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Felty's syndrome

A clinical and pathological survey of 21 patients and their response to treatment*

C. G. BARNES, A. L. TURNBULL, AND B. VERNON-ROBERTS
The London Hospital

In the 36 years since Felty (1924) described a clinical syndrome of 'chronic arthritis in the adult, associated with splenomegaly and leucopenia', a number of individual cases and a few series of patients have been described, but some fundamental questions remain unanswered.

With isolated exceptions (Denko and Zumpft, 1962), most authors agree that Felty's syndrome is not merely a variant of systemic lupus erythematosus (SLE) or a coincidence of arthritis with some unassociated disease. However, there is little unanimity as to its aetiology and pathology, its relationship to the various manifestations of rheumatoid disease, the range of clinical and haematological manifestations that may occur, and, most important for the individual patient, how the disease should be treated.

Material and methods

SELECTION OF PATIENTS

The diagnosis was accepted when the patient presented with features of 'classical or definite' rheumatoid arthritis (RA) (Ropes, Bennett, Cobb, Jacox, and Jessar, 1959), splenic enlargement without other demonstrable cause, and leucopenia with a total white cell count of less than 3,500 per cu. mm. and a neutrophil count of 2,000 per cu. mm. or less.

IMMUNOLOGY

Latex tests were performed by a modification of the method of Singer and Plotz (1956). Waaler-Rose tests and subsequently differential sheep cell agglutination titres were performed by modifications of the method of Ball (1950).

Tests for antinuclear factor (ANF), white cell ANF, and salivary gland antibody were performed by immunofluorescence (Roitt and Doniach, 1966).

Serum white cell antibodies were sought by the complement-fixation technique of van Rood, van Leeuwen, and Eernisse (1959). Platelet antibodies were sought by agglutination, indirect antiglobulin consumption, and complement fixation, by the methods of van de Wiel, van de Wiel-Dorfmeyer, and van Loghem (1961) and Aster, Cooper, and Singer (1964).

HAEMATOLOGY

Routine haematological measurements were performed by standard techniques (Dacie and Lewis, 1968). For the determination of their survival, red cells from the patient were labelled with ^{51}Cr by the method of Mollison and Veall (1955). The first (100 per cent. activity) blood sample was drawn after initial equilibration of labelled cells in the spleen as determined by counting *in vivo* over the organ. The normal range in our laboratory for 50 per cent. disappearance of activity is 23 to 29 days. The accumulation of excess counts over the liver and spleen was calculated by the method of Hughes Jones and Szur (1957); in normal subjects the excess counts at 50 per cent. disappearance of activity in the blood do not exceed 250 for the spleen and 150 for the liver.

HISTOLOGY OF THE SPLEEN

5μ sections of paraffin-embedded formol-fixed material from the available spleens from patients with Felty's syndrome ('Felty spleens') were stained with haematoxylin and eosin, Gomori's reticulin, elastic Van Gieson, Perls' iron stain, and congo red.

For comparison, sections were also prepared from 22 spleens weighing less than 300 g. from patients with RA coming to autopsy ('RA control spleens') The exclusion of control spleens weighing more than 300 g. was necessary, since in many of these spleens the presence of amyloid, infection, or malignancy obscured other structural changes.

Results

CLINICAL MATERIAL

21 patients (6 men and 15 women) satisfied the criteria for the diagnosis of Felty's syndrome. The clinical and pathological findings are summarized in Table I (overleaf).

* Some of these data were presented at the XII International Congress of Rheumatology, Prague, in October, 1969; at the combined meeting of the Heberden Society with the Société Française de Rhumatologie, Paris, in May, 1970; and at the XIII International Congress of Haematology Munich, in August, 1970
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Table I *Clinical and pathological findings in 21 patients with Felty's syndrome (continued on pp. 362–363)*

Group	*Patient no.*	*Sex*	*Age at onset of RA (yrs)*	*Rheumatoid disease*					*Relative precedence of splenic enlargement and leucopenia*
				Duration of RA before Felty's syndrome (yrs)	*Articular involvement at onset of Felty's syndrome*	*Nodules*	*Sjögren's syndrome*	*Other rheumatoid manifestations*	
I Severe	1	F	25	27	Quiescent	0	+	–	Leucopenia 2 yrs
	2	F	38	5	Mildly active	0	0	–	Simultaneous
	3	M	52	10	Moderately active	0	+	–	Leucopenia 4 mths
	4	M	60	7	Active	+	0	Neuropathy	Simultaneous
	5	M	53	7	Severe 'burnt out'	0		–	–
	6	F	32	15	Quiescent	+	+	Neuropathy	Leucopenia 7 mths
	7	M	44	1	Active	0	0	Raynaud's	Simultaneous
	8	F	46	6	Active	0	+	Raynaud's	Simultaneous
	9	F	38	6	Moderately active	+		Arteritis	Splenic enlargement 3 mths
II Moderate	10	F	35	7	Quiescent	+	0	–	Leucopenia 3 mths
	11	F	28	34	Active	+		Carpal tunnel Arteritis	Leucopenia 4 yrs
	12	F	59	14	Quiescent	+	+	Carpal tunnel Arteritis	—
	13	F	30	39	Severe 'burnt out'	+	+	–	Leucopenia 4 mths
	14	F	40	3	Active	+	0	Polymyositis	Simultaneous
III Mild	15	F	26	8	Quiescent	+	+	–	Simultaneous
	16	F	35	14	Severe 'burnt out'	+	+	Scleritis	—
	17	M	46	5	Quiescent	+		Arteritis	Splenic enlargement 2 yrs
	18	M	38	6	Mildly active	+	+	–	—
	19	F	50	14	Quiescent	+	+	–	—
	20	F	59	17	Quiescent	+		—	Splenic enlargement 3 yrs
	21	F	26	?	Severe 'burnt out'	+	+	Neuropathy Arteritis	—

