosity, and ultracentrifuge patterns (Fig 1, Fig 2*A* and 2*B*). When globulin levels are high, rheumatoid factor titers and serum viscosity are also elevated, and intermediate complexes become more prominent in the analytical ultracentrifuge patterns. Despite these parallel changes, it is apparent that the hyperviscosity has not been a clinical problem in the past four years. During this later period, the highest recorded relative viscosity was 2.7, a value not associated with hyperviscosity symptoms.

Management of this patient's illness has been difficult. In the first phase of therapy, cyclophosphamide and penicillamine produced no apparent benefit.[1] Since January, 1971, prednisone has been the only immunosuppressive agent used. There has been an inverse correlation between prednisone dose and laboratory evidence of serum protein abnormalities. This impressive effect of prednisone therapy was most clearly apparent after the three periods in which the patient decided to stop her medications. The most prolonged period of interruption was the last three months of 1973. Although she had been receiving only 10 mg of prednisone daily, this dosage was apparently effective in partially normalizing serum protein abnormalities. After three months without therapy, rheumatoid factor titers, gamma globulin levels, and serum viscosity clearly increased. Again, intermediate complexes were prominent in the sedimentation profile. (See pattern 1-7-74 in Fig 2*B*.) More recently, the prednisone dosage has been maintained at 5 to 10 mg daily with satisfactory control of serum protein abnormalities.

Discussion. The most striking features in this case of Sjögren's syndrome have been the long-standing nature of the underlying disease process, the dramatic but relatively short-lived hyperviscosity syndrome, and the effect of prednisone therapy.

Any relationship of earlier illnesses, including syphilis, with a long-standing sero-fast state to the present connective tissue disease is problematical. Alopecia, however, is almost certainly part of the present disease. The alopecia was first noted in 1956,

