Eskeland (1962) has pointed out that fatal pulmonary embolism is rare in patients below the age of 75 with fractures of the femoral neck and has suggested that anticoagulant treatment might be reserved for this group. This is, however, the group in which control is so difficult and in which the complications of anticoagulant treatment are most common. While there can be little doubt that the mortality from embolism can be reduced in this way, it seems likely that early operation and early weight-bearing may achieve a similar effect without the risks which anticoagulant treatment involves. In these patients such a regime may make prophylactic anticoagulants unnecessary.

### Conclusions

The merits of early operation in a patient with a trochanteric fracture are almost entirely self-evident, but it is still surprising how many of these patients wait for some days before the fracture is secured. Most of the injuries in this series had been treated within 24 hours. Delay has usually been either in diagnosis or in arranging for admission. Occasionally an elderly woman living alone may fall and remain unable to move until she is discovered by her neighbours a day or two later.

There appears to be nothing to be gained from delaying the operation to correct medical defects. Few of these patients might be regarded as fit for their age, but most of their disabilities will not improve by a few days' medical treatment, and it is almost always preferable to secure the fracture first and afterwards to engage in such medical treatment as is appropriate.

It is doubtful whether there is any trochanteric fracture which cannot be secured by internal fixation, and splintage of any other sort is normally unnecessary. The relief of pain and the associated improvement in general condition are so marked that even in a patient who was not ambulant before the fracture occurred operation is always worth performing.

Internal fixation should normally be secure enough to permit immediate weight-bearing, and it is rare indeed to find a patient in whom this cannot be achieved. After a day or two of discomfort these patients progress rapidly to walking with a frame and later with sticks, and half the survivors can be expected to return to their own homes within three weeks of the accident.

The dangers of anticoagulant treatment in the elderly are formidable, and it is doubtful whether its value in preventing thrombosis and embolism outweighs its dangers.

### Summary

Sixty-nine trochanteric fractures of the femur have been treated by immediate fixation with a Jewett nail-plate, early weight-bearing, and anticoagulants.

There were 18 deaths in this series, giving a mortality of 26%. The average stay in hospital in the survivors was 26 days, and more than half of them went home bearing weight, using one or two sticks, within three weeks of the injury.

Most of these patients received prophylactic phenindione treatment during the post-operative period. It seems likely that the risks of anticoagulant treatment in these patients are greater than the risks of femoral thrombosis and embolism.

There was no complication attributable to immediate weight-bearing, and the anatomical reconstitution of the femoral neck and upper femoral shaft was uniformly good.

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# ANTINUCLEAR FACTOR AND OTHER ANTIBODIES IN BLOOD AND LIVER DISEASES

BY

**E. J. HOLBOROW, M.D.**

**G. L. ASHERSON,* B.M., B.Ch., M.R.C.P.**

**G. D. JOHNSON, F.I.M.L.T.**

*Rheumatism Research Unit (M.R.C.), Canadian Red Cross Memorial Hospital, Taplow, Maidenhead, Berkshire*

AND

**R. D. S. BARNES, M.B.**
*Department of Clinical Pathology*

**D. S. CARMICHAEL, M.B.**
*Department of Haematology*
*Guy's Hospital, London*

Auto-antibodies have been demonstrated in systemic lupus erythematosus, Sjögren's disease, rheumatoid arthritis, and other conditions. They include the antinuclear factors, complement-fixing antibodies against liver and other organs, the rheumatoid factor, and antibodies against red cells (see Hijmans, Doniach, Roitt, and Holborow, 1961). As immunological mechanisms are thought to play a part in certain blood and liver diseases it was of interest to determine the incidence of antibodies in these conditions.