n.d. = not done

Infections	*Spleen maximum size (cm.) weight (g.)*	*Blood studies (lowest values)*			*Highest lymphocyte count (per cu. mm.) before splenectomy*	*Lowest platelet count ($\times 10^3$)*	*Highest reticulocyte count (%)*	*Red cell survival (days) (^{51}Cr half life)*
		Hb (g. per cent.)	*White cell count (per cu. mm.)*	*Neutrophils (per cu. mm.)*				
Pneumonia Bronchitis Urine Vulva	Tip —	9·5	2,200	90	3,650	n.d.	2·1	n.d.
Bronchitis Mastoiditis Urine Pharyngitis	6 714	8·8	700	0	644	120	1·7	n.d.
Bronchitis Pneumonia Furunculosis Buccal and perineal ulcers	3 435	12·5	1,200	38	4,600	162	5·0	n.d.
Oral moniliasis Pneumonia Bronchitis	2·5 —	9·6	1,000	75	2,340	114	9·0	12
Carbuncle Pyrexia unknown origin	6 1,572	6·0	1,200	530	1,125	25	18	9
Mouth ulcers Pneumonia Urine	14 2,150	7·0	1,000	128	1,450	82	4	18
Pharyngitis Pneumonia	3 390	11·8	2,400	0	4,640	254	n.d.	n.d.
Diarrhoea Vomiting Pyrexia unknown origin	2 560	9·1	1,000	170	1,260	47	7	20
Pneumonia	5 1,248	10·4	1,000	360	1,760	38	3·5	n.d.
None	Tip —	8·8	900	230	1,020	368	<2	23
Urine	3 —	9·8	650	26	1,740	108	1	30
Bronchitis	2 428	9·1	2,100	132	2,938	202	<2	26
Leg ulcers	5 810	7·5	700	335	400	142	3·4	16
None	1 —	9·0	2,000	300	2,130	440	2·6	>30
Sinusitis Conjunctivitis Urine Furunculosis	4 685	10·7	1,500	725	950	207	3·5	20
Urine	3 —	10·2	2,400	576	3,528	114	<2	>30
Pneumonia Tuberculosis	2 1,319	10·8	2,100	1,200	800	n.d.	n.d.	n.d.
None	2 —	13·0	2,000	620	1,386	252	<2	29
Leg ulcers	5 (by *x* ray and scanning)	9·5	1,700	715	1,615	268	<2	25
Urine Pneumonia Sacral ulcers	2 —	9·0	1,700	504	2,610	44	1	n.d.
None	Not palpable 588	9·9	3,000	2,100	2,000	n.d.	n.d.	n.d.

Table I (*continued*)

Group	*Patient no.*	*Rheumatoid factor serology at diagnosis of Felty's syndrome**		*LE cells*	*Antinuclear factor*	*Plasma proteins*		
		Latex	*SCAT*			*Alb.*	*Glob.*	*Electro.*
I Severe	1	+	Neg.*	0	1/50	2·4	6·2	γ ++
	2	1/320*	8/256*	0	0	3·2	3·1	γ+
	3	>1/320	n.d.	0	0	4·1	2·5	$\alpha_2\downarrow$ γ+
	4	1/160	8/1,024	0	0	3·3	3·2	α_2 + γ +
	5	Neg.	n.d.	0	0	3·8	2·5	Normal
	6	1/10,240	Neg.	+	n.d.	2·8	3·9	γ +
	7	n.d.	1/128*	n.d.	+	3·8	4·6	γ +
	8	>1/320	1/160	0	0	2·9	4·7	γ + α_2 +
	9	>1/320	8/8,000	+	>1/100	3·4	3·8	α_2 + γ +
II Moderate	10	>1/320	1/64	0	1/100	4·5	3·5	Normal
	11	1/2,560	1/640*	0	0	3·6	2·5	γ +
	12	>1/320	8/512	0	+	4·4	4·0	γ +
	13	>1/320	Neg.	n.d.	1/10	4·2	3·4	γ +
	14	1/160	n.d.	0	0	2·9	3·1	γ +
III Mild	15	1/320	Neg.*	0	+	4·9	3·5	γ +
	16	>1/320	16/8,000*	n.d.	+	4·8	3·0	γ +
	17	n.d.	1/32*	++	n.d.	3·6	4·5	n.d.
	18	Neg.	Neg.	n.d.	+	4·5	3·2	Normal
	19	1/320	0/8,000	n.d.	1/500	n.d.	n.d.	n.d.
	20	1/640	Neg.	0	1/50	2·7	5·7	γ +
	21	1/1,280	1/28	++	n.d.	n.d.	n.d.	n.d.

* Subsequent result.

ESR at diagnosis of Felty's syndrome	*W.C. Antinuclear factor*	*Salivary gland antibody*	*Steroids*	*Splenectomy*	*Survival after diagnosis (yrs)*	*Current status*
113	+	0	Yes	Yes	8 8/12	Alive—Normal blood count
57	n.d.	n.d.	No	Yes	14½	Alive—Normal blood count
91	0	+	Yes	Yes	6	Alive—Minimal leucopenia after 5½ years severe leucopenia Recurrent infections
98	n.d.	n.d.	Yes	No	1 5/12	Dead—Leucopenia Pneumonia (No autopsy)
50	n.d.	n.d.	Yes	Yes	¾	Dead—Leucocytosis Pyrexia unknown origin (no autopsy)
117	n.d.	n.d.	Yes	Yes	3 2/12	Dead—Leucopenia (no autopsy)
78	n.d.	n.d.	Yes	No	1 7/12	Dead—Leucopenia Pneumonia
88	n.d.	n.d.	Yes	Yes	2¼	Dead—Leucocytosis Postoperative infection and portal vein thrombosis
68	+	n.d.	Yes	Yes	4½	Alive—Leucopenia
71	+	0	Yes	No	2 10/12	Alive—Normal white cell count Spleen tip palpable
82	n.d.	n.d.	Yes	No	7	Alive—Normal blood count Spleen not palpable
51	0	n.d.	Yes	Yes	2 8/12	Alive—Neutropenia Infections
91	+	n.d.	No	Yes	1½	Dead—Leucopenia
46	0	n.d.	No	No	1½	Alive—Leg ulcers worse Renal failure Leucopenia
85	0	+	No	Yes	6	Alive—Normal blood count Recurrent sinusitis
35	+	0	No	No	3¾	Alive—Normal blood count Spleen tip only palpable
48	n.d.	n.d.	Yes	No	3	Dead—Cause unknown
21	n.d.	n.d.	No	No	1½	Alive—Normal blood count Spleen not palpable
65	+	0	No	No	1	Alive—Neutropenia
70	n.d.	n.d.	No	No	2 4/12	Alive—Leucopenia Thrombocytopenia
	n.d.	n.d.	No	No	*Post mortem* diagnosis	Dead—Cerebrovascular accident

The age at onset of the rheumatoid arthritis and at the diagnosis of Felty's syndrome are shown in Table II. The men developed rheumatoid arthritis later than the women, but progressed to Felty's syndrome far earlier in the course of their rheumatoid disease. These differences are statistically significant ($0{\cdot}01 < P < 0{\cdot}02$).

CHARACTERISTICS OF THE RHEUMATOID DISEASE

Onset and clinical course

All patients presented with an inflammatory polyarthritis principally affecting peripheral small joints. In nineteen patients the arthritis was progressive from the onset with continuing inflammatory activity and an increasing number of affected joints, although the disease remained mild in two. At the time of diagnosis of Felty's syndrome, the inflammatory activity had become entirely 'burnt-out' in four patients, was quiescent in eight, and remained active in nine. At this time residual joint changes were very severe in two men and seven women; there was only moderate deformity in one man and six women, and little if any deformity in the remaining three men and two women.

Rheumatoid nodules were present in three men and twelve women and absent in three men and three women. Eleven patients were judged to have Sjøgren's syndrome as indicated by an abnormal Schirmer's test, while in five patients this test remained normal. Three patients had peripheral neuropathy, two carpal tunnel syndrome, five clinical evidence of arteritis, two Raynaud's phenomenon, one scleritis, and one polymyositis (by electromyography).

Rheumatoid serology

The results of tests for serum rheumatoid factor are detailed in Table I. Tests for rheumatoid factor were positive in nineteen patients and repeatedly negative in two.

At the diagnosis of Felty's syndrome, either ANF tests or LE-cell preparations were positive in eleven of twenty patients, and at some time one or other test was positive in fourteen of the 21 patients reviewed.

White cell ANF tests were positive in six of the ten patients tested.

Salivary gland antibodies were demonstrated in two of five patients with Sjøgren's syndrome. Both the salivary gland antibody test and Schirmer's test were negative in a further patient.

TREATMENT BEFORE ONSET OF FELTY'S SYNDROME

Most of the patients had received analgesic drugs over long periods. Specific enquiry was made into phenylbutazone and gold medication because these may occasionally produce leucopenia.

Phenylbutazone

Three of the 21 patients had received phenylbutazone (200-400 mg. daily) immediately before the diagnosis of Felty's syndrome, and eleven had received this drug one or more years previously. Six patients were known not to have received the drug.

Of the three patients receiving phenylbutazone up to the time of diagnosis, one (Case 15) subsequently responded haematologically to splenectomy, one (Case 10) improved spontaneously 6 months later, and one (Case 16) improved spontaneously slowly. None of the patients who stopped taking phenylbutazone between 1 and 2 years before the diagnosis of Felty's syndrome showed any spontaneous improvement in the blood count (Cases 6, 12, 18, 20).

Gold salts

Seven of the 21 patients had received short courses of injections of sodium aurothiomalate. In no case were these injections given immediately before the development of Felty's syndrome, and in none was there any abnormality in the blood count during chrysotherapy.

Corticosteroids

Eight of the 21 patients (Cases 1, 4, 6, 8-12) were receiving corticosteroids at the time of development

Table II *Age differences in* 21 *patients with Felty's syndrome, by sex*

Sex	*Male* (6)		*Female* (15)		*Total* (21)	
	Range	*Mean*	*Range*	*Mean*	*Range*	*Mean*
Age at onset of RA (yrs)	30–60	*48·8	25–59	*38·5	25–60	40·0
Age at diagnosis of Felty's syndrome (yrs)	44–67	54·8	34–76†	53·4†	34–76†	53·9†
Duration of RA before diagnosis of Felty's syndrome (yrs)	1–10	**6	3–34†	**14·2†	1–34†	11·7†

*/** By 't' test $0{\cdot}01 < P < 0{\cdot}02$
These figures exclude one female patient in whom the diagnosis of Felty's syn drome was made at autopsy

of Felty's syndrome, in a dosage of 5-15 mg. prednisolone (or its equivalent) daily.

FEATURES OF FELTY'S SYNDROME

Onset

In ten patients, routine examination revealed either leucopenia or splenic enlargement in the absence of relevant symptoms. Six patients presented with infection, two with haemolytic anaemia, and two with skin ulceration. One patient was diagnosed at autopsy.

The time relationship between the detection of splenic enlargement and the development of neutropenia was variable. The priority of leucopenia (7 patients: up to 4 years) or splenic enlargement (3 patients: up to 3 years) was not related to any other feature of the illness (Table I). As in other series (Collier and Brush, 1966; Ruderman, Miller, and Pinals, 1968) there was no correlation between the size of the spleen and the degree of haematological abnormality.

On review of the clinical features of their illness before treatment the patients appeared to fall into three groups:

I. SEVERE The nine patients (5 women; 4 men) in this group had neutrophil counts frequently below 500 per cu. mm. and a variety of infections. Four patients also had haemolytic anaemia (Cases 4-6, 8). Seven patients were seriously ill from the time of recognition of leucopenia and splenic enlargement; in the other two the onset of severe symptoms was delayed for 2 years.

II. MODERATE Five patients (all women) had only mild clinical manifestation despite neutropenia as severe as those in Group I. One patient had moderate haemolytic anaemia (Case 13).