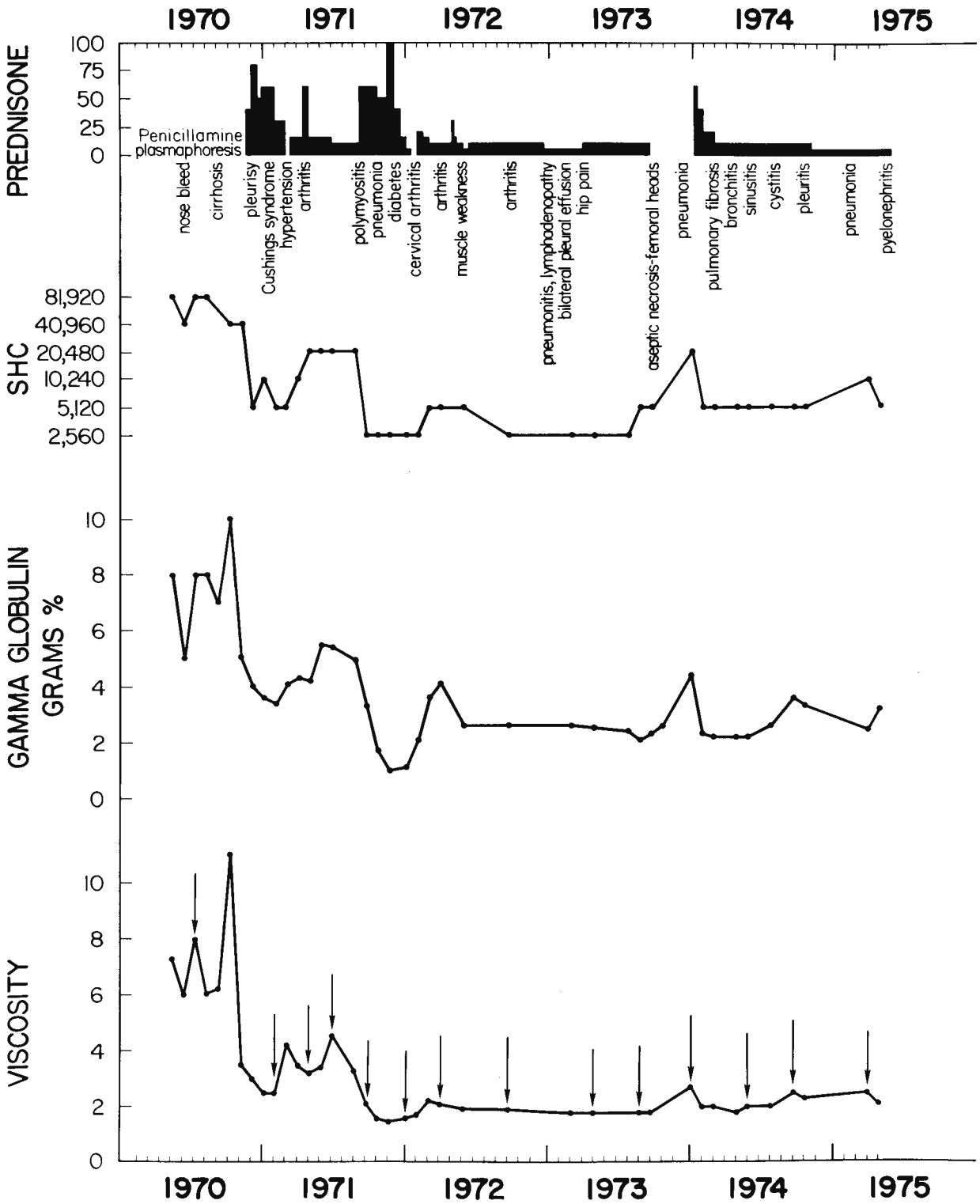

Fig 1—Five-year documentation of clinical events and laboratory measurements in patient with hyperviscosity associated with Sjögren's syndrome. Arrows refer to patterns on Fig 2*A* and 2*B*.

