Felty’s syndrome

Clinical and serological analysis of 34 cases

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SUMMARY  Review of 34 cases of Felty’s syndrome showed this to be a form of ‘super’ rheumatoid disease because of the severity of joint disease, the prominence of extra-articular features, and the remarkable incidence of infection. The response to splenectomy in these 34 patients was shown by a return towards normal of peripheral blood abnormalities and a decrease in bone marrow granulopoiesis. Although some patients remained free of infection after splenectomy, others have continued to have infections despite the return of white blood cell counts to normal levels. Although splenectomy and subsequent increase in white blood cell levels may be beneficial, our experience suggests that other factors are important in the susceptibility to infection of Felty’s syndrome patients. Moreover, we think that splenectomy may have been instrumental in the fatal infection of one of our patients.

There has been a greater awareness of the clinical syndrome of rheumatoid arthritis, leucopenia, and splenomegaly since Felty described his 5 patients in 1924. Although the association of splenomegaly, leucopenia, and increased frequency of infections is well recognized, these features do not always present together in one patient, thus excluding a simple cause and effect explanation. Furthermore, several aspects of the clinical course of Felty’s syndrome remain unclear, for example the features of the articular and extra-articular disease, the aetiology of the leucopenia, the role of splenectomy, the duration of leucocytosis, and the frequency of infections after splenectomy. We attempted to answer these questions by reviewing 34 cases with Felty’s syndrome observed for a mean of 56 months.

Materials and methods

Thirty-four patients with Felty’s syndrome at the Wellesley Hospital were selected for study. They fulfilled all of the following criteria. (1) Classical or definite rheumatoid arthritis (ARA criteria). (2) Splenomegaly as detected by physical examination or by radioisotope scan. (3) Leucopenia of <4.0 × 10⁹/l, or neutropenia of <2.0 × 10⁹/l, or thrombocytopenia of <100 × 10⁹/l. (4) No other known causes for the cytopenia (e.g. drugs) or the splenomegaly (e.g. lymphoma).

All patients were evaluated at the time of diagnosis of Felty’s syndrome, and 27 were still being followed. 4 died and 3 have been lost to follow-up. Splenectomy had been performed in 12 of these patients. A detailed clinical and laboratory evaluation according to a predesigned protocol was carried out on 18 of these patients in the first half of 1975. The level of joint inflammatory activity was estimated according to the articular index method of Lansbury (1972), and by a count of inflamed joints and of synovial effusions. The severity of destruction in each joint was scored from stage 1+ to 3+ according to the method of Steinbrocker et al. (1949) and all those with 2+ or 3+ were considered to have advanced joint destruction. X-rays of the hands and feet were evaluated according to the method of Kellgren et al. (1963) and those with stage III and IV were tabulated.

Bone marrow aspirations were performed in 30 patients at the time of diagnosis and evaluated by an independent assessor. Serological tests included latex fixation for rheumatoid factor, fluorescent antinuclear antibody test, total haemolytic complement, C3, cellulose acetate electrophoresis, quantity-determination of immunoglobulins (IgG, IgA, IgM), and DNA-binding by the Farr technique using ¹²⁵I. Intradermal skin tests using SKS (10 U SK and 2.5 U SD/0.1 ml), PPD (5 U), Candida (1/100), and Trichophyton (1/30) were performed and the...
induration measured in mm 48 hours after application. Peripheral blood B and T lymphocyte populations were estimated by immune (Bianco et al., 1970) and nonimmune (Jondal et al., 1972) sheep erythrocyte rosette formation, respectively, in 8 patients. \textit{In vitro} lymphocyte responses to phytohaemagglutinin, pokeweed mitogen, and concanavalin A were determined by estimating the incorporation of \textsuperscript{3}H-thymidine into the DNA of blast cells (Greaves et al., 1974). These mitogen studies were performed before skin testing in 10 patients. Results are expressed as ratios of values compared with those of age- and sex-matched controls.