III. MILD In seven patients (5 women; 2 men) less severe neutropenia (500-2,000 per cu. mm.) was associated with only moderate or mild symptoms. In two of these (Cases 15, 16) there had been moderately severe infections, but in both they antedated the neutropenia by some years. One elderly patient (Case 20) had recurrent urinary infections and bronchopneumonia.

The clinical and serological features of the arthritis, and the relationship between the onset of leucopenia and clinical enlargement of the spleen did not differ in the three groups (Table I).

Splenic enlargement

The spleen was palpable in nineteen of the 21 patients. In one grossly obese patient the spleen could not be palpated with certainty, but was shown to be considerably enlarged by plain *x* ray and by scintiscanning after the administration of heated ^{51}Cr-labelled red cells. In the last severely crippled patient, an enlarged spleen (588 g.) was discovered only at autopsy.

Lymph nodes

Conspicuously enlarged lymph nodes were present in four patients. Biopsy of an enlarged node in two patients, and *post mortem* examination in a third, revealed only benign follicular hyperplasia of the type associated with rheumatoid arthritis (Motulsky, Weinberg, Saphir, and Rosenberg, 1952).

Weight loss

In five of eleven patients there was a loss of more than 7 lb. in the preceding 6 months.

Skin pigmentation

Some mild general increase in skin pigmentation was present in three patients.

Ulceration

Ulceration of the legs was present in four patients without clinical evidence of varicose veins, of the perineum in one, of the mouth and genitalia in one patient each, and of both the latter sites in a further patient.

Infections

These occurred in 14 of the 21 patients (Table I).

Purpura

Four patients developed bruising or purpura. Three were thrombocytopenic, two of whom were receiving corticosteroids. The fourth had a normal platelet count and was not receiving corticosteroids.

Liver

Severe haematemesis in one patient (Case 9) suggested the presence of portal hypertension and this was confirmed at laparotomy. Percutaneous (2) and operative hepatic biopsies showed some portal fibrosis without the changes characteristic of cirrhosis.

Clinical features of liver disease were not seen in any other patient. Flocculation tests were often abnormal in the presence of hyperglobulinaemia. A mild unexplained increase in serum alkaline phosphatase was noted in one patient (Case 2).

HAEMATOLOGY

Peripheral blood

Red cells (Fig. 1, overleaf). All patients were anaemic (haemoglobin less than 13·5 g./100 ml. in men and less than 12 g./100 ml. in women) but this was severe (less than 8 g./100 ml.) in only one man and two women. The mean corpuscular haemoglobin concentration was less than 30 per cent. in five of the 21 patients, in only three of whom was the blood film considered to be hypochromic. The red cells were normochromic in all other patients, including six in whom polychromasia was present; two showed macrocytosis (Cases 5 and 8).

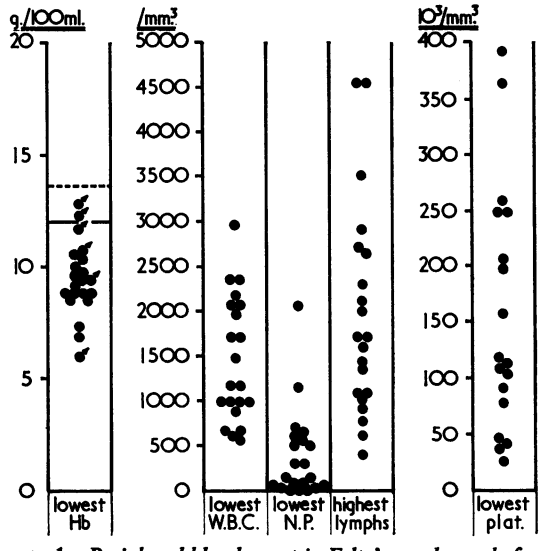

FIG. 1 *Peripheral blood count in Felty's syndrome before splenectomy.*

Leucocytes. The lowest total white cell, lowest neutrophil, and highest lymphocyte counts recorded are shown in Fig. 1 (before splenectomy when this was performed). The lymphocyte count usually exceeded the neutrophil count in 17 of the 21 patients. In 5 patients neutropenia was noted before the total white cell count fell below 3,500 per cu. mm; in these cases there was a mild lymphocytosis of between 2,300 and 4,400 per cu. mm.

Platelets (Fig. 1). Counts were performed in eighteen patients. Thrombocytopenia (less than 150,000 per cu. mm) was present in ten, but in only four was the count less than 50,000 per cu. mm.

Erythrocyte sedimentation rate

At the time of diagnosis of Felty's syndrome (Fig. 2), this did not correlate with the clinical assessment of inflammatory joint activity.

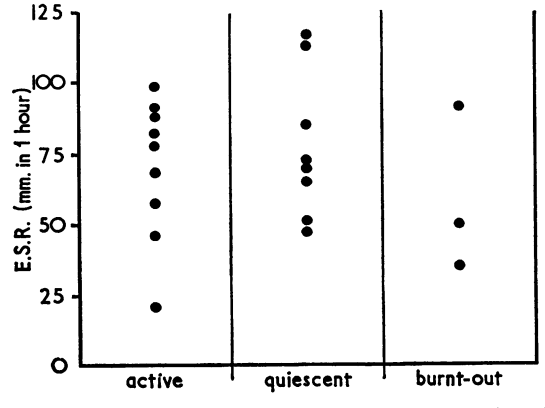

FIG. 2 *Erythrocyte sedimentation rate compared with the clinical activity of the inflammatory joint disease.*

Bone marrow

Smears were available for re-examination in nineteen cases. Repeated aspiration in one patient produced peripheral blood only (Case 19). The findings are summarized in Table III.

