

# SPLENECTOMY IN RHEUMATOID ARTHRITIS\*

BY

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Chevallier (1930) emphasized the similarity of the Chauffard-Still's disease to the "rhumatisme biliaire" described by Gilbert and by Fournier, and to the arthritic manifestations of the "cirrhoses bilaires" mentioned by Hanot. After describing the ineffectiveness of various forms of medical treatment, he noted that, as far as he knew, in no instance had the spleen been removed, although it was known that in patients with splenic enlargement the associated symptoms often abated after removal of the spleen, and commented that splenectomy might be worth trying. Hanrahan and Miller (1932), and Craven (1934), reported the result of splenectomy in Felty's syndrome in two women aged 50 and 40 respectively. After the operation a clinical improvement was noted with reduction of pain and joint stiffness. Fitz (1935), however, in a discussion on Felty's syndrome, stated that both these patients had died within 18 months of the operation. Loeper, Lemaire, and Patel (1937) reported the successful removal of the spleen in a woman aged 28 who was suffering from advanced rheumatoid arthritis; but 35 days after the operation she developed pneumonia and died. Pointing out that in this disease there is a diffuse mesenchymal reaction characteristic of an infective disease, they suggested that it might be looked on as one of the "reticulo-endothelioses" and that although the aetiology might be unknown, this would give a reason for the clinical improvement following splenectomy.

In 1938, at my instigation, the spleen was removed in three patients under my care at St. Stephen's Hospital, who were suffering from rheumatoid arthritis in an active and advanced stage. In reporting this, we stated (Bach and Savage, 1940) that we did not know the aetiology of rheumatoid arthritis, and were not prepared to estimate the role of the spleen in this disease. As the clinical improvement following splenectomy impressed me, two more patients in the unit were subjected to this operation in 1944-45, and two or three elsewhere, of whom I have no further record. I then stopped this somewhat drastic treatment until after my return from the United States in 1949. The work of Hench and Thorn had now given us much to think about, though I was not convinced that cortisone was the final answer, nor that the adrenal cortex was the only "villain of the piece". I reviewed my splenectomy patients, and seeing that they had not done too badly,

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asked my surgical colleagues to try again. Their results in six cases are summarized below, but before passing to the clinical reports, one or two more articles in the literature deserve attention. Mention was made by McElin and Mussey (1950) of Galen's ancient comment that the spleen was an organ full of mystery, and to the more recent statement by Zondek (1944) that the spleen is an endocrine gland. Barcroft and Stevens (1928) and Barcroft (1930a, b) noted a decrease in the size of the spleen in pregnant dogs, and pointed out that the contraction could be divided into "heat" contraction, "pregnancy" contraction, and "lactation" contraction. Contraction could be abolished by denervation in the first two, but not in the third. This suggested that contraction during heat and pregnancy are neurogenic in origin, but that in lactation there is a large humoral element, and the theory was advanced that the spleen contracted during pregnancy to supply more blood to the genital organs because of the dilatation of the uterine vessels, and to aid in foetal haematopoiesis.

Gottesman and Perla (1930) and Perla (1936) showed that the removal of the hypophysis in the adult rat was followed by progressive atrophy of the spleen, which suggested that the anterior hypophysis secreted a stimulating factor for the spleen. Edwards and Wright (1937) removed the spleen in rats and noted that two weeks later the hypophyses in these rats had become some 25 per cent. larger than those in the control animals. The pituitary showed an increase in the reticulo-endothelial elements and increased mitosis of the basophil cells.

Valid proof of an internal secretion of the spleen did not exist, but Ungar (1945) presented experimental evidence suggesting that the spleen produced, and could release into circulation, a substance which acted like a hormone. This he termed Splenin (Splenin A, which decreases capillary permeability and bleeding time, and Splenin B, which increases capillary permeability and bleeding time). Witts (1948) reported on splenectomy in the "reticuloses", a generic histological term to describe all the progressive hyperplasias of the reticular tissues, which include Hodgkin's disease, certain of the leukaemias, and other forms of non-malignant lymphadenopathy. It was noted that in experimental animals, splenectomy had been followed by moderate anaemia, leukocytosis, and thrombocytosis, together with increase in bone marrow and hyperplasia of lymphoid tissue. In general, removal of the spleen appears to stimulate the mesenchymal reticular cells throughout the body to increased function and differentiation. He pointed out that there is little exact information as to what happens when the normal adult human spleen is removed. There is no significant anaemia, but there is considerable leukocytosis and thrombocytosis. In brief, the spleen appears to exert an inhibitory influence on the bone marrow. When this inhibition is removed the emission of white cells and platelets from the bone marrow is accelerated. Duthie (1950) suggested the possibility that in certain circumstances the spleen secretes a substance which antagonizes the action of the adrenal steroids. A review of the literature does suggest the existence of an interrelationship between spleen and pituitary, spleen and ovaries, spleen and bone marrow, and, finally, between spleen and adrenal cortex.