The coil test as described by Jensen et al. (1973) was used to study neutrophil kinetics in 7 Felty's patients (2 had had splenectomy), in 1 rheumatoid patient without Felty's, and in 2 normal subjects. Blood was withdrawn from each subject and approximately 500 ml blood was run into a Gambro dialyser with a 13.5 μm membrane (purchased from Gambro Lundia, Mississauga, Ontario). When the coil was filled the blood was allowed to stagnate for 30 minutes and then was infused back into the subject. Blood specimens for total white blood cell count and differentials were drawn from the opposite arm immediately before and after the original sample was taken, immediately before reinfusion of the coil blood and at 5, 15, 30, and 45 minutes, and 1, 2, 3, and 4 hours after the reinfusion was begun. The mean of the three preinfusion blood counts was taken as the baseline value for the neutrophil counts. The peak count was the highest recorded after the reinfusion was begun. The per cent increase in the neutrophil count after reinfusion was calculated by the formula:

\[
\frac{\text{peak count} - \text{baseline count}}{\text{baseline count}} = \% \text{ increase.}
\]

Results

\section*{Clinical evaluation}

Of the 34 patients with Felty's syndrome, 23 (68\%) were females and 11 (32\%) were males. The mean age at onset of the rheumatoid arthritis was 39 years (range 15–67 years), whereas the mean age at diagnosis of Felty's syndrome was 56 (range 41–72) years. Diagnosis of Felty's syndrome followed the onset of rheumatoid arthritis by a mean of 16.7 (range 0–38) years. Follow-up ranged from 3 months to 11 years (mean 4-7 years).

In Tables 1, 3, 4, describing the clinical and laboratory features of the patients with Felty's syndrome, comparison was made when possible with two previous studies of Felty's syndrome (Ruderman et al., 1968; Barnes et al., 1971) and with a large group of patients (127) with definite or classical rheumatoid arthritis severe enough to be admitted for treatment (Gordon et al., 1973).

At the time of diagnosis of Felty's syndrome, 87\% of the patients had active arthritis (Table 1). The mean (±SD) number of active joints, effusions, and articular index were 20.6±12.8 (n = 26), 2.8±3.5 (n = 22), and 92.6±52.1 (n = 21), respectively. Joint destruction was found in 91\%. Evaluation of hand x-rays showed stage 4 changes in 16 patients, stage 3 in 9, stage 2 in 6, stage 1 in 1, and stage 0 in 1 (Table 1).

Extra-articular manifestations of rheumatoid disease in addition to Felty's syndrome and anaemia were present in all but 2 patients, the mean number per patient being 2.9 (Tables 2, 3). Rheumatoid

\begin{table}
\caption{Articular features of 34 patients with Felty's syndrome compared with 127 hospitalized RA controls*}
\begin{tabular}{lcc}
\hline
& Felty's & RA controls \\
\hline
Articular index & 93 & 61 \\
Synovial effusions (\%) & 77 & 55 \\
Effusions/patient (n) & 2-8 & 2 \\
Active joint count (n) & 21 & 91 \\
Incidence of active arthritis (\%) & 100 & 55 \\
Joint destruction 2–3+ (\%) & 91 & 56 \\
X-ray stage III & IV (\%) & 74 & 40 \\
\hline
*Gordon et al. (1973).
\end{tabular}
\end{table}

\begin{table}
\caption{Number of extra-articular features in patients with Felty's syndrome (excluding Felty's syndrome and anaemia)}
\begin{tabular}{lcccccc}
\hline
No. of features & 0 & 1 & 2 & 3 & 4 & 5 & 6 \\
\hline
No. of patients & 2 & 6 & 7 & 7 & 6 & 4 & 2 \\
Mean = 2.9/patient \\
\hline
\end{tabular}
\end{table}