Table III *Bone marrow*

Characteristics	+	*N*	−
Cellularity	10	6	3
Erythropoietic activity	4	14	1
Leucopoietic activity	10	8	1
Mature granulocytes	0	6	13
Plasma cells	10	9	0
Megakaryocytes	2	17	0
Reticuloendothelial iron	3	2	7

Occasional macronormoblasts and transitional megaloblasts were seen in four patients with haemolytic anaemia, in none of whom was there evidence of vitamin B_{12} or folate deficiency. In only one patient was leucopoiesis apparently depressed (Case 1). Mature granulocytes were deficient in the presence of plentiful precursors in thirteen patients, but in six patients mature granulocytes were plentiful in the marrow sample.

Smears stained for iron were available in eleven patients. Reticuloendothelial haemosiderin was increased in three, who were all found to have haemolytic anaemia; it was normal in two and much reduced or absent in seven.

Plasma iron

This was low in all of the ten patients tested, with a diminished total iron-binding capacity (TIBC) in six. The TIBC was elevated in two patients: in one no marrow could be obtained, and in the other, and in four patients in whom the TIBC was not performed, marrow storage iron was grossly diminished or absent.

Haemolytic anaemia (Fig. 3, opposite)

Red cell survival was reduced in six of thirteen patients studied. *In vivo* counting in these six patients showed an initial sequestration of labelled cells in the spleen in four (spleen : heart ratio after equilibration > 1·0). In three there was subsequently a significant accumulation of excess counts over the spleen, indicating splenic destruction of labelled cells. In one there was also a significant increase in excess counts over the liver.

Red cell survival was normal (^{51}Cr. 50 per cent. greater than 22 days) in seven, in four of whom there was some initial sequestration of labelled cells in the spleen.

There was suggestive evidence of increased haemolysis in one of the remaining eight patients

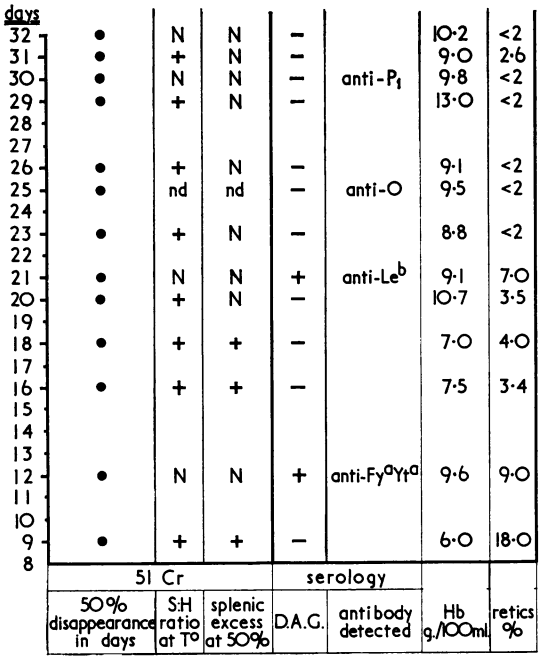

FIG. 3 *Results of investigations for haemolysis.*
DAG = Direct antiglobulin reaction.
S : H ratio T_0 = Spleen : Heart ratio at time zero.

in whom red cell survival was not measured. In this man (Case 3) the haemoglobin was 12·5 g./100 ml. with 5 per cent. reticulocytes; the direct antiglobulin reaction was positive, the red cells being sensitized with cold anti-I.

White cell and platelet antibodies
These were present in only one out of four patients tested.

Treatment after diagnosis

The outline of treatment received is summarized in Table IV.

SYSTEMIC CORTICOSTEROIDS (Table V, overleaf)

I. Severe group

Eight (Cases 1, 3-9) of the nine patients with severe disease were treated with oral corticosteroids. In the six (Cases 3-5, 7-9) who were given prednisolone 20 mg./day or more for at least one month (of whom five were previously receiving 10 mg./day or less for arthritis), there were two (Cases 4, 7) who showed temporary haematological and clinical remission lasting 11 and 8 months respectively, after which both relapsed and died. None of the other four patients remitted and all underwent splenectomy (see below).

Neither of the two patients (Cases 1, 6) given less than 20 mg./day prednisolone remitted, and both later proceeded to splenectomy.

II. Moderate group

One patient (Case 11), in whom steroids were increased from 10 to 20 mg./day prednisone and continued for 6 months before dose reduction, underwent complete, apparently permanent, clinical and haematological remission (follow-up now 7 years). Haematological remission occurred apparently spontaneously in one patient (Case 10) who continued to receive the same small dose of prednisone (7·5 mg./day) which had been started 7 years before the decline in her white cell count.

III. Mild group

Only one patient (Case 17) in this group received corticosteroids. This was in high dosage and unfortunately no record exists of further blood counts during this period. He died suddenly from bronchopneumonia.

Two of the remaining six patients in this group, who have not received steroids since the diagnosis of Felty's syndrome, have had spontaneous haematological remissions (Cases 16, 18).

Table IV *Outline of treatment with steroids and splenectomy*

Grade of disease	*No. of cases*	*Neutrophil polymorphs per cu. mm.*	*Infections*	*Haemolytic anaemia*	*No. of cases*	*Steroids*	*Splenectomy*	*Died*
Severe	9	< 500	All	4	9	6	3	
						8		
							2	
						1		
Moderate	5	< 500	2	1	5	3	1	
						1		
Mild	7	500–2,000	4	1	1		1	
					7		1	
						1		

Table V *Results of steroid treatment*

Grade of disease		*Prednisone (mg./day)*			*Result*			
		> 20	*< 20*	*Nil*	*Remission*	*Relapse*	*Splenectomy*	*Died*
Severe	Neutrophils < 500 per cu. mm.	6			2	2		2
	Infection + +		2		0		2	
				1	0		1	
Moderate	Neutrophils 500 per cu. mm.	1			1			
			2				1	
	Infection ±			2			1	
Mild	Neutrophils 500–2,000 per cu. mm.	1						1
	Infection ±		0					
				6	2			1
							1	

Table VI *Indications for, and results of, splenectomy*

*Patient no.**		*Indications*				*Previous prednisone (mg./day)*
		Infection	*Hb*	*Neutropenia*	*Thrombocytopenia*	
Severe	1	++	A+	+++	0	15
	2	++	A+	+++	+	0
	3	+++	?HA+	+++	±	40
	5	+	HA+++	+++	++	40
	6	++	HA+	+++	+	17
	8	+++	HA+	+++	++	30
	9	+++	A+	+++	++	40
Moderate	12	±	A+	+++	0	7·5
	13	±	HA++	+++	+	0
Mild	15	++	HA+	++	0	0

* See Table I A = Non-haemolytic anaemia HA = Haemolytic anaemia

Thus, in the whole series, remissions were seen in three of eight patients given at least 20 mg./day prednisone for a minimum of one month, but only one of these did not relapse. Of those given less than 20 mg./day prednisone, only one patient, receiving 7·5 mg./day, underwent partial remission.