### Clinical Material

**First Group.**—Three patients whose spleens were removed in 1938.

*Case 1.*—*Woman, aged 29*, followed up for 12 years. Seen last summer. Severe long-standing rheumatoid arthritis which has remained relatively inactive for 12 years. She presents three points of interest:

(1) At the present time she is in hospital for an orthopaedic operation to strengthen her deformed knees. The "fire" has burnt out, and she is left with the "ashes" of the disease.

(2) There has been definite radiological evidence of increased destruction of the joints of the hands and wrists.

(3) Twelve years ago at operation amyloid changes were seen in the spleen. The blood sedimentation rate has returned to the upper normal limit.

*Case 2.*—*Girl, aged 18*, followed up for 6 years from 1938-1944. The spleen at operation showed amyloid disease. She was later admitted with gastro-enteritis to another hospital, where she died. I saw the *post-mortem* examination. Very few joint changes were noted, but the liver showed amyloid disease.

*Case 3.*—*Boy, aged 18*, not traced in spite of repeated efforts.

**Second Group.**—Two patients whose spleens were removed in 1944 and 1945.

*Case 1.*—*Girl, aged 24*, followed up for 6 years from 1944 to 1950. She was under my care at St. Thomas's Hospital for three years prior to operation, and failed to respond to routine methods of treatment. After the operation there was marked relief of pain and stiffness and improvement of her general health, and she has been at work for the past five years. The blood sedimentation rate, before operation, was always around 60 mm. in the first hour, but since the operation it has varied from 10 to 15 mm.

*Case 2.*—*Boy, aged 24*, followed up for 5 years from 1945 to 1950. At the age of 24, the onset of acute rheumatoid arthritis followed thyrotoxicosis. Since splenectomy, the disease has been clinically inactive, and the patient has been leading a restricted but full life as a cripple. Again the "fire" has been extinguished, but the "ashes" remain. Prior to operation the blood sedimentation rate was 80 mm., and since, it has remained constant at about 5 mm. It is interesting to consider the possible relationship between thyrotoxicosis, thyroidectomy, and the onset of rheumatoid arthritis.

**Third Group.**—Six cases operated on in 1949 and 1950. The findings in this last group are set out in the Table, and the pathological reports are summarized below. Two patients were suffering from acute rheumatoid arthritis and four from chronic arthritis. As they had all been under observation for a considerable period, and had failed to respond to other forms of therapy, it was decided to carry out splenectomy to see if this would arrest the progress of the disease. No immediate clinical improvement appeared in the first few months after the operation, but the follow-up 8 to 13 months later showed that one acute case (No. 6) appeared to be quiescent, four cases had improved, and one (No. 1) had had a slight relapse but was better than before the operation.

In all cases the sedimentation rate fell; the red-cell count rose in three cases (Nos 2, 4, 6), and the white-cell count showed a consistent rise in all. The plasma proteins rose in four cases (Nos 1, 2, 3, 4), but fell again in the following months. The alkaline phosphatase rose in the five cases in which it was estimated.