\begin{table}
\caption{Clinical features in 34 patients with Felty's syndrome compared with previous series* and RA controls†}
\begin{tabular}{lcccc}
\hline
Features & Present study (\%) & Ruderman (\%) & Barnes (\%) & RA controls (\%) \\
\hline
Rheumatoid nodules & 74 & 82 & 71 & 53 \\
Splenomegaly & 100 & 100 & 100 & 12 \\
Lymphadenopathy & 42 & 30 & 19 & 12 \\
Hepatomegaly & 68 & -- & -- & -- \\
Leg ulcers & 16 & 41 & 19 & -- \\
Periarticular neuropathy & 14 & 19 & 24 & 10 \\
Sjögren's & 48 & -- & 69 & -- \\
Episceritis & 3 & 11 & 5 & 9 \\
Pericarditis & 0 & 7 & 0 & 2 \\
Pleuritis & 22 & 15 & 0 & 2 \\
Pulmonary fibrosis & 20 & -- & -- & 20 \\
\hline
* Ruderman et al., 1968; Barnes et al., 1971. \\
† Gordon et al., 1973. \\
-- = not ascertained.
\end{tabular}
\end{table}
nodules developed in 20/27 patients (74%). Splenomegaly, present in all patients by definition, was detected in 30 patients by palpation and in 4 by radioisotope scanning. Hepatomegaly and lymphadenopathy were present in 23/34 (68%) and 14/33 (42%) patients respectively. Systemic symptoms including fever and substantial weight loss (>10%) occurred in 22/34 (65%) patients. Leg ulcers and skin pigmentation were present in 5/31 (16%) and 7/32 (22%) patients, pigmentation accompanying 4 of the 5 leg ulcers. Sjögren's syndrome was diagnosed in 13/27 (48%) patients using Schirmer's test. Abnormalities of the nasal septum were found in 8/27 (30%) patients: perforation 1, ulceration 3, and erythema 4. Ocular disorders in addition to Sjögren's syndrome occurred in 13/34 (38%) patients: 8 instances of conjunctivitis, 4 of cataracts, 1 of episcleritis, and 3 of unilaterally irregular pupils. Of the 8 patients with conjunctivitis 6 had Sjögren's syndrome.

No examples of cardiac lesions definitely attributable to rheumatoid disease were found. However, 4 patients had hypertensive heart disease, 4 ischaemic heart disease, 3 unexplained cardiomegaly, and 6 nonspecific electrocardiographic changes. Type IV hyperlipidaemia was present in 5 patients. Pulmonary fibrosis and pleurisy were detected in 16/32 (50%) and 7/32 (22%), respectively. Other pulmonary lesions included atelectasis in 4, Ghon complex in 3, apical infiltrates or scarring in 3, nodules in 2, and a cavity lesion in 1. Noncompressive neuropathies occurred in 4/29 (14%) patients. Proximal muscle weakness in 10/30 (33%) patients was associated with raised creatine phosphokinase in only one. Six neoplasms occurred in 5 patients, including one case each of squamous cell carcinoma of the skin, basal cell carcinoma of the scalp, malignant melanoma, adenocarcinoma of colon, lymphosarcoma, and chronic lymphocytic leukaemia. A further patient may have multiple myeloma.

Of the 4 patients who died, only the one with chronic lymphocytic leukaemia had had a splenectomy. One patient died from bronchopneumonia superimposed on lungs markedly affected by fibrosis and amyloidosis, the latter also affecting the liver and gastrointestinal tract. A third patient died of generalized inanition, and the fourth of myocardial infarction.

LABORATORY EVALUATION

The erythrocyte sedimentation rate (ESR, Westergren) (Table 4) at diagnosis was 85±31 (SD) mm/h. 27 of the 34 patients were anaemic, the mean haemoglobin being 11·1±2·0 (SD) g/dl. The mean highest recorded reticulocyte count was 3·2% (range 0·4–6·1%). 12 of 15 patients had low serum iron concentrations (mean 41·3±29·7 μg/100 ml; 7·4±5·3 μmol/l) and 2/15 had a raised iron binding capacity (mean 319±54 μg/100 ml; 57±9·7 μmol/l).

All but one patient was leucopenic (lowest mean recorded value 2·14±1·06 (SD) ×109/l), and 29/33 patients were neutropenic including the patient who was not leucopenic. The mean (±SD) lymphocyte, monocyte, and eosinophil counts were 0·9±0·85, 0·11±0·08, 0·07±0·08 ×109/l. All but one patient was lymphopenic (<1·5×109/l) and none had eosinophilia. Thrombocytopenia (<100 platelets ×109/l) was present in 5/33 patients, the mean lowest platelet count being 195±108 ×109/l.

Bone marrow aspirations performed on 30 of the patients at the time of diagnosis (Table 5) showed hypercellularity in most instances. In 90% of the 30 patients granulopoiesis was accelerated or normal with a left shift in 60%. A surprising finding was the lack of iron staining in 67% of patients. Patients were thought to be losing blood through the rectum if 3 or more stool specimens gave a 2+ or greater guaiac result. 5 of 13 patients were thought losing blood through the rectum at the time of stool examination.