There were also two spontaneous haematological remissions in the nine patients not treated with corticosteroids, in one of whom the spleen became impalpable.

SURGICAL TREATMENT—SPLENECTOMY

The indications for operation and its effect in the ten patients submitted to splenectomy are shown in Table VI.

The immediate good effect of splenectomy seen in eight of the ten patients was maintained in only three patients, but one of them (Case 5) died 4 months after operation, probably from infection (no autopsy), without any deterioration in his white cell count. The other two patients (Cases 2, 15) have continued to have a completely normal blood picture 14½ and 6 years respectively after splenectomy. A complete and spontaneous remission eventually occurred in one of the five patients who relapsed (Case 1). Three other patients died: one shortly after operation, one 15 months after operation of unknown cause (no autopsy), and one 15 months after operation in renal failure.

Histopathological changes

(1) SPLEEN

The histopathological findings are shown in Table VII (overleaf). None of the spleens showed involvement by primary or secondary malignant disease, or evidence of a specific infection, or perivascular fibrosis of the 'onion-skin' type. Amyloid material was not seen in any Felty spleen.

White pulp

The walls of the follicular arteries in all the Felty spleens were thickened by a structureless hyaline material lying immediately under the endothelium. In five spleens this change was marked with obliteration of the lumen of some vessels. This was not

Immediate response (0–28 days after operation)		*Survival after operation (yrs)*	*Late response*		
Clinical	*Haematological*		*Clinical*	*Infections and ulcers*	*Haematological*
Good	Leucocytosis	Alive 8½	Good	0	Relapse at 3 mths Spontaneous and complete remission at 3½ years
Good	Normal	Alive 14½	Active RA	0	Normal
Improved	Normal	Alive 5½	Improved	+	Severe relapse at 3 mths Spontaneous improvement 5 yrs
Improved	Leucocytosis Remission of haemolysis	Died 4 mths	Died ?infection	+++	Leucocytosis
Good	Normal	Died 1½	Improved Sudden death	+	Relapse at 3 mths
Died 13 days portal thrombosis	Leucocytosis	Died 13 days			
Transient porto-systemic encephalopathy	Immediate improvement Relapse within 28 days	Alive 10 mths	Improved	0	Moderate neutropenia
Good	Normal	Alive 2½	Poor	++	Severe neutropenia
No change	Stabilized haemoglobin Persistent leucopenia	Died 15 mths	Poor until death in renal failure	+	Neutropenia
Good	Normal	Alive 6	Improved	+	Normal

Table VII *Histopathological findings in the spleen of thirteen cases of Felty's syndrome compared with 22 rheumatoid arthritis 'control' spleens*

Site		*Histopathological changes*	*Felty spleens* (13)		*RA control spleens* (22)	
			No.	*Per cent.*	*No.*	*Per cent.*
White pulp	Follicular arteries	Amyloid	0		2	9
		Hyaline arteriolosclerosis	13	100	13	57
		Endothelial hyperplasia	13	100	6	26
		Increased elastic	11	85	0	
		Perivascular fibrosis	0		0	
	Lymphoid tissue	Hyperplasia	7	54	0	
		Germinal centre hyperplasia	7	54	0	
		Active germinal centres	4	31	1	4
		Hyaline	10	77	5	26
		Amyloid	0		2	9
Red pulp	Venous sinusoids	Congestion	10	77	17	77
		Sinus cell hyperplasia	13	100	8	35
		Erythrophagocytosis	13	100	10	43
		Excess iron	7	54	13	59
		Non-iron pigment	12	92	22	100
		Amyloid	0		1	4
	Splenic cords	Reticulin increase	7	54	3	13
		Plasma cell hyperplasia	13	100	9	41
		Reticulum cell hyperplasia	6	46	1	4
		Excess iron	7	54	13	59
		Non-iron pigment	13	100	22	100
		Extramedullary haemopoiesis	13	100	3	14
		Amyloid	0		1	4

related to age or splenic size. This hyaline change was present in thirteen (57 per cent.) of the RA control spleens, generally to a much lesser extent.

Slight to moderate hyperplasia of the endothelial cells was constant in the Felty spleens but was seen in only six (26 per cent.) of the RA control spleens. An increase in elastic tissue in the region of the internal elastic lamina was present in eleven Felty spleens but in none of the RA control spleens.

The *lymphoid tissue* showed no constant features. Absence of lymphoid hyperplasia did not correlate with steroid therapy. Hyperplasia was not seen in any of the RA control spleens.

Red pulp

In the *venous sinusoids* proliferation of the sinusoidal macrophages was a constant feature in the Felty spleens, apparently proportional to the degree of erythrophagocytosis which was also a feature observed in all cases. Similar changes, but to a lesser degree were seen in some RA control spleens. Excess iron was present in the sinusoidal cells in the seven

Felty spleens in which erythrophagocytosis was most marked. Excess iron was also seen in a similar proportion of the RA control spleens. In all but one of the Felty spleens, and in all the RA control spleens, varying amounts of birefringent particulate material were present in the cytoplasm of the sinusoidal macrophages. This had the characteristics of formalin pigment, since it disappeared after exposure to picric acid and did not stain for iron. After treatment with picric acid the cytoplasm of these cells was seen to contain ill-defined colourless inclusions. This birefringent particulate material was not found in spleens from 25 patients without rheumatoid disease.

