EXTRA-ARTICULAR MANIFESTATIONS OF RHEUMATOID ARTHRITIS

Medical Grand Rounds
July 8, 1976

Eric R. Hurd, M.D.

EXTRA-ARTICULAR MANIFESTATIONS OF RHEUMATOID ARTHRITIS

I. Introduction

II. Manifestations

A. Rheumatoid Nodules

B. Ocular

C. Cardiac

D. Pulmonary

E. Felty's Syndrome

F. Lymphadenopathy

G. Neurologic

H. Muscle

I. Sjögren's Syndrome

J. Skin

K. Circulating Immune Complexes and Serum Hyperviscosity Syndrome

L. Bones

M. Hematologic

N. Gastrointestinal and Liver

O. Miscellaneous

1) Psychiatric
2) Amyloidosis
3) Laryngeal

III. Summary

I. INTRODUCTION

One usually thinks of rheumatoid arthritis as a disease which only affects joints. While it is true that in the majority of patients the arthritis is the most prominent feature, many patients have extra-articular manifestations. These manifestations can be quite severe, leading possibly to blindness or even death. Death due solely to rheumatoid arthritis is rare. When it occurs it is almost inevitably due to the extra-articular manifestations.

The extra-articular manifestations tend to be associated with those patients who have positive rheumatoid factor in their blood and also generally occur more frequently in those patients with a higher rheumatoid factor titer than in those with a lower titer. Because rheumatoid nodules are usually present in patients with high titers of rheumatoid factor in their sera, extra-articular manifestations usually occur in patients with rheumatoid nodules.

Several studies have suggested that the presence of extra-articular features varies directly with the severity and duration of rheumatoid disease (1-4). Some studies have suggested that extra-articular features appear when rheumatoid articular disease activity subsides (1,5). Others have suggested that extra-articular features may be a consequence of corticosteroid therapy (1,6-9). A more recent study, however, found no relationship between the presence of extra-articular features and use of corticosteroids or duration of disease (10). The extra-articular manifestations did correlate with evidence of persistent articular inflammatory activity, roentgenologic stages of more severe disease and the presence of soluble immune complexes and high titers of rheumatoid factor. There was also an increased mortality in patients with extra-articular features.

REFERENCES (Introduction)

1. Schmid FR, Cooper NS, Ziff M and McEwen C: Arteritis in rheumatoid arthritis. Amer J Med 30:56, 1961.

2. Thompson M: The clinical features of rheumatoid disease. Chap. 2, Progress in Clinical Rheumatology. Dixon A.St.J. ed., London, J&A Churchill Ltd., 1965.

3. Kellgren JH: Epidemiology of rheumatoid arthritis, chap. 1, Rheumatic Diseases (Dutker JJR, Alexander WRM, eds). Baltimore, Pfizer Medical Monograph 3, Williams & Wilkins & Co., 1968.

4. Hart FD: Rheumatoid arthritis extra-articular manifestations. Brit Med J 3:131, 1969.

5. Barnes CG, Turnbull AL, Vernon-Roberts B: Felty's Syndrome. Ann Rheum Dis 30:359, 1971.

6. Ogryzlo MA: Diffuse systemic rheumatoid disease. Ann Rheum Dis 12:323, 1953.

7. Hart FD, Golding JR, MacKenzie DH: Neuropathy in rheumatoid disease. Ann Rheum Dis 16:471, 1957.

8. Bywaters EGL, Scott JT: The natural history of vascular lesions in rheumatoid arthritis. J Chem Dis 16:905, 1963.

9. Hollingsworth JW: Local and systemic complications of RA, Philadelphia, W.B. Saunders Co., 1968.

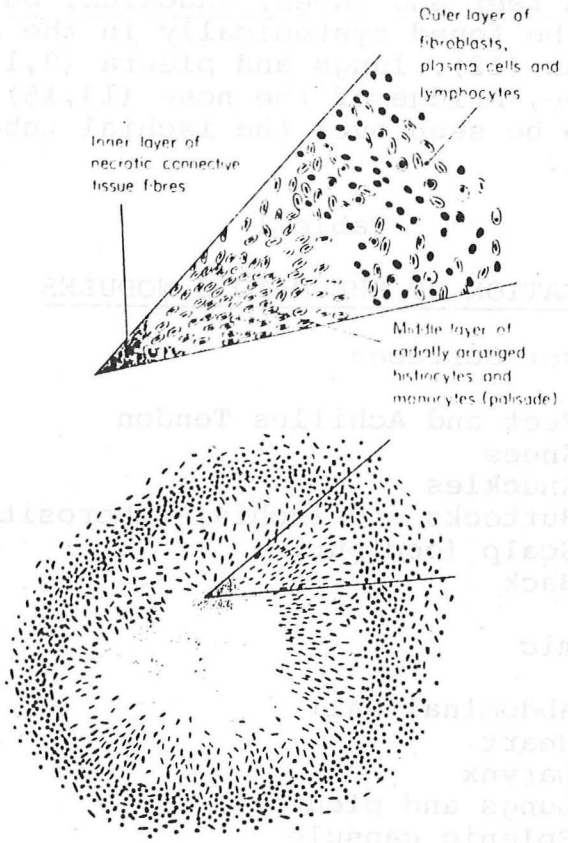
10. Gordon DA, Stein JL, Broder I: Extra-articular features of RA, a systematic study of 127 cases. Am J Med 54:445-452, 1973.

II. MANIFESTATIONS

A. *Rheumatoid Nodules*

Rheumatoid nodules are some of the most characteristic findings in rheumatoid arthritis.

Histologically (see Fig. 1) they are composed of three zones. The central zone consists of necrotic connective fibers and is surrounded by the middle layer of histiocytes, fibroblasts and monocytes which are radially arranged to form a palisade. The outer layer is composed primarily of chronic inflammatory granulