ultrasound probe is a valuable tool for detecting thrombi in the deep veins of the lower limb. If the limb is normal on ultrasonic examination there is no thrombus present proximal to the calf and in most cases no thrombus present at all. But if the vein is abnormal on ultrasonic examination the limb probably contains a thrombus though its extent is not accurately indicated by this form of examination. Accordingly, a positive ultrasound result is an indication for phlebography.

These conclusions on the scope and accuracy of the Doppler ultrasound probe may be applied to the results obtained in the post-operative group. The A waves were studied up to the external iliac vein in 212 legs throughout the period of study. In 64 legs the common femoral vein was the highest point studied on the first day after operation, but on subsequent days full testing to the external iliac level was possible. Theoretically, therefore, abnormalities might have been present in the iliac veins on the first day which were missed because of incomplete screening. The normal findings a day later, however, indicate that a thrombus, had it been present, must have embolised or spontaneously lysed within 24 hours, which is unlikely. It is reasonable therefore to assume that though the ultrasound screening was incomplete in 64 legs on the first day the overall screening was adequate to have detected iliofemoral thrombus had it been present.

In 272 legs the ultrasound showed nothing abnormal and it may be concluded that no thrombus was present in the iliofemoral ultrasonic examination in those legs. Four legs were found to be abnormal on ultrasonic examination, but in only one leg was a calf vein thrombus confirmed by the ^{125}I -fibrinogen uptake test. In the remaining three legs the absence of thrombus was shown by ascending phlebography in two and the third had evidence of a previous deep vein thrombosis. Hence we conclude that no patient in this group developed a thrombus in the

iliofemoral segment during the period of screening despite thrombosis developing in the calf veins of 37 legs. Our results lend no support to the suggestion that the development of dangerous iliofemoral thrombosis in the early postoperative period in the absence of calf vein thrombosis is a common occurrence.

In two patients thrombosis developed or extended proximal to the calf after the period of screening was completed. In both cases the postoperative course was complicated, which illustrates that in patients with a complicated course this type of thrombosis may develop late.

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MEDICAL MEMORANDA

Mixed Connective Tissue Disease with Digital Gangrene

D. KITCHINER, J. EDMONDS, C. BRUNEAU,
G. R. V. HUGHES

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In 1969 Sharp *et al.* proposed the term "mixed connective tissue disease" for an apparently distinct rheumatic disease syndrome with features of systemic lupus erythematosus, progressive systemic sclerosis, and dermatomyositis but characterized by a good prognosis and by the finding of a specific antinuclear antibody in the serum (Sharp *et al.*, 1969). The patient described here showed many of the characteristics of this syndrome, a distinctive feature being the severity of Raynaud's phenomenon, leading ultimately to gangrene of multiple digits.

Department of Medicine, Royal Postgraduate Medical School,
London W12 0HS

D. KITCHINER, M.R.C.P., Senior House Officer
 J. EDMONDS, M.R.A.C.P., Senior Registrar
 C. BRUNEAU, M.D., Research Fellow
 G. R. V. HUGHES, M.D., M.R.C.P., Consultant Physician

After 12 years of follow-up there was no evidence of renal disease. It is felt that the recognition of distinct syndromes within the general heading of systemic lupus erythematosus is justified to assess prognosis.

Case Report

The patient, a housewife, presented in 1960 at the age of 22 years with joint pains and morning stiffness. The following year she developed Raynaud's phenomenon, recurrent abdominal pain, and pleuritic chest pain. She was first seen at Hammersmith Hospital in January 1962 with active synovitis of her hands and knees and generalized lymphadenopathy. Investigations showed: haemoglobin 10.9 g/100 ml and E.S.R. 60 mm/hr. Tests were positive for rheumatoid factor (Laxtex fixation test) and antinuclear factor and negative for L. E. cells, and the Wassermann reaction was negative. A diagnosis of systemic lupus erythematosus was made.

Two months later she had further pleuritic chest pain and prednisone 5 mg three times a day was begun. Over the next two years Raynaud's phenomenon became severe, resulting in progressive sclerodactyly, infection, ischaemic necrosis, and amputation of the tips of most of her fingers. Bilateral cervical and later transthoracic sympathectomies were performed with only transient improvement.

Apart from the severe Raynaud's phenomenon and its sequelae she remained well on prednisone 7.5 mg daily until January 1974 when she presented with weakness and fatigue.