In the *splenic cords* increased reticulin formation and reticulum cell hyperplasia were found more often in the Felty spleens than in the RA control spleens. In all Felty spleens plasma cells were increased and there were scattered foci of megakaryocytes and myeloid cells indicating extramedullary haemopoiesis. In only three RA control spleens was there any extra-medullary haemopoiesis.

(2) LIVER

Histological examination of the liver in the five cases which came to autopsy (Nos 4, 7, 8, 17, and 21) and in the one patient who had liver biopsies (No. 9) revealed no evidence of cirrhosis or amyloidosis.

Discussion

Some authors have doubted the specific entity of Felty's syndrome. In this series there was no evidence of another cause of splenic enlargement, *e.g.* lymphoma or cirrhosis, and no patient diagnosed as Felty's syndrome had later to be excluded because of the discovery of another disease or of splenic amyloidosis. We have seen one patient with seronegative psoriatic arthropathy and leucopenia, whose splenic enlargement was found at operation to be due to lymphosarooma, but we have been unable to find a single case of 'idiopathic' splenomegaly and leucopenia in degenerative joint disease, nor has splenectomy been performed in any such patient in The London Hospital over the last 12 years. The clinical features of the patients under review provide further evidence for the existence of a specific syndrome, and the pathological material from splenectomies and autopsies supports this view.

While leucopenia is one of the accepted criteria for the diagnosis, five of our patients showed neutropenia with a normal total white count in the early stages of their haematological illness, and therefore it would be preferable to specify neutropenia in the definition of the syndrome. While Felty's syndrome has been considered to develop mainly in the elderly (de Gruchy, 1965), one-third of our patients were under 60 years. The men were significantly older than the women at the onset of arthritis, but developed Felty's syndrome far earlier in the course of their illness. This was not related to any obvious sex differences in the character of their rheumatoid disease.

Rheumatoid nodules and Sjøgren's syndrome were both common in our patients, but other nonarticular manifestations of rheumatoid disease were not unduly frequent. No patient showed a skin rash, inflammation of serous surfaces or myocarditis, or any other features suggestive of SLE. One patient had moderate renal failure, but the renal biopsy showed chronic glomerulonephritis.

As in other series (Ruderman and others, 1968), most of our patients had positive tests for rheumatoid factor, often in high titre. Two patients had negative latex tests but were considered to have undoubted rheumatoid arthritis because in each the joint involvement was typical with erosive radiological changes. Biopsy of a nodule from the elbow of one showed the classical histology of a rheumatoid nodule, and in the other splenic histology did not show any features suggestive of SLE. Such patients have previously been reported (de Gruchy and Langley, 1961).

The finding of ANF and/or LE cells in two-thirds of our patients does not necessitate a diagnosis of SLE since about 25 per cent. of patients with rheumatoid arthritis have positive ANF tests, particularly those with severe systemic disease (Willkens and Decker, 1963). The absence of histological features of SLE in the thirteen spleens examined makes it extremely unlikely that Felty's syndrome is a manifestation of this disease as suggested by Denko and Zumpft (1962).

The nonarticular clinical features in our patients were much the same as previously described (de Gruchy, 1965; Ruderman and others, 1968). Infections may be directly related to neutropenia. Other clinical manifestations, such as leg ulceration and lymph node enlargement, cannot be attributed directly to the haematological abnormality. These should probably be regarded not as features of Felty's syndrome but as manifestations of severe rheumatoid disease, since they all occur in rheumatoid patients without splenic enlargement or neutropenia (Willkens and Decker, 1963).

Every patient was anaemic. Haemolysis appeared to be the major factor in the three patients with severe anaemia, and was also found in three others. In two of these six shortened red cell survival was probably due to sensitization by immune antibodies (positive direct antiglobulin test). Destruction of red cells by the spleen appeared to be the cause in three, in whom together with the sixth patient the

^{51}Cr study also revealed significant pooling (sequestration) of red cells in the organ. However, pooling by itself cannot account for haemolysis in this sixth patient because it was also found in four patients with a normal red cell survival. While haemolytic anaemia in Felty's syndrome has been attributed to the direct action of the large spleen (Hume, Dagg, Fraser, and Goldberg, 1964) this does not seem to be the only mechanism.

The mechanism of anaemia in the remaining patients was less certain, many showing disturbance of iron metabolism as is frequently seen in RA. An increase in plasma volume is commonly associated with enlargement of the spleen and probably contributes to anaemia in patients with Felty's syndrome (Blendis, Ansell, Lloyd-Jones, Hamilton, and Williams, 1970a). In most patients the neutrophil count was lower than lymphocytes. Absolute lymphocytosis is claimed only to occur after splenectomy (de Gruchy, 1965), but five of our patients had, early in the course of their disease, sufficient lymphocytes to keep the total white cell count within normal limits in the presence of neutropenia.

The variability of the manifestations of the syndrome make it difficult to assess prognosis in individual patients and the value of the treatment given. This may explain the conflicting reports of the effects of corticosteroids (Pengelly, 1966; Ruderman and others, 1968) and of splenectomy (Collier and Brush, 1966; Green and Fromke, 1966; Ruderman and others, 1968). To make a more valid assessment we have divided our patients into three groups according to the severity of their disease.

As in other series the benefit of corticosteroid treatment was variable and generally unspectacular. One moderately affected patient appeared to have been cured by prednisone. The results in this patient and in one reported by Pengelly (1966) indicate that corticosteroid therapy may occasionally be successful. On the other hand the same dosage of prednisone produced only partial improvement in two out of six severely affected patients. Corticosteroids in small dosage did not have any significant beneficial effect on the haematological abnormality.

The rarity of dramatic benefit from steroid therapy in our series agrees with previous reports (Collier and Brush, 1966; Ruderman and others, 1968) and must be considered in the light of the spontaneous remissions in this series seen in two patients, albeit mildly affected, who never received corticosteroids and in one on a small constant dose.