TABLE  
PARTICULARS OF SIX CASES IN GROUP THREE

Case No. and Year of Onset	Date of Test	Red Blood Count	Haemoglobin (per cent.)	White Blood Count	Blood Sedimentation Rate	Serum Protein		Thymol Turbidity Test	Colloidal Gold Reaction	Alkaline Phosphatase
						Total	A/G Ratio			
1. 1937	9.1.50	4.96	81	5,100	50	7.8	2.9 : 1	2	Neg.	11.2
	16.1.50	—	—	—	—	<i>Splenectomy</i>		—	—	—
	13.2.50	4.05	75	10,300	25	8.3	2.5 : 1	2	Neg.	7.5
	19.10.50	3.96	80	10,900	20	—	—	—	—	—
	29.11.50	—	—	—	30	6.3	1.7 : 1	1	Neg.	12.6
2. 1940	11.11.49	4.16	83	6,900	60	6.8	1.7 : 1	6	3+	7.1
	15.11.49	—	—	—	—	<i>Splenectomy</i>		—	—	—
	12.12.49	4.36	88	12,100	60	7.8	2.8 : 1	5.5	2+	14.6
	17.6.50	—	92	—	32	—	—	—	—	—
	23.11.50	5.3	105	10,100	28	6.6	1.7 : 1	—	—	—
3. 1942	11.11.49	4.08	83	9,300	30	7.8	2.3 : 1	4	Neg.	4.7
	15.11.49	—	—	—	—	<i>Splenectomy</i>		—	—	—
	12.12.49	4.29	88	10,700	20	8.9	2.3 : 1	3	Neg.	6.1
	23.9.50	4.17	78	11,000	12	7.2	1.7 : 1	—	—	—
4. 1946	14.4.49	3.76	75	5,400	40	7.9	1.3 : 1	14	5+	3.6
	18.10.49	—	—	—	—	<i>Splenectomy</i>		—	—	—
	3.11.49	4.19	85	9,700	50	—	—	13	5+	9.2
	14.11.49	—	—	—	50	10.5	0.9 : 1	—	—	—
	28.4.50	4.15	80	8,500	62	10.3	1.1 : 1	15	5+	8.4
	29.11.50	4.25	80	11,600	28	—	—	12.5	5+	10.1
5. 1949	20.7.49	3.8	58	17,600	46	—	—	—	—	—
	22.9.50	4.5	76	20,000	60	6.0	0.7 : 1	—	—	—
	—	—	—	—	—	<i>Splenectomy</i>		—	—	—
	4.11.50	4.07	77	18,500	42	—	—	—	—	—
6. 1949	16.11.50	4.08	82	18,000	27	5.7	1.5 : 1	—	—	—
	6.1.50	3.88	77	12,100	50	—	—	—	—	—
	22.2.50	3.74	70	10,000	98	9.3	1.5 : 1	13	2+	4.2
	11.4.50	—	—	—	—	<i>Splenectomy</i>		—	—	—
	3.5.50	2.66	53	11,650	100	8.9	2.2 : 1	5	2+	6
	7.6.50	3.61	84	—	90	—	—	—	—	—
	27.10.50	5.62	110	8,500	5	7.0	1.3 : 1	3	Neg.	11.2

Case 6 is of unusual interest. This patient was first admitted to the Middlesex Hospital in July, 1949, under the care of Dr. Beaumont, complaining of joint pains, and the development of bruises. Examination revealed the presence of ecchymoses and petechiae. His platelet count at repeated examinations was found to be 80,000, bleeding time was prolonged at 6½ minutes. The Hess capillary test was positive and his bone marrow showed scanty megacaryocytes. No cause was discovered for his joint pains and a diagnosis of thrombocytopoenic purpura was made. Three months later he was admitted to our Rheumatic Unit with pyrexia, cold and clammy hands, and typical rheumatic swellings of the interphalangeal joints. His platelet count was then 240,000, and bleeding time was normal, but he refused a further sternal puncture.

Since many clinicians believe that the earliest features of rheumatoid arthritis may well be explained on the basis of undue capillary fragility, it is interesting to speculate on the relationship of the hypersplenism in this patient to the development of his rheumatoid arthritis and his subsequent recovery after splenectomy.

**Pathological Reports on Spleen and Liver**

(1) *Mrs. H.*, aged 50, chronic polyarticular arthritis. Spleen shows non-specific hyperplasia. There is hyperplasia of the malpighian corpuscles with enlarged Fleming's centres, many of which contain eosinophilic material. The increase in the pulp is less marked and many of the sinusoids are empty.

(2) *Mrs. N.*, aged 36, polyarticular arthritis. Spleen shows hyperplasia of the pulp.



FIG. 1.—Case 6, low-power view showing hyperplasia of Malpighian corpuscles.