On examination she was found to be pale and had the digital changes shown in fig. 1, with sclerodactyly and amputation of most of her fingertips. The rest of her skin was normal. There was no telangiectasia or other evidence of scleroderma, and she had no muscle weakness or tenderness.

Fig. 1—Hands of patient showing amputation of most finger tips after severe Raynaud's phenomenon.

Fig. 2—Ouchterlony plate. Precipitin line is seen between the centre well (S.T.), containing patient's serum, and well 1, containing extractable nuclear antigen. No precipitin line is seen where antigen is treated with trypsin (well 2) or RNase (well 3).

INVESTIGATIONS

The E.S.R. was 60 mm/hr, haemoglobin 8.9 g/100 ml, reticulocytes 1.4%, Fe 18 µg/100 ml, transferrin 320 µg/100 ml (normal 200-400 µg/100 ml), and the Coombs test was negative. Bone marrow showed iron-deficiency anaemia. W.B.C. and platelet count were normal as were serum B₁₂ and red cell folate. The glucose tolerance curve was flat and the xylose tolerance test gave a result of 2.4 g in 5 hours. Barium meal and follow through examination and jejunal biopsy showed nothing abnormal. Lactic acid and γ-glutamyl transpeptidase were normal, and an electromyogram was also normal.

Pulmonary function tests showed transfer factor to be 7.91 ml/min/mm (expected 25.4 ml/min/mm) and lung volume normal.

Both E.C.G. and electrocardiogram were normal. Urea and electrolytes, plasma proteins, protein electrophoresis and immunoglobulins, creatinine clearance were all normal, and urinalysis and x-ray examination of the chest showed nothing abnormal. X-ray examination of hands showed loss of distal phalanges but there was no soft tissue calcification or erosions.

Immunological Investigations.—Serum contained antinuclear factor at 1/1250 with a prominent speckled pattern on immunofluorescence. This speckled pattern had also been noted in 1966. She was negative for rheumatoid factor on both latex and Rose-Waaler tests. Immunoglobulins and serum C3 were normal. DNA binding capacity was 16% (normal under 30%).

Extractable Nuclear Antigen was prepared by the method of Mattioli and Reichlin (1971). Immunodiffusion of the patient's serum against the antigen by Ouchterlony technique gave a positive precipitin reaction (fig. 2). Treatment of the antigen with trypsin and the RNAse abolished the reaction.

Comment

The patient's illness began with features consistent with a diagnosis of systemic lupus erythematosus (Cohen and Canoso, 1972) but her course over the last 10 years was more suggestive of systemic sclerosis, being dominated by severe Raynaud's phenomenon and the development of sclerodactyly and ischaemic necrosis with eventual loss of most of the fingertips. More recent investigations showed raised muscle enzyme levels suggesting myositis, mildly abnormal small-bowel study results, pulmonary diffusion defects, iron-deficiency anaemia, and a persistently raised E.S.R. In suggesting that this patient did not have systemic lupus erythematosus the important negative findings were the persistent absence of significant titres of antibodies to native DNA and normal C3 levels. (Hughes *et al.*, 1971).

Sharp *et al.* (1972) over an eight-year period of observation noted a group of patients combining features of systemic lupus erythematosus, polymyositis, and scleroderma. They noted that, as distinct from systemic lupus erythematosus, high titres of antinuclear factor of the "speckled" pattern persisted through periods of clinical remission. This led to the isolation of a distinct extractable nuclear antigen, an RNA-protein. Patients with so-called "mixed connective tissue disease" showed extraordinarily high titres to this antigen. This group of patients showed low or absent titres of anti-DNA antibodies and were notable for their absence of renal disease.

Reichlin and Mattioli (1972) reported a similar group of patients with precipitating antibodies against a soluble nuclear ribonucleoprotein. While the RNA protein antigen used by Reichlin and Mattioli (1972) (and by ourselves) differed in some respects from that of Sharp *et al.* (1972) it seems that the two groups of patients have much in common.

Since mixed connective tissue disease can show many of the features of systemic lupus erythematosus, the early differentiation of this group with its less aggressive clinical course, absence of renal disease, and good response to steroids is clearly required for prognostic purposes. Extractable nuclear antigen may provide an easily detectable immunological marker for such cases.

The point has been made that patients with mixed connective tissue disease have a better prognosis for life than those with systemic lupus erythematosus, but our patient illustrates that the morbidity can be severe—in this case, with necrosis and subsequent amputation of most of her finger tips due to Raynaud's phenomenon.

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