**Table 4 Laboratory features in 34 patients with Felty syndrome compared with previous series* and RA controls†**

<table>
<thead>
<tr>
<th></th>
<th>Present study</th>
<th>Ruderman</th>
<th>Barnes</th>
<th>RA controls</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hb (g/dl or %)</td>
<td>11±1</td>
<td>31%</td>
<td>31%</td>
<td>9–6</td>
</tr>
<tr>
<td>WBC (lowest mean)</td>
<td>2·138</td>
<td>1·74</td>
<td>1·545</td>
<td>8·2</td>
</tr>
<tr>
<td>Granulocytes</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(lowest mean) (×109/l)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Reticulocytes (%)</td>
<td>0·894</td>
<td>0·77</td>
<td>0·422</td>
<td>—</td>
</tr>
<tr>
<td>ESR (mm/h)</td>
<td>3·2</td>
<td>4·0</td>
<td>4·0</td>
<td>—</td>
</tr>
<tr>
<td>Platelets</td>
<td>85</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>(lowest mean) (×109/l)</td>
<td>195</td>
<td>172</td>
<td>166</td>
<td>—</td>
</tr>
<tr>
<td>24-hour urine protein</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(&gt;500 mg) (%)</td>
<td>39%</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Serum albumin (mean, g/l)</td>
<td>31</td>
<td>—</td>
<td>37</td>
<td>—</td>
</tr>
<tr>
<td>Serum globulin (mean, g/l)</td>
<td>19</td>
<td>26</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>RF titre (mean)</td>
<td>1·2898</td>
<td>1·3520</td>
<td>90</td>
<td>93</td>
</tr>
<tr>
<td>% positive</td>
<td>100</td>
<td>100</td>
<td>93</td>
<td>—</td>
</tr>
<tr>
<td>LE positive (%)</td>
<td>41%</td>
<td>12·5</td>
<td>25</td>
<td>17</td>
</tr>
<tr>
<td>ANF positive (%)</td>
<td>55</td>
<td>85</td>
<td>61</td>
<td>—</td>
</tr>
<tr>
<td>IgG (mean, g/l)</td>
<td>12·91</td>
<td>22·97</td>
<td>11·48</td>
<td>—</td>
</tr>
<tr>
<td>IgA (mean, g/l)</td>
<td>3·56</td>
<td>6·06</td>
<td>2·92</td>
<td>—</td>
</tr>
<tr>
<td>IgM (mean, g/l)</td>
<td>8·32</td>
<td>2·75</td>
<td>1·78</td>
<td>—</td>
</tr>
<tr>
<td>Total haemolytic</td>
<td>177</td>
<td>111%</td>
<td></td>
<td>—</td>
</tr>
<tr>
<td>complement</td>
<td></td>
<td>of control</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* - Ruderman et al. (1968); Barnes et al., (1971).
† - Gordon et al. (1973).

— = means not ascertained.
Lever function tests were not uncommonly abnormal. Alkaline phosphatase was increased in 7/31 (23%) patients. Raised aspartate transaminase (SGOT) or alanine transaminase (SGPT) was found in 6 patients, one of whom also had a raised alkaline phosphatase. Only 1/26 patients had a mildly raised serum bilirubin level. Sulphobromophthalein excretion after 45 minutes was abnormal in 6/22 (27%) patients, 4 of whom had abnormal liver enzymes. A prolonged prothrombin time and prolonged partial thromboplastin time were present in 4/27 (15%) and 10/19 (53%) patients, respectively. Mean serum albumin and gammaglobulin levels were 31 ±6 and 19 ±8 g/l respectively (Table 4). 15 of 34 (44%) patients were hypergammaglobulinemic. Liver specimens (biopsy 6, autopsy 1) showed lipoid granulomata in 2 (normal liver enzymes), increased fatty infiltration in 2 (raised alkaline phosphatase in 1), lobular hepatitis in 1 (raised SGOT and SGPT), simple liver cyst with normal parenchyma in 1 (raised alkaline phosphatase), and haemangiomata, amyloidosis, and liver congestion in the autopsy specimen. No cirrhosis or oesophageal varices were found in our patients.