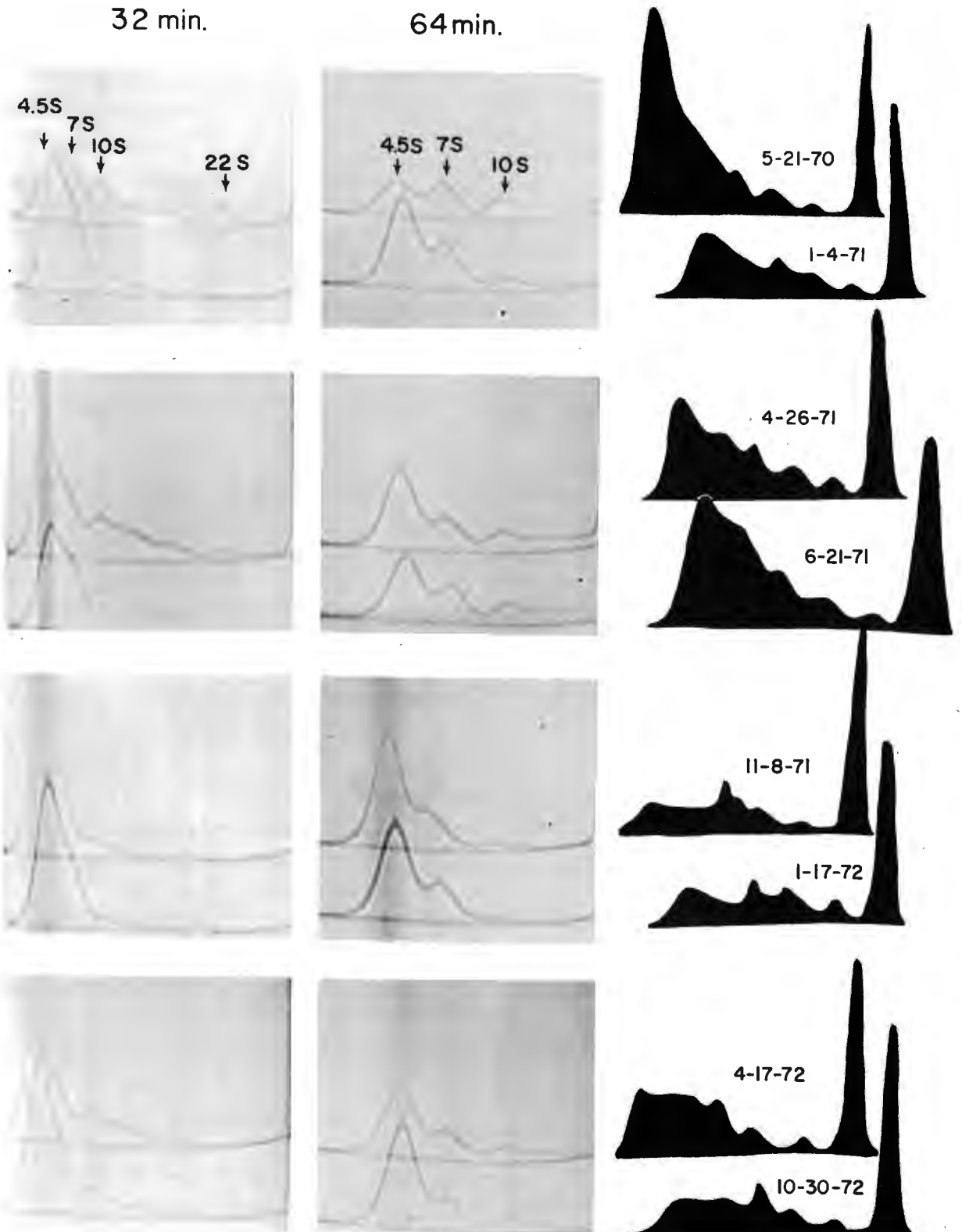

Fig 2A—Serum electrophoretic patterns and ultacentrifuge patterns of serum samples taken over a five-year period following hyperviscosity syndrome. Direction of sedimentation is to the right. Photographs taken on dates indicated at 60,000 rpm and 20 C.

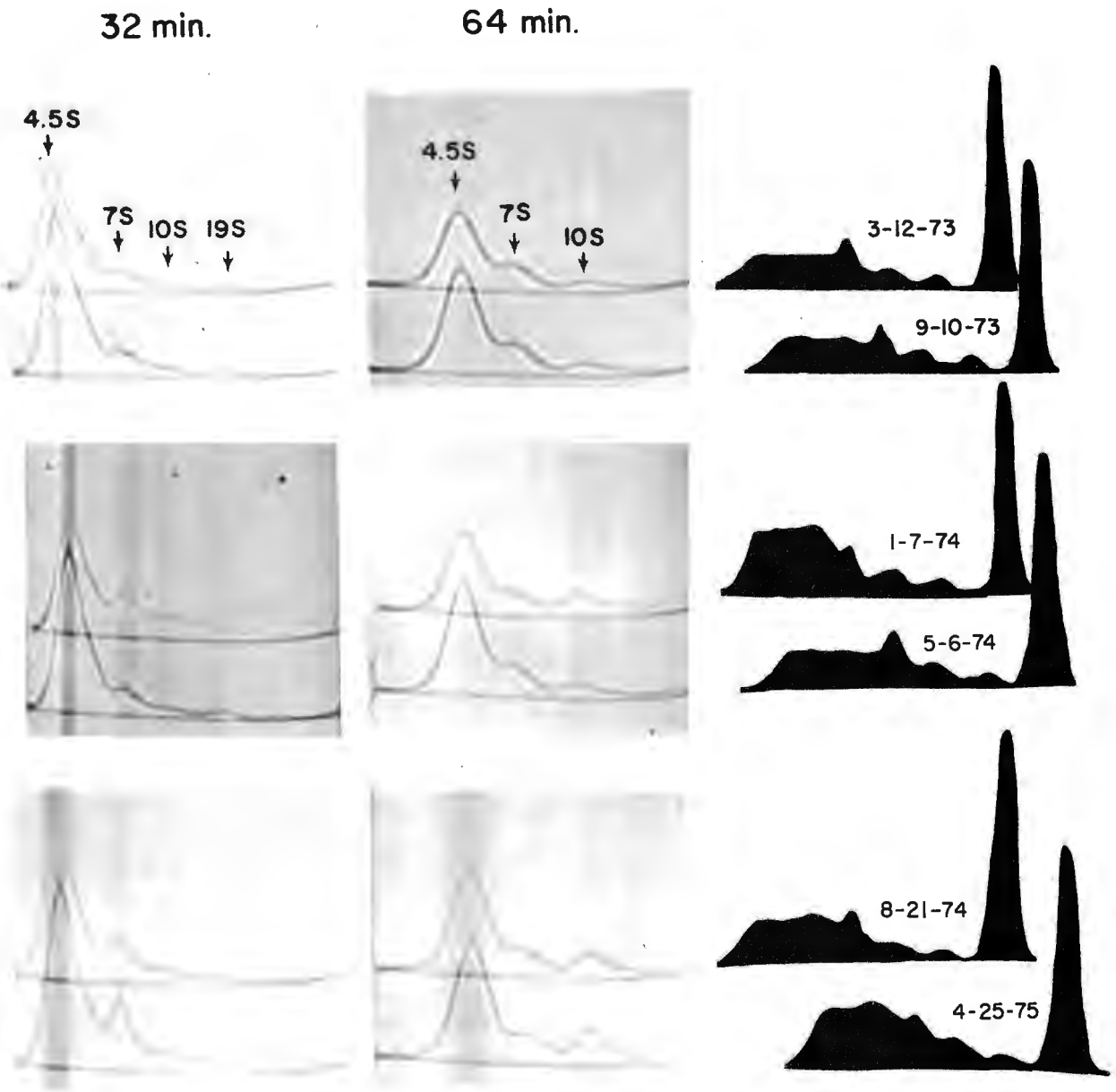

Fig 2*B*—Serum electrophoretic patterns and ultracentrifuge patterns of serum samples taken over a five-year period following hyperviscosity syndrome. Direction of sedimentation is to the right. Photographs taken on dates indicated at 60,000 rpm and 20 C.