The initial haematological response to splenectomy was as good in this series as has previously been described (de Gruchy, 1965; Collier and Brush, 1966; Ruderman and others, 1968), and was associated with comparable clinical improvement.

There was less complete correlation between clinical and haematological status in the months after splenectomy. Only one patient achieved a complete permanent remission. Three patients maintained normal blood counts for more than 3 months but all continued to have infections which proved fatal in one. The blood count relapsed in four patients within 3 months of operation but only one of these has since had severe infections.

This experience is very similar to that of Ruderman and others (1968) but is much less favourable than has been suggested in some previous reports in which the follow-up has been shorter (Green and Fromke, 1966; Hahn, Mayne, and Kiely, 1963). Only three of the ten splenectomized patients in this series still have fully normal blood counts, 14½, 8½, and 6 years since operation respectively, and one of these went through a haematological relapse lasting 3 years from which she recovered spontaneously. However, even those who relapsed haematologically appear to have had a better chance of survival than before. Thus we believe that splenectomy remains the treatment of choice for patients with very severe infection.

The second indication for splenectomy is severe anaemia due either to sequestration of red cells and haemodilution (Blendis and others, 1970a) or to haemolysis when this is not controlled by small doses of steroids, and particularly when the spleen is the site of red cell destruction.

The third definite indication for splenectomy is severe haemorrhage associated with thrombocytopenia (Cudkowicz, 1956). If, as in Case No. 9, haemorrhage is due to portal hypertension, this must be treated on its own merits.

The lack of correlation between infection and the blood count before and after operation in their patients led Ruderman and others (1968) to conclude that leucopenia alone was not an indication for splenectomy. Only one of our patients had a splenectomy for leucopenia without serious infection. The relapse in her blood count 4 months later and the development of recurrent chest infections 1½ years after operation support this conclusion. Furthermore, in our own cases, the similar lack of correlation between the level of the neutrophil count and the severity of infection (as indicated by differences in patients in groups I and II), and the lack of correlation between infection and the white cell count after splenectomy, all confirm the belief that neutropenia alone does not warrant splenectomy.

The pathological findings in the thirteen spleens from patients with Felty's syndrome, when compared with those from rheumatoid arthritis without Felty's syndrome, give further evidence of a specific pathological entity.

The severity of the changes in the follicular arteries could not be correlated with the age of the

patient nor with the degree of splenic enlargement. In the absence of essential hypertension, these changes with endothelial hyperplasia and reticulin increase suggest that some degree of portal hypertension is a constant feature in Felty's syndrome (Ellman, Cudkowicz, and Elwood, 1955).

The lymphoid follicles showed no constant changes, but the germinal follicles were generally inactive and hyaline material was present in the majority. This is in direct contrast to the view that striking hyperplasia of germinal centres in enlarged follicles is a characteristic feature of the spleen in Felty's syndrome (Gardner, 1965).

Sinus cell hyperplasia accompanied by erythrophagocytosis was present in all the Felty spleens. Those in which erythrophagocytosis was most marked also displayed an excess of iron in macrophages and reticulum cells. These findings clearly indicate that excessive blood destruction within the spleen is a constant feature in Felty's syndrome, although this is not always sufficient to cause significant shortening of red cell survival. Whether neutrophil polymorphs are similarly destroyed is uncertain. Amyloid was not found in any of the specimens.

These consistent pathological abnormalities do not adequately explain the role of the spleen in Felty's syndrome. The presence of portal hypertension does not necessarily imply that this was the cause of the enlargement of the spleen, since some rise in portal blood pressure may be related to the increased blood flow characteristic of many types of splenic enlargement (Williams, Parsonson, Somers, and Hamilton, 1966; Blendis, Banks, Ramboer, and Williams, 1970b).

Although an improvement in white cell count usually follows splenectomy, the frequency of subsequent relapse and occasional spontaneous remission later suggest that hypersplenism is only one factor in pathogenesis, probably not the most important. The lack of correlation between splenic size and the severity of the haematological abnormality is further evidence for this view. Our findings do not, however, indicate what other mechanism is primarily responsible.

It is never possible fully to exclude the effect of drugs on the bone marrow. The chief reasons for discounting their influence are the usual rapid recovery of bone marrow activity following the discontinuation of the drug (de Gruchy, 1965), the absence of sustained splenic enlargement in a drug-induced neutropenia and the usual good early response to splenectomy in patients with Felty's syndrome. In the individual case it is always important to exclude other causes of bone marrow dysfunction, particularly deficiences of vitamin B_{12} or folic acid, and paroxysmal nocturnal haemoglobinuria which may present as mild haemolysis with leucopenia and thrombocytopenia without any macroscopic blood pigment in the urine. These conditions did not account for the haematological abnormalities in the cases reviewed.

Summary

21 patients with Felty's syndrome have been reviewed. The six men were significantly older than the fifteen women at the onset of arthritis but developed the syndrome sooner. Nonarticular rheumatoid features were common, Sjøgren's syndrome being found in eleven of sixteen patients tested. Sera of all but two contained rheumatoid factor, and LE cell preparations and/or ANF tests were positive in fourteen patients. Absolute neutropenia was characteristic but its degree did not fully correlate with the severity of infections. All patients were anaemic, red cell survival being reduced in six of thirteen patients studied with excessive splenic destruction in three.

Haematological remission occurred in two patients spontaneously and in one of two on a small constant dose of prednisone. Of eight patients given 20 mg. prednisone per day or more, four had transient partial improvement and one apparent clinical cure.

Ten patients underwent spleneotomy of whom two appear to have been cured. Two patients eventually achieved normal blood counts after early relapses.

Eight patients have died including four following splenectomy.

The following histological features were found in all thirteen spleens examined:

(*i*) Hyaline change and endothelial hyperplasia of follicular arteries;

(*ii*) Sinus cell hyperplasia with erythrophagocytosis;

(*iii*) Plasma cell hyperplasia and extramedullary haemopoiesis in the cords;

(*iv*) A birefringent particulate material in macophages and reticulum cells.

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