Spleens from 12 splenectomies and 1 autopsy were examined. Spleen masses ranged from 210 to 1650 g, with no correlation to the degree of cytopenia. A subcapsular infarct was present in one patient and a subcapsular haematoma in another. An accessory spleen was removed in one case. Lipoid granulomata were present in the spleen of one patient and were also found in the liver. Aggregates of lipid-filled macrophages were present in another spleen. Venous sinusoids were congested in 7 spleens but sinus cell hyperplasia was not present. Reticular cell hyperplasia was found in 2 specimens. Lymphoid tissue in 2 cases showed germinal centre hyperplasia. No amyloidosis was present in any of the spleens. Thirty-one patients had at least one 24-hour urine collection for protein estimation. 25 (81%) excreted protein >200 mg/24 hours. Proteinuria >500 mg and 1000 mg/day was found in 12/31 (39%) and 4/31 (13%) patients, respectively (Table 4). No significantly abnormal urinary sediment was associated with these changes in most cases. Renal function tests in 22 patients showed a mean serum creatinine of 0.91 mg/100 ml (80.5 μmol/l) and a creatinine clearance of 82 ml/min. Only 2/29 patients had been taking potentially nephrotoxic drugs within 3 months of the assessments. Renal histology was available for 3. focal glomerulonephritis and ischaemic changes due to arteriosclerosis was present in one patient with >4.0 g protein/24 hours. Another patient with proteinuria had mild glomerular alterations with hypercellularity and increased mesangial matrix. Immunofluorescence was negative but electron microscopy showed fusion of the foot processes of the epithelial cells. The third specimen, taken post mortem from the kidney of the patient with amyloidosis, showed arterial and arteriolar nephrosclerosis but no amyloidosis though there was significant proteinuria.

### IMMUNOLOGICAL EVALUATION (Table 4)

All patients had rheumatoid factor as determined by the latex fixation test. With no titre being diluted out to >1/5120, the mean titre was 1/2898 ±1/1945 (SD). A titre of >1/640 was present in 29/34 patients. LE cells were detected in 11/27 (41%) patients and a positive antinuclear factor was present in 16/29 (55%). DNA-binding was not raised in the 8 patients in whom the test was performed, including 2 patients with antinuclear factor. Hypocomplementaemia was present in 2/22 (9%) patients. The mean total haemolytic complement was 177 ±42 units (normal 130–220) and the mean C3 1.25 ±0.33 g/l (normal 1.25–1.65 g/l). VDRVL was negative in all 21 patients tested.

Circulating B lymphocytes detected by the EAC-rosette technique in 8 patients numbered 27 ±11 (absolute number 0.758 ±0.827 cells ×10⁹/l) in the controls. Immunoglobulin determinations in 18 patients showed raised IgG in 6 (33%), IgM in 13 (72%), and IgA in 10 (56%). Circulating T lymphocytes as determined by the E-rosette technique in 8 patients numbered 62% ±8 (abs. no. 1658 ±1773/mm³), compared to 61% ±9 (abs. no. 1327 ±397/mm³) in the controls.

Anergy as determined by the four skin tests was present in 4/16 (25%) patients. In the mitogen studies, the mean (±SD) results for phytohaemagglutinin (PHA), concanavalin A (Con A), and pokeweed mitogen (PWM), expressed as a ratio of patient to control, in 10 patients were 0.9 ±0.3, 0.9 ±0.3, and 0.9 ±0.3, respectively.
0.8±0.6, and 1.0±0.5, respectively. Of these 10 patients, 3 were tested after splenectomy. PHA stimulation was considered to be significantly low in 2, both of whom had had splenectomies. 5 patients had low counts when stimulated by Con A, including the 3 splenectomized patients. 3 patients had a poor response to PWM including 1 of the splenectomized patients. One patient had increased responses to Con A and PWM and another to PWM alone. Both of these patients still had their spleens.

**Comparison of 12 Patients before and after Splenectomy (Table 6)**

Twelve patients were evaluated after splenectomy, after a mean of 27.6 months (Table 6). Mean haemoglobin values rose only slightly from 11.8-13.0 g/dl. However, the white cell count increased from a mean of 1.5 to 8.4×10^9/l (P<0.001), the increase being reflected both in the neutrophils (0.4-4.2×10^9/l; P<0.01) and the lymphocytes (0.8-4.0×10^9/l; P<0.01). The platelet count rose from 130 to 407×10^9/l (P<0.001). All patients had white cell counts >4.2×10^9/l, neutrophil counts >1.4×10^9/l, and platelets >220×10^9/l after splenectomy. The mean ESR was reduced from 72 to 53 mm/h and the gammaglobulin level reduced from 22.6 to 20.3 g/l after splenectomy.