11 years before she developed seropositive arthritis and a positive ANA, and 13 years before the first symptoms of hyperviscosity.

After approximately one year in which hyperviscosity symptoms dominated the clinical picture, the patient has remained free of those symptoms for four years. Thus, the dramatic clinical occurrence of a hyperviscosity syndrome and attendant therapeutic problems need not imply that the patient's basic illness is of recent origin or that the hyperviscosity syndrome will be a persistent problem.

Prednisone therapy has been effective in the control of both serum protein abnormalities and symptoms of hyperviscosity. Probable side effects of steroids including aseptic necrosis of the femoral head and infections have presented emphatic evidence that

in this patient's case steroid therapy also has been harmful. Despite these side effects, her current relative well-being indicates that the steroids are useful therapeutically and that in long-term management the dosage can and must be maintained at a low level. The effectiveness of low dosage in this case may be attributable in part to prolonged steroid action because of its abnormally slow metabolism by a cirrhotic liver. Cessation of prednisone therapy was rapidly reflected in increased levels of gamma globulins, serum viscosity, and rheumatoid factor levels.

Pharmacologic effects of adrenal steroids on serum immunoglobulins and immunoglobulin metabolism in normal volunteers were reported by Butler and co-workers.[4] A three- or five-day course of methylprednisolone, 96 mg daily, produced marked decreases in serum IgG levels which persisted for at least three months. These effects were largely attributable to inhibition of IgG synthesis. Levels of IgA were also decreased, but IgM was not affected. These pharmacologic studies of steroid effects provide a rationale for steroid usage in patients with undesirable effects of IgG, such as IgG-IgG complex formation.

The immunologic and physiochemical events that presage and maintain the hyperviscosity syndrome are poorly understood. In 1968, our patient had a normal electrophoretic pattern and a normal percentage of gamma globulin. In 1969, the total serum protein was found to be 11.2 gm% and nosebleeds were a recurrent problem. Hyperviscosity was first suspected in 1970, when the full clinical pattern of vertigo, headaches, blurred vision, and dyspnea made their appearance.

Bjørneboe and Jensen[5] studied a case of myelomatosis with normal colloid osmotic pressure in spite of extremely high serum protein concentration and postulated that extremely high levels of protein led to aggregation (complexing) of the protein molecules which in turn led to hyperviscosity. The studies of Pope et al[6] on the hyperviscosity syndrome in rheumatoid arthritis due to intermediate complexes formed by the self-association of IgG-rheumatoid factors would seem to strengthen this concept. Our study shows that the presence of intermediate complexes waxes and wanes with the level of immunoglobulins. In the samples from November and December, 1971, and January, 1972, there are practically no demonstrable intermediate complexes in the patient's serum; one of the lowest levels of gamma globulin and with a viscosity of 1.8 occurred at the same time.

The possibility that intermediate complexes represent compensatory responses to maintain the osmotic equilibrium in face of extremely high levels of globulins cannot be completely dismissed.

On the basis of the response of this patient, one might recommend that the hyperviscosity syndrome of connective tissue disease be managed initially with plasmaphoresis, followed by long-term treatment with progressively decreasing doses of adrenal steroids.

REFERENCES

1. Blaylock WM, Waller M, Normansell DE: Sjögren's syndrome: Hyperviscosity and intermediate complexes. *Ann Int Med* 80:27–34, 1974.

2. Fahey JL, Barth WF, Solomon A: Serum hyperviscosity syndrome. *JAMA* 192:464–467, 1965.

3. Waller MV, Decker B, Toone EC Jr, et al: Evaluation of rheumatoid factor tests. *Arthritis Rheum* 4:579–591, 1961.

4. Butler WT: Corticosteroids and immunoglobulin synthesis. *Transplant Proc* 7:49–53, 1975.

5. Bjørneboe M, Jensen KB: A case of myelomatosis with normal colloid osmotic pressure in spite of extremely high serum protein concentration (Hyperviscosity syndrome due to aggregation of myeloma globulin molecules?). *Acta Med Scand* 179(suppl 445):212–215, 1966.

6. Pope RM, Mannik M, Gilliland BC, et al: The hyperviscosity syndrome in rheumatoid arthritis due to intermediate complexes formed by self-association of IgG-rheumatoid factors. *Arthritis Rheum* 18:97–106, 1975.