FELTY'S SYNDROME

RADIO-ACTIVE ISOTOPE STUDIES AND SPLENECTOMY

BY

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Felty (1924) described five patients with chronic arthritis, splenomegaly, leucopenia, and pigmentation. Since then the association between rheumatoid arthritis, splenomegaly, and leucopenia has been referred to as Felty's syndrome, although it is generally believed that it is not a separate disease entity (Curtis and Pollard, 1940; Short, Bauer, and Reynolds, 1957).

The aetiology of the leucopenia in Felty's syndrome is unknown. Originally it was considered that chronic sepsis was the cause (Singer and Levy, 1936), but it is now thought that hypersplenism is the chief factor. Hutchison and Alexander (1954) postulated that a splenic factor inhibited the normal production of white cells in the bone marrow of patients with Felty's syndrome. Hirschboeck (1946) suggested that the white cells might also be removed from the circulation by the spleen. He measured the white cells in the splenic artery and vein in a patient undergoing splenectomy for Felty's syndrome and the results showed removal of the cells by the spleen, but Hutchison and Alexander (1954) were unable to confirm this.

The bone marrow in Felty's syndrome has been reported as showing a variety of changes—either maturation arrest (Hirschboeck, 1946; Gauld, 1949), hypoplastic granulopoiesis (Smith and McCabe, 1948), or hyperplastic granulopoiesis (De Gruchy and Langley, 1961), or it may be normal (Steinberg, 1953).

Investigations of patients with hypersplenism from causes other than Felty's syndrome have also supported both the theory that white blood-cell production was abnormal (Welch and Dameshek, 1950) and the theory that there is an increased destruction or sequestration of white cells by the

spleen (Wiseman and Doan, 1939; Wright, Doan, Bouroncle, and Zollinger, 1951). Fluorescent anti-human globulin has been used to demonstrate antibodies to leucocytes in leucopenic patients, including some cases of Felty's syndrome (Calabresi, Edwards, and Schilling, 1959). It is probable that the mechanism of the leucopenia in Felty's syndrome involves more than one process (Hirschboeck, 1946; Hutt, Richardson, and Staffurth, 1951; Wiard and Robbins, 1952).

Drug therapy for Felty's syndrome has not been successful. Steinberg (1942) reported that liver extract had helped two out of three cases of Felty's syndrome and Ellman, Cudkowicz, and Elwood (1955) mentioned the importance of blood transfusion as an ancillary aid. Although corticosteroids may help for a short period (Varadi, 1955), they do not significantly affect the leucopenia (Steinberg, 1953; Hutchison and Alexander, 1954; Fitzpatrick and Woodruff, 1955; De Gruchy, 1958). Since Hanrahan and Miller (1932) reported the beneficial effects of splenectomy on the leucopenia, many confirmatory reports have appeared (Steinberg, 1953; Cudkowicz, 1956; Blau and Willcox, 1957; Geer and Laszlo, 1957; De Gruchy and Langley, 1961). Custer and McKee (1958) stated that, of 67 reported patients who had had a splenectomy for Felty's syndrome, the operation had provided worth-while relief in 52, the leucocyte count rising within a short time of the splenectomy. De Gruchy and Langley (1961) noted response within fifteen minutes in one case. Occasionally there is only a partial improvement in the leucocyte count (Dougherty, 1953) and in some cases the initial rise is not fully maintained (De Gruchy and Langley, 1961). In those patients in whom leucopenia was accompanied by infection, the improvement in the leucocyte count after the operation was also accompanied by a diminution of septic complications.

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The effects of the splenectomy on the arthritis were less definite. Hanrahan and Miller (1932) and Hutt and others (1951) noted an improvement, but Gauld (1949) observed a deterioration.

We report two patients in whom radio-isotope and antibody studies were made who were treated by splenectomy, and the effects followed for one year.