Seven patients had bone marrow examinations before and after splenectomy, the mean interval after splenectomy being 30.6 months (Table 7). Cellularity was increased in all 7 before splenectomy and judged to be normal in 3 after splenectomy. Increased granulopoiesis returned to normal in 6 of the 7 after splenectomy. Erythropoiesis was increased in 6 of 7 before splenectomy and returned to normal in 2 after splenectomy. Before splenectomy, megakaryocytes were increased in 6 patients and decreased in the seventh, but afterwards were normal in 4 of the 6 and in the seventh. Stainability

**Table 6** Laboratory values in 12 patients before splenectomy and at follow-up

<table>
<thead>
<tr>
<th>Case no.</th>
<th>Follow-up (m)</th>
<th>Hb (g/dl)</th>
<th>WBC (×10^9/l)</th>
<th>Polymorphs (total) (×10^9/l)</th>
<th>Lymphocytes (×10^9/l)</th>
<th>Platelets (×10^9/l)</th>
<th>ESR (mm/h)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Pre</td>
<td>Post</td>
<td>Pre</td>
<td>Post</td>
<td>Pre</td>
<td>Post</td>
<td>Pre</td>
</tr>
<tr>
<td>2</td>
<td>39</td>
<td>13.3</td>
<td>15.1</td>
<td>1.2</td>
<td>6.7</td>
<td>0.20</td>
<td>2.75</td>
</tr>
<tr>
<td>3</td>
<td>22</td>
<td>11.2</td>
<td>10.8</td>
<td>1.7</td>
<td>11.6</td>
<td>0.73</td>
<td>7.31</td>
</tr>
<tr>
<td>4</td>
<td>56</td>
<td>11.1</td>
<td>12.9</td>
<td>0.7</td>
<td>10.5</td>
<td>0.17</td>
<td>3.38</td>
</tr>
<tr>
<td>8</td>
<td>28</td>
<td>11.9</td>
<td>13.8</td>
<td>3.4</td>
<td>6.9</td>
<td>1.70</td>
<td>3.10</td>
</tr>
<tr>
<td>11</td>
<td>37</td>
<td>9.8</td>
<td>11.5</td>
<td>1.5</td>
<td>5.5</td>
<td>0.15</td>
<td>3.13</td>
</tr>
<tr>
<td>13</td>
<td>4</td>
<td>6.6</td>
<td>12.1</td>
<td>0.8</td>
<td>5.8</td>
<td>0.14</td>
<td>1.39</td>
</tr>
<tr>
<td>15</td>
<td>42</td>
<td>12.8</td>
<td>18.0</td>
<td>1.0</td>
<td>16.7</td>
<td>0.99</td>
<td>9.52</td>
</tr>
<tr>
<td>17</td>
<td>23</td>
<td>13.3</td>
<td>14.7</td>
<td>1.5</td>
<td>9.5</td>
<td>0.22</td>
<td>2.59</td>
</tr>
<tr>
<td>18</td>
<td>29</td>
<td>15.8</td>
<td>11.8</td>
<td>1.0</td>
<td>8.2</td>
<td>0.37</td>
<td>6.48</td>
</tr>
<tr>
<td>20</td>
<td>6</td>
<td>12.3</td>
<td>9.6</td>
<td>2.3</td>
<td>4.2</td>
<td>-</td>
<td>1.64</td>
</tr>
<tr>
<td>26</td>
<td>74</td>
<td>12.0</td>
<td>-</td>
<td>42.8</td>
<td>-</td>
<td>-</td>
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<td>11.3</td>
<td>13.1</td>
<td>1.5</td>
<td>6.6</td>
<td>0.56</td>
<td>2.64</td>
</tr>
<tr>
<td>Mean</td>
<td>27.6</td>
<td>11.8</td>
<td>13.0</td>
<td>1.5</td>
<td>8.4</td>
<td>0.43</td>
<td>4.23</td>
</tr>
</tbody>
</table>

\[P < 0.2 < 0.01 < 0.01 < 0.01 < 0.01 < 0.01 < 0.01 < 0.01 < 0.01 < 0.01 < 0.01\]

- not ascertained.