### Materials and Methods

*Selection of Cases.*—Patients with blood diseases, including pernicious anaemia, haemolytic anaemia, thrombocytopenia, agranulocytosis, leukaemia, Hodgkin's disease, lymphosarcoma, multiple myeloma, and infectious mononucleosis, seen by the pathologist during six months were examined as well as sera from normal subjects. The miscellaneous group in the accompanying Table included single cases of anaemia due to folic-acid deficiency without steatorrhoea, post-gastrectomy anaemia, anaemia with steatorrhoea, familial acholuric jaundice, auto-immune haemolytic anaemia, anaemia secondary to uraemia, idiopathic aplastic anaemia, agranulocytosis possibly due to sulphonamides, anaemia secondary to carcinoma of the stomach, anaemia secondary to subacute bacterial endocarditis, and haemophilia. The patients with infectious mononucleosis had Downey cells and a positive Paul–Bunnell reaction. Patients with liver disease were selected on the basis of abnormal liver-function tests and clinical evidence of hepatobiliary disorder. The patient with scleroderma was included because she presented with agranulocytosis. The following laboratory tests were read without knowledge of the diagnosis.

*Fluorescent Test for Antinuclear Factor.*—The indirect technique was used (Weir, Holborow, and Johnson, 1961).

*Beit Memorial Fellow.

*Complement Fixation.*—The complement-fixation test for antibody against rat liver and kidney was performed following Asherson and Broberger (1961). However, 3 $MHD_{100}$ of complement were used. Rat tissue was employed, as Gajdusek (1958) had found that active sera gave similar titres with human and rat tissue. The results were expressed as the reciprocal of the highest dilution of serum giving 2+ (50%) haemolysis, estimated visually. A titre greater than 8 was regarded as significantly raised.

*L.E. Cell Test.*—All sera were tested by the indirect method (Dacie, 1954). The direct method (Zimmer and Hargraves, 1952) was also used in some cases.

*Miscellaneous Methods.*—The Hyland "RA-test" for rheumatoid factor (Greenbury, 1960), and the Hyland "CR-test" for C-reactive protein were employed.

## Results

The sera of 72 patients and 21 normal subjects were examined for antibodies, and the results are shown in the Table.

*Liver Disease.*—The patients with infectious hepatitis had a high incidence of rheumatoid factor and complement-fixing antibodies to rat liver. Seven of the 13 patients had a titre against rat liver from 16 to 64, while five had a positive latex test. Both tests were positive in four patients. One patient gave a positive Wassermann reaction and two a doubtful weak positive antinuclear-factor test. All the patients showed abnormal flocculation tests, most had a raised serum bilirubin, and four had a positive C-reactive protein test. One of the three patients with extrahepatic obstructive jaundice had a titre of complement-fixing antibody of 16 and biochemical evidence of parenchymal liver damage. Both the patients with biliary cirrhosis had complement-fixing antibodies in a titre of 32 to 64 and one had a positive latex test. One of these patients also had pernicious anaemia and the other had rheumatoid arthritis. The two patients with portal cirrhosis had a positive latex test.

*Incidence of Antinuclear Factor, Complement-fixing Antibodies to Rat Liver and Kidney, and Rheumatoid Factor in Various Conditions*

| Diagnosis | No. of Cases | Antinuclear Factor Test | | Complement-fixing Antibodies to Rat Liver in Titre of | | | | | Rheumatoid Factor |
|---|---|---|---|---|---|---|---|---|---|
| | | Positive | Doubtful Weak Positive | 8 | 16* | 32 | 64 | a.c.† | |
| Liver disease: | 22 | 0 | 2 | 1 | 5 | 2 | 4 | 0 | 10 |
| Infectious hepatitis .. | 13 | 0 | 2 | 1 | 4 | 0 | 3 | 0 | 5‡ |
| Hepatic necrosis .. | 1 | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 1 |
| Portal cirrhosis | 2 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 2 |
| Cirrhosis due to haemochromatosis | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Primary biliary cirrhosis .. | 2 | | 0 | 0 | 0 | 1 | 1 | 0 | 1 |
| Obstructive jaundice (extrahepatic) | 3 | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 1§ |
| Blood disease: | 50 | 3 | 3 | 3 | 4 | 0 | 0 | 3 | 6 |
| Acute leukaemia | 3 | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 0 |
| Chronic myeloid leukaemia .. | 5 | 0 | 1 | 0 | 1 | 0 | 0 | 0 | 1‖ |
| Chronic lymphatic leukaemia .. | 7 | 0 | 1 | 0 | 0 | 0 | 0 | 0 | 1 |
| Lymphosarcoma .. | 2 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Hodgkin's disease .. | 3 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Multiple myeloma .. | 3 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 1 |
| Primary polycythaemia | 2 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Pernicious anaemia .. | 4 | 0 | 0 | 0 | 0 | 0 | 0 | 2 | 0 |
| Pyridoxine-responsive anaemia .. | 1 | 0 | 0 | 1 | 0 | 0 | 0 | 0 | 1 |
| Aplastic anaemia and thymoma | 1 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Scleroderma with agranulocytosis .. | 1 | 1 | 0 | 0 | 1 | 0 | 0 | 0 | 1 |
| Infectious mononucleosis .. | 7 | 1 | 1 | 2 | 1 | 0 | 0 | 0 | 1 |
| Miscellaneous | 11 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Normal controls | 21 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |

* Lowest titre of complement-fixing antibody regarded as significantly raised.
† Serum anticomplementary.
‡ Four of these patients had a positive complement-fixation test.
§ Latex test equivocally positive.
‖ This patient also had a positive complement-fixation test.

*Blood Disease.*—The Table shows the diagnosis in 50 patients. Antinuclear factor was detected in a patient with thymoma and aplastic anaemia, one with scleroderma who presented with agranulocytosis, and one with infectious mononucleosis. A doubtful weak positive reaction occurred in one patient with chronic myeloid leukaemia, one with chronic lymphatic leukaemia, and one with infectious mononucleosis. The L.E. cell test and the test for antibodies against nucleoprotein were negative. A raised titre of complement-fixing antibodies against rat liver or kidney was found in one of five patients with chronic myeloid leukaemia, in one of the three with acute leukaemia, and in the patient with scleroderma. Two of the seven patients with infectious mononucleosis gave a positive reaction and three other patients gave a reaction below the titre regarded as significant. One patient with multiple myeloma had an anticomplementary titre of 256. The sera of two patients with pernicious anaemia were also anticomplementary. The latex test for rheumatoid factor was positive in single cases of chronic lymphatic leukaemia, multiple myeloma, infectious mononucleosis, pyridoxine-responsive anaemia, and scleroderma. C-reactive protein was detected in many of these patients, including one with macrocytic anaemia due to folic-acid deficiency and one with pyridoxine-responsive anaemia.

## Discussion

In this series antibodies against nuclei were uncommon. Complement-fixing antibody to rat liver and kidney and the rheumatoid factor occurred mainly in patients with liver disease. These findings were in keeping with those previously reported. Antinuclear factor occurs in systemic lupus erythematosus, scleroderma, and Sjögren's disease (Bunim, 1961) and in certain patients with rheumatoid arthritis and liver disease (Weir *et al.*, 1961), including primary biliary cirrhosis (Paronetto, Schaffner, and Popper, 1961).

Antibodies against human and rat liver occur in systemic lupus erythematosus and Sjögren's disease, primary biliary cirrhosis (Deicher, Holman, and Kunkel, 1960, infectious hepatitis (see Gajdusek, 1958; Mackay and Gajdusek, 1958), and in lower incidence in rheumatoid arthritis (Asherson and Broberger, 1961) and portal cirrhosis. These antibodies also occur in syphilis and other conditions with a positive Wassermann reaction.

Positive latex tests occur in most patients with rheumatoid arthritis and Sjögren's disease and in some patients with sarcoid, syphilis, liver disease, and viral infections (Dresner and Trombly, 1959). In this series patients with infectious hepatitis showed a high incidence of complement-fixing antibody and rheumatoid factor.

The occurrence of autoantibodies in infectious hepatitis may be an example of autoantibody formation following intracellular infection (Davis, 1944).

The patient with thymoma and aplastic anaemia who gave a positive antinuclear factor test was of particular interest. The association of thymoma with myasthenia gravis in which antibodies to muscle occur (Strauss, Seegal, Hsu, Burkholder, Nastuk, and Osserman, 1960) suggests that the thymus may play a part in autoimmune disease. The occurrence of antinuclear factor in a patient with thymoma provides circumstantial evidence for this view.

Hijmans *et al.* (1961) and others have shown that antinuclear factor is nearly always present in systemic lupus erythematosus. Our finding that it is usually absent in blood and liver disorders underlines the value of the antinuclear factor test in the diagnosis of systemic lupus erythematosus.

**Summary**

Tests for antibodies commonly associated with autoimmune disease were carried out on sera from patients with blood and liver disorders. Antinuclear factor was definitely present in one case of scleroderma with agranulocytosis, one case of thymoma with aplastic anaemia, and one case of infectious mononucleosis.

Complement-fixing antibodies against rat liver and kidney were significantly raised in 7 of the 13 patients with infectious hepatitis and in two of the seven patients with glandular fever.

The latex test for rheumatoid factor was positive in 10 of the 22 patients with liver disease.

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**Correction.**—The beginning of the second paragraph of the summary of the paper by Drs. Hugh Garland and David Sumner and by Mr. J. M. P. Clark (March 2, p. 581) should have read as follows: "The most frequent symptom is pain, which may involve the whole hand or extend up to the shoulder. The second commonest symptom is tingling, which is limited to the hand."

# Medical Memoranda

## B.C.G. and Sarcoidosis

Scadding (1960) restated his view that most cases of sarcoidosis seen in England are probably a manifestation of a tuberculous infection. He also considers that "there may well be other agents, known and as yet unknown, besides the tubercle bacillus, which can cause sarcoidosis in a susceptible individual."

That B.C.G. may be such an agent has been suggested by reports of cases of sarcoidosis occurring after B.C.G. vaccination (Larsen, 1950; Richards and Steingold, 1952; Pfisterer *et al.*, 1954; Birkhäuser, 1957; Fried and Genz, 1958; Ellman and Andrews, 1959). It cannot be denied that most or all such cases may be no more than mere coincidence (Törnell, 1954). However, five of Larsen's (1950) eight cases were found to have bilateral hilar lymphadenopathy only one to four months after B.C.G., having had normal chest *x*-ray pictures immediately before B.C.G. in four cases and immediately after in the fifth. He considered a coincidental relationship unlikely.

The case described developed symptoms attributable to sarcoidosis within 48 hours of a B.C.G. vaccination. This is probably the most dramatic temporal relationship of sarcoidosis to B.C.G. yet published, and is reported in the belief that it may throw some light on the mystery surrounding the aetiology of sarcoidosis.

### CASE REPORT

A coloured nurse from British Guiana was found to be Mantoux-positive at the start of her training in England in 1956 at the age of 25. In February, 1961, a routine chest x-ray film was normal. In March, at the start of a health visitors' training course, she was found to be Heaf-negative —this is approximately equivalent to 10 tuberculin units (T.U.) (Stewart *et al.*, 1958)—and was given B.C.G. (0.1 ml. intradermally of fresh liquid vaccine batch No. 1454, prepared by the State Serum Institute, Copenhagen, and supplied by the Ministry of Health). This produced, according to the patient herself, a papule after a few days, a small ulcer after two to three weeks, and later healing.

In August she was still Heaf-negative, and on 18th of that month was given a further dose of B.C.G. (batch No. 1477) as above. The local reaction, according to the patient, followed an identical course to that of the March vaccination.

However, having been entirely well and symptom-free throughout this period, she developed breathlessness on exertion, with cough and a little mucoid sputum, 24 to 48 hours after this second B.C.G. Within two weeks she also had retrosternal pain on coughing, malaise, and fever, with persistent vomiting, and a few days before being first seen at University College Hospital on September 22 she noticed swelling of her face and bilateral conjunctivitis. A chest *x*-ray examination on September 15 showed bilateral hilar lymphadenopathy.

On admission on October 4 she was unwell, with a continued pyrexia of about 100° F. (37.8° C.), and had lost 22 lb. (10 kg.) during her illness. The recent vaccination site showed a scab on a healed ulcer about 1 cm. in diameter, with only a flat scar at the March vaccination site. Both submandibular salivary glands were palpably enlarged and non-tender, and there was bilateral conjunctivitis. Slit-lamp microscopy (Mr. E. J. Arnott) showed translucent follicles scattered throughout the conjunctivae, especially in the lower palpebral fissures, but also on the ocular conjunctivae. This appearance was thought to be suggestive of a sarcoid conjunctivitis, but unfortunately conjunctival biopsy gave an inadequate specimen for histological confirmation. There