Case Reports

Case 1, a female born in 1907, whose mother had rheumatoid arthritis, gave a history of rheumatoid arthritis which began in 1947. The first symptoms were in the fingers, and later the hands, wrists, elbow, shoulders, feet, ankles, knees, and hips were involved. In 1954 the affected joints showed the changes of active rheumatoid arthritis. Rheumatoid nodules were present. The Waaler-Rose test was positive at a titre of 1:256 and the radiological changes were those of typical rheumatoid arthritis.

In 1954 there was no splenomegaly and the blood count was normal. By 1957 the arthritis had progressed and treatment with prednisolone 15 mg. daily was begun.

In 1962 the patient developed an infection of the foot and later cellulitis of the cheek and ear. This required intensive chemotherapy and repeated blood transfusions. It was decided to carry out a splenectomy in March, 1962. Removal of the spleen (528 g.) showed prominent Malpighian bodies with hyperplastic centres. The pulp was congested and unusually cellular, with numerous plasma cells and macrophages containing haemosiderin. Prussian-blue staining showed considerable intra- and extra-cellular iron. After the splenectomy, there was a rise in the circulating neutrophils (Fig. 1) and a general improvement in the arthritis.

The patient has remained well for over a year since the operation. Treatment with betamethasone continues.

Haematological Aspects of Case 1

In spite of recurrent infections, in the ten months preceding splenectomy the total leucocyte count remained at about 1,000/c. mm. On one occasion the count rose to 4,500/c. mm., but neutrophils comprised only 10 per cent. of the total count. The total leucocytes fell to below 800/c. mm. several times. The neutrophils showed a marked "shift to the left", metamyelocytes being a constant feature.

Fig. 1.—Findings in Case 1.

In 1958 deformity of the joints of the hands was present and the spleen was palpable just below the costal margin; the blood count was still normal.

An attempt to withdraw prednisolone in 1961 was followed by a relapse of arthritis, and at this time the spleen was found to be approximately 5 cm. below the costal margin. Neutropenia was first noted and full haematological investigations were carried out. The rheumatoid changes in the joints had increased and treatment with betamethasone 3 mg. daily was begun.

There was persistent normochromic anaemia (mean corpuscular haemoglobin concentration 31 per cent., Hb 60-70 per cent.); reticulocytes 2 to 5 per cent.; platelets 150,000 to 90,000/c. mm.; lupus erythematosus (L.E.) cells were negative on several occasions; urinary urobilinogen normal.

Bone Marrow.—There was intense hyperplasia (nucleated count 450,000/c. mm.) involving both red and white cell precursors. Erythropoiesis was normoblastic.

Myelocytes and promyelocytes were numerous, but later forms and mature polymorphs were very scanty. Plasma cells were present in increased numbers. Numerous megakaryocytes were present in all stages of development.

Radio-isotope Studies.—The patient's red cells were labelled with radio-active sodium chromate (^{51}Cr) (Mollison and Veall, 1955). There was considerable shortening of the red cell life; the mean red cell life being 26 days (normal 110 days). Specimens of faeces collected during this period showed no significant loss of chromium-labelled cells from the gut.

Surface counting for radio-chromium, in accordance with the method of Hughes Jones and Szur (1957), failed to demonstrate any abnormal uptake of radio-active chromium by the liver or spleen (Fig. 2). Spleen:liver ratio showed an insignificant rise from 2.0 on Day 1 to 2.5 on Day 10.

These investigations clearly indicated a haemolytic element in the anaemia, but did not attribute any causative role to the spleen or liver.

Fig. 2.—Surface counting (^{51}Cr) in Case 1. "Excess counts" refer to the amount by which actual counts recorded over the liver and spleen exceed the calculated counts. The latter are calculated by assuming that radioactivity over these organs will fall in proportion to radioactivity over the heart. (All counts are adjusted to an initial counting rate of 1,000 per sec. over the heart on Day 1).

Immunological Features.—Total serum proteins—7.2 g./100 ml.; electrophoresis—raised gamma globulin. Direct Coombs' test—repeatedly negative; antinuclear factor—weakly positive.

Leucocyte and Platelet Antibodies.—These were not detected by saline or antiglobulin-consumption tests when sera were examined nine months before splenectomy. At the time of splenectomy leucocyte agglutinins were present to a titre of 1:16, but this may have been due to two blood transfusions which the patient received in the interval between the tests.

Haematological Effects of Splenectomy.—Splenectomy produced the expected rise in leucocytes and platelets within 24 hours and the increase has been sustained for the fifteen months since the operation (see Fig. 1).

Target cells and Howell-Jolly bodies appeared in the peripheral blood and there was an increase in the number of metamyelocytes. The haemoglobin has remained at a normal level. The estimation of the red cell survival was repeated six months after operation and was then normal (Fig. 3).

Fig. 3.—Red cell survival (^{51}Cr labelled red cells) in Case 1.

Case 2, a female born in 1895, developed in 1953 symptoms in both wrists which later spread to involve the hands, elbows, shoulders, neck, feet, ankles, knees, and hips. When she was seen in 1957 she had advanced rheumatoid arthritis, rheumatoid nodules were present, and the spleen was palpable. The Waaler-Rose test was positive at a titre of 1:512 and there were radiological changes of severe rheumatoid arthritis. There was no neutropenia. Gold treatment had been given in the past and after this simple analgesic drugs only. In 1959, during investigations for proctitis, the spleen was found to be enlarged to the umbilicus, and leucopenia was present.

There was a gradual deterioration in the arthritis; this required hospital admission in 1961, when haematological investigations were carried out. There was no evidence of infection, but she experienced recurrent episodes of pain in the left upper abdomen, possibly due to splenic inflammation.

In 1962 it was decided to carry out a splenectomy, and this was done in March. The operation was technically difficult, because of considerable perisplenitis. The spleen (771 g.) showed prominence of the Malpighian bodies with hyperplastic germinal centres. There was fibrosis of the pulp, plasma cells were not prominent, and no haemosiderin was present. There was no evidence of a splenic infarct.

The post-operative course was protracted, but the patient made a gradual recovery with steady improvement. The haematological abnormalities improved at first with some fluctuation later (Fig. 4). The symptoms of rheumatoid arthritis improved greatly and she remains well fifteen months after operation.

Haematological Aspects of Case 2

In the months preceding splenectomy there was persistent leucopenia and anaemia, but the haematological abnormalities were less severe than in Case 1. The findings before splenectomy were as follows:

Hb 67 per cent. (9.9 g./100 ml.), mean corpuscular haemoglobin concentration 30 per cent.; white blood cells 1,400; neutrophil polymorphs 28 per cent.; platelets 100,000/c. mm. reticulocytes 3 per cent.; urinary urobilinogen normal.

Fig. 4.—Findings in Case 2.

Bone Marrow.—A moderately cellular marrow (nucleated count 80,000/c. mm.); erythropoiesis normoblastic; all stages in white cell development well represented; plasma cells increased; megakaryocytes present in adequate numbers.

Radio-isotope Studies.—Red-cell survival and surface counting for radio-chromium (^{51}Cr) were carried out, using the same techniques as in Case 1. The mean cell life was normal (110 days) and there was no excessive accumulation of chromium in the liver or spleen.

Immunological Features.—Serum proteins—6.5 g./100 ml.; electrophoresis—raised gamma globulin; direct Coombs' test—negative on several occasions; L.E. cells—never found despite repeated examinations; anti-nuclear factor—negative.

Leucocyte Platelet Antibodies.—Not detected.

Haematological Effects of Splenectomy.—After the operation the haemoglobin and leucocyte levels improved within four hours (but transfusion with fresh whole blood was given). Thereafter this improvement was maintained (see Fig. 4).

Discussion

These two patients illustrate the beneficial effect of splenectomy, especially on haematological abnormalities and possibly on arthritis. Yet the type of haematological defect differed in the two cases. In the first case there was conclusive evidence of haemolytic anaemia, with shortening of red cell life. Surface counting data showed that the spleen was not the site of red cell destruction and an auto-

immune mechanism was unlikely with negative tests for red cell antibodies. In the second case there was no evidence of haemolysis. Nevertheless, the beneficial effect of splenectomy in both cases showed that the spleen was in some way responsible for the anaemia. It seems likely that the red cells were altered in their passage through the congested and hypertrophied splenic pulp, but that actual destruction (in Case 1) was not confined to the reticulo-endothelial system of the spleen. In experimental animals, following the intraperitoneal injection of methyl cellulose (Giblett, Motulsky, Cassard, Houghton and Finch, 1956), reticulo-endothelial hyperplasia with marked splenic enlargement developed. The red cell life was greatly reduced and this was corrected by splenectomy. There was no evidence for an auto-immune mechanism and the authors concluded that the haemolytic anaemia was the result of sequestration and increased phagocytosis by the hyperplastic reticulo-endothelial system of the spleen.

There is as yet no way of determining accurately the fate of the white blood cells. In both cases leucocyte antibodies were unlikely to have played a part in destruction of the circulating white cells. In both these cases a severe neutropenia was immediately corrected by splenectomy and the improvement has been maintained for a year. With the haematological improvement sepsis in Case 1 has resolved and not recurred. Infection was not

present in Case 2, in spite of a marked reduction in the neutrophil count. In neither case were platelet antibodies found.

Improvement in the rheumatoid arthritis over a year may occur during the natural course of the disease.

Both patients had a definite remission in their arthritis with reduction of joint pain and stiffness and greater mobility, and in Case 1 the requirement of steroid drugs was halved. This experience confirms the value of splenectomy in these cases and their failure to respond to repeated blood transfusion, antibiotics, and steroid therapy. The procedure is not unduly hazardous, even for patients with extremely low neutrophil counts.

Conclusion

Because of the improvement in the white and red blood cell counts following splenectomy, it is postulated that the spleen was the site of the haematological abnormality in these patients. The mechanism of the abnormality is uncertain. There was no evidence of depression of the white cell production in the bone marrow or of the white cell antibodies, and it is possible that the white cells were destroyed in the spleen. The findings for the red blood cells were different in the two cases. In the first case it is unlikely that the rheumatoid disease itself was the cause of the haemolysis, because the abnormality was not found after splenectomy and it is probable that a splenic factor was responsible for the haemolysis. In the second case the role of the spleen is less certain.

These findings suggest that the mechanism of Felty's syndrome is a variable one and support the view that Felty's syndrome is not a clinical entity but rather a non-specific hypersplenism associated with the splenic enlargement sometimes found in rheumatoid arthritis.

Summary

Two cases of rheumatoid arthritis with leucopenia and splenomegaly (Felty's syndrome) are described.

Both patients were anaemic; radio-isotope studies demonstrated a haemolytic process in one case but not in the other.

There were no significant circulating red or white cell or platelet antibodies.

Blood transfusion and steroids failed to control the disease.

Splenectomy produced a haematological and clinical improvement in both cases observed, so far, for one year.

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Le syndrome de Felty—études par des isotopes radioactifs et splenectomie**RÉSUMÉ**

On décrit deux cas d'arthrite rhumatismale avec leucopénie et splénomégalie (syndrome de Felty).

Les deux malades étaient anémiques; l'examen par des radio-isotopes révéla un processus hémolytique chez un malade mais non pas chez l'autre.

On ne trouva pas d'anticorps significatifs contre les érythrocytes, les leucocytes ou les thrombocytes dans la circulation.

On ne put pas arrêter la maladie par la transfusion sanguine ni par un traitement stéroïde.

La splenectomie amena dans les deux cas une amélioration hématologique et clinique encore présente, après un an.

El síndrome de Felty—estudios con isótopos radioactivos y esplenectomía**SUMARIO**

Se describen dos casos de artritis reumatoide con leucopenia y esplenomegalía (síndrome de Felty).

Ambos enfermos fueron anémicos; investigaciones con radio-isótopos revelaron un proceso hemolítico en un caso, pero no en el otro.

No se encontraron anticuerpos significativos contra los eritrocitos, los leucocitos o los trombocitos en la circulación.

No se llegó a controlar la enfermedad por transfusiones de sangre ni por tratamiento esteroide.

La esplenectomía produjo en ambos casos una mejoría hematológica y clínica aún presente, desde un año.