**Table 7** Pre- and postsplenectomy bone marrow studies in 7 patients (pre- over postsplenectomy values)

<table>
<thead>
<tr>
<th>Case no.</th>
<th>Months of post splenectomy</th>
<th>Cellularity</th>
<th>Granulopoiesis</th>
<th>Erythropoiesis</th>
<th>Iron</th>
<th>Megakaryocytes</th>
</tr>
</thead>
<tbody>
<tr>
<td>3</td>
<td>22</td>
<td>↑</td>
<td>↑</td>
<td>↑</td>
<td>0</td>
<td>↑</td>
</tr>
<tr>
<td>4</td>
<td>56</td>
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<td>↑</td>
</tr>
<tr>
<td>11</td>
<td>37</td>
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N = normal cellularity; ↑ = increased cellularity; ↓ = decreased cellularity; 0 = absence of iron; NA = not assessed
iron was absent in 6 of 7 patients before splenectomy and returned to normal in only 1, 29 months after splenectomy.

INFECTION
Twenty-seven patients were diagnosed as having 41 episodes of infection. Of these, 8 underwent splenectomy. In most infection occurred between a few months and 2 years before splenectomy and was indeed the indication for splenectomy. Infections in the 27 patients tended to be due to common organisms (staphylococcus, streptococcus, haemophilus, and Gram-negative bacilli comprising 92% of the infections) and responded to usual antibiotic therapy. In 9 instances of 'clinical sepsis', consisting of fever and rigors, no specific infectious agent was isolated, but recovery occurred with antibiotic therapy. In the 8 patients who underwent splenectomy 17 episodes of infection occurred in 4 during a mean follow-up of 27.6 months. The type and location of infection had a similar distribution to those occurring before splenectomy. The other 4 have remained free of bacterial infection after a mean follow-up of 48 months, although 2 developed herpes zoster. 4 additional patients who had no prior infections underwent splenectomy. 1 died in the immediate postoperative period of Gram-negative sepsis. The other 3 have remained free of bacterial infection for a mean of 63 months.

Prednisone was taken by 22 patients, none receiving more than 15 mg/day. Of 27 patients who had infection before splenectomy, 19 had received steroids compared with 3/7 patients who developed no infections.

LEUCOCYTE KINETICS (TABLE 8)
We studied leucocyte kinetics by the coil test, which has been shown to express bone marrow neutrophil reserve (Brubaker and Nolph, 1971). Although our numbers are small, none of our patients with splenomegaly showed as great a neutrophil reserve as did the two patients with Felty's syndrome without spleens, and 4/5 patients with splenomegaly had lower neutrophil reserves than the 3 control patients.

Discussion
Our experience shows that Felty's syndrome is a form of 'super' rheumatoid disease as reflected by the severity of joint disease, the prominence of extra-articular features, and a remarkable incidence of infections. Assessment of joint disease showed that patients had very destructive arthritis with a much higher incidence of deformities and bone and cartilage destruction than did a group of patients with definite or classical rheumatoid arthritis (Table 1). When compared to patients with severe rheumatoid disease, the group with Felty's syndrome showed a higher percentage of deformity (91% vs 66%) and of destruction on x-ray (74% vs 56%).

We also found our Felty's patients to have more active (inflammatory) articular disease than the comparison group as reflected by the articular index and the percentage of patients with joint effusions (77%) (Table 1). This severe articular disease has not been emphasized in the past (Felty, 1924; Ruderman et al., 1968; Barnes et al., 1971; Louie and Pearson, 1971). Excluding the haematological features of Felty's syndrome, 94% of our patients had extra-articular features, with a mean of 2.9 per patient. This compares with an overall incidence of 76% in Gordon's group of hospitalized rheumatoid arthritis patients (Gordon et al., 1973). In comparing the three studies of Felty's syndrome (Table 3) it appears that nodules, splenomegaly, and lymphadenopathy are more frequent in these patients than in the large group of hospitalized rheumatoid patients.