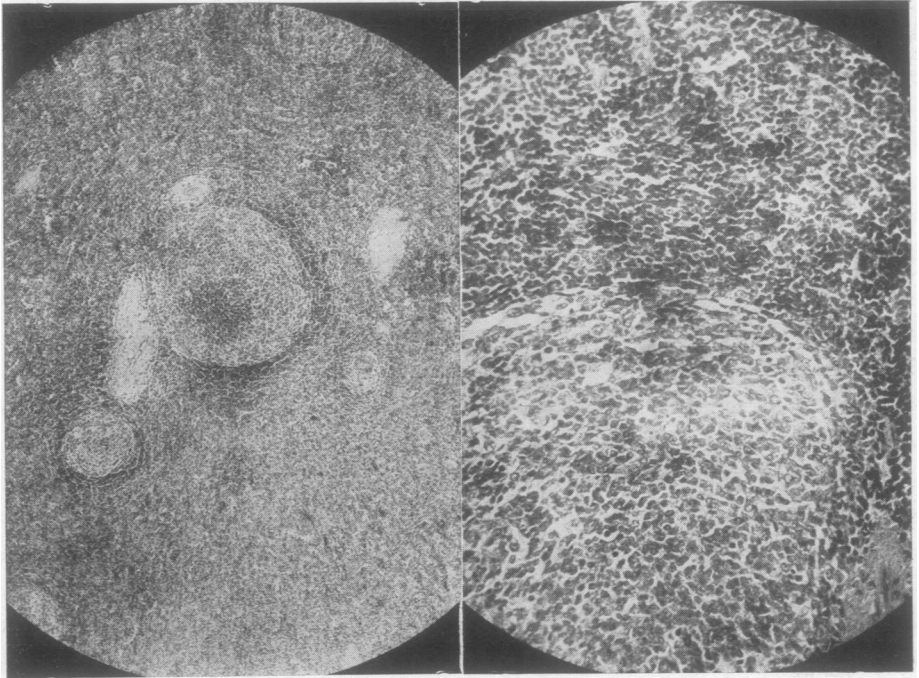


FIG. 2.—Case 6, hyperplasia of the Malpighian corpuscles. Higher-power view.

FIG. 3.—Case 6, showing Fleming centre surrounded by dense zone of lymphocytes and an outer looser layer of lymphocytes.

There is more marked hyperplasia of the malpighian corpuscles, with enlarged Fleming's centres which are mostly cuffed by reticulum cells. There is eosinophilic material within the centres. There is increased density of the pulp but no increase in fibrous tissue.

(3) *Mrs. C.*, aged 32, polyarticular arthritis. Spleen shows no hyperplasia of the malpighian corpuscles. Pulp shows some hyperplasia with many eosinophils. There is some eosinophilic material in the few malpighian corpuscles showing Fleming's centres. No increase in fibrous tissue.

(4) *Mrs. R. S.*, aged 37, chronic polyarticular arthritis. Spleen shows tremendous lymphatic hyperplasia of the malpighian bodies with large Fleming's centres. Medulla rather fibrous but empty of cells. No increase in fibrous tissue. Amyloid—nil.

Liver shows a thickened capsule, and dilated but empty sinusoids, and cells appear normal. Some early increase is seen in fibrous tissue, mainly peri-portal. Amyloid—nil.

(5) *Mrs. E.*, aged 61, acute polyarthritis. Spleen shows hyaline changes in some of the lymph nodules.

(6) *G. C.*, aged 26, acute polyarticular arthritis. Spleen shows hyperplasia of the pulp and follicles. The Fleming's centres are particularly large and there is albuminoid material in places. No increase in fibrous tissue. Amyloid—nil. (Figs 1, 2, 3.)

Liver shows fatty degeneration around the central venules, but is otherwise normal.

In general, the pathological examinations of the spleen showed non-specific hyperplasia of the malpighian corpuscles, with hyaline changes in the central arterioles in some sections. One case also had excessive activity of the reticulo-endothelial cells of the pulp. There was no evidence of amyloid change in any of the sections.

#### Comment

Hench and others (1950), later quoted by Davidson (1950), refer to the pathological physiology which constitutes the "fire" in rheumatoid arthritis, and to the pathological anatomy which represents the "ashes" of the disease.

(1) Clinically the disease has been relatively, and in some instances, completely inactive since operation. In no instance has there been a definite flare-up. In some cases, the relief of pain, stiffness, and joint swelling, was immediate, in others, delayed. It is interesting to compare this re-action with that following cortisone and ACTH therapy.

(2) In two cases, there has been a definite progression of articular deformity, judged by clinical and x-ray signs. It is possible that the reduction of joint-swelling and the absence of muscle spasm has contributed to this deformity by allowing the patients to use their hands freely and without pain.

(3) Certain features in its pathological physiology have been reversed. Certain of the laboratory findings have returned towards normal after operation. We do not know the significance of certain changes, among them the so-called "hepatic-function tests" and the histological changes seen in the spleen and lymph glands. The evidence on bone-marrow changes, bleeding times, and Splenin A and B, is insufficient to be worthy of report.

When the laboratory findings are compared with those that follow cortisone or ACTH therapy, a similar, but somewhat delayed and less dramatic response is seen. The blood sedimentation rate falls, the haemoglobin increases, and in some cases there is an increase of the red-cell count. The white-cell count also increases, and when the serum protein total and albumin globulin ratio is abnormal it tends to return to normal. The hepatic-function tests, when abnormal, tend to improve with the serum protein tests.

We make no claims for this form of therapy which we consider entirely experimental in nature, especially as we have no similar series of rheumatoid arthritis patients who have been operated on for other reasons for comparison. However, we hope that the follow-up of these patients may help to throw some light on the effect of splenic function on the progress of rheumatoid disease.

### Summary

The case histories and follow-up are presented of twelve patients suffering from rheumatoid arthritis in whom the spleen had been removed at some time during the previous 12 years.

After operation, the disease, judged by the clinical picture, had become completely or relatively inactive. There was improvement of general health, with relief of pain, joint stiffness, and joint swelling. Laboratory findings showed a reversal of certain features in the pathology of the disease.

These findings are compared with those known to follow cortisone and ACTH therapy. A brief historical review is given, and evidence presented, to show why the spleen is considered to be an endocrine gland. The inter-relationship between the spleen, pituitary, ovaries, bone marrow, and adrenal cortex is discussed. The removal of the spleen in rheumatoid arthritis is not advocated, but the need for a further study of the spleen and bone marrow in their relationship to this disease is strongly emphasized.

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### Splénectomie dans l'Arthrite Rhumatismale

#### RÉSUMÉ

Les auteurs présentent les observations de douze cas d'arthrite rhumatismale chez qui la rate avait été enlevée au cours des douze dernières années.

Après l'opération, la maladie, jugée d'après son aspect clinique, devint complètement ou relativement inactive. L'état général s'améliora et la douleur, la rigidité, et la tuméfaction articulaires s'atténuèrent. L'examen de laboratoire révéla l'inversion de certains éléments pathologiques.

On compare ces résultats à ceux qu'on obtient généralement avec la cortisone et l'ACTH.

Les auteurs passent en revue l'histoire du problème et donnent leurs raisons de considérer la rate comme une glande endocrine. Ils discutent les rapports existants entre la rate, l'hypophyse, les ovaires, la moelle osseuse, et l'écorce surrénale. Sans préconiser la splénectomie dans l'arthrite rhumatoïdale, ils soulignent la nécessité d'études ultérieures de la rate et de la moelle osseuse par rapport à cette maladie.

#### **Esplenectomía en Artritis Reumatoide**

##### **SUMARIO**

Los autores presentan la historia clínica de doce casos de artritis reumatoide en los cuales se había efectuado la esplenectomía en algun período comprendido en los últimos doce años.

Después de la operación, la enfermedad, juzgando por el cuadro clínico, había devenido en completa o relativamente inactiva. El estado general había mejorado, constatándose atenuación de dolor, de rigidez, y de tumefacción articulares. Los exámenes de laboratorio revelaron la inversión de ciertos elementos patológicos de la enfermedad.

Se efectúa una comparación de estos resultados con aquellos que reconocidamente suceden al tratamiento con la cortisona y la ACTH. Los autores efectúan una breve revisión histórica y presentan evidencias demostrativas del por qué consideran el bazo como una glándula endocrina. Se discute la inter-relación entre el bazo, la pituitaria, los ovarios, la médula ósea, y la corteza suprarrenal. Sin pregonizar la esplenectomía en la artritis reumatoide, los autores acentúan enfáticamente la necesidad de estudiar ulteriormente el bazo y la médula ósea en relación con esta enfermedad.