The majority of patients with Felty's syndrome were anaemic (79%) or leucopenic (97%), but only 15% were thrombocytopenic. All but one patient in our series showed lymphocytopenia (<1.5 x 10^9/l). In agreement with previous reports (Felty, 1924; Ruderman et al., 1968; Barnes et al., 1971; Louie and Pearson, 1971; Moore et al., 1971), bone marrow studies in these patients showed normal or increased cellularity in 74% and increased granulopoiesis in 90%. In only 3 patients was decreased cellularity observed. Surprisingly, iron stores were absent in 67% and significantly reduced in a further 17%, but an obvious site for blood loss was not found in the majority. Previous marrow studies in rheumatoid arthritis showed increased or normal
iron staining (Raymond et al., 1965; Cartwright, 1966; Wardle and Attan, 1967; Douglas and Adamson, 1975). It is possible that in our series blood loss had occurred previously and stores had not been replenished, or that iron absorption was faulty in these patients.

Liver involvement occurred in at least one-quarter of our patients (raised sulphobromophthalein in 27%). However, pathological studies showed lobular hepatitis in 1, amyloidosis and haemangiomata in 1, and nonspecific findings in 5. Previous studies (Ritland, 1973; Blendis et al., 1974) have reported finding nodular regenerative hepatitis, cirrhosis, or lymphocytic infiltration of the sinusoids and portal triads in Felty's syndrome.

The kidney is often thought to be spared in rheumatoid disease, proteinuria being explained by complications such as urinary tract infections, amyloidosis, or as secondary to drug therapy. 39% of our patients excreted more than 500 mg protein/24 hours in the absence of any other obvious cause for proteinuria. Histology in 3 patients showed focal glomerulonephritis in 2 and nephro sclerosis in 1. Whether this proteinuria is glomerular in origin (Baggenstoss and Rosenberg, 1943; Pollak et al., 1962; Brun et al., 1965) secondary to immune complex deposition, or tubular in origin secondary to an interstitial nephritis (Bulger et al., 1968) occasionally seen in rheumatoid arthritis cannot be answered without more pathological and immunofluorescent data. Light-chain excretion in the urine as described by Gordon et al. (1966) was not detected in 2 of our patients.

Many patients in all three studies of Felty's syndrome had raised immunoglobulin levels and a number of circulating autoantibodies (Table 4). The incidence of positive LE cells, rheumatoid factor, and antinuclear factor was greater in these patients than in other studies of rheumatoid arthritis (Ziff and Baum, 1972). Tests of cell-mediated immunity showed that 4 of 16 patients were anergic to a battery of skin tests but T and B cell counts and mitogen stimulation studies were near normal. Thus no constant defect in cell-mediated immunity was shown.

Twenty-seven patients were diagnosed as having episodes of infection, and 8 underwent splenectomy. Infections occurred within a few months to 2 years before splenectomy in most, and were usually the indication for splenectomy. Infections in the 27 patients tended to be due to common organisms and responded to usual antibiotic therapy. In the 8 patients who underwent splenectomy, 17 episodes of infection occurred during a mean follow-up of 27.6 months. The type and location of infection had a similar distribution to those occurring before splenectomy. As with previous studies, we also failed to show any correlation between severity of leucopenia and frequency or severity of infections. Thus, we could not explain the susceptibility of Felty's patients to infections by a quantitative defect of immunoglobulins, T cells, B cells, polymorphonuclear cells, as suggested by Hurd et al. (1974), or by other qualitative defects of the immune response.

We failed to show a correlation between severity of leucopenia and spleen size in agreement with Moore et al. (1971) and Ruderman et al. (1968). An specific antileucocyte antibody, as described by Faber and Elling (1966) and Calabresi et al. (1959), might be implicated in the leucopenia of some Felty's patients. Our kinetic studies suggest that Felty's patients with spleens have decreased neutrophil reserves. Bone marrow examinations in these patients show an exhaustion of the normal intra marrow reserves of mature neutrophils (a shift to the left). The 2 patients in whom we studied leucocyte kinetics after splenectomy showed normal neutrophil reserves.

Splenectomy in our patients resulted in a sustained rise of white blood cell count, return of bone marrow to normal granulopoietic morphology, improvement of anaemia, and sustained rise of platelet counts. Splenectomy did not, however, result in increased bone marrow iron stores nor did it significantly affect the incidence of infections. In fact, we cannot exclude the possibility that splenectomy might have been instrumental in the fatal infection in one of our patients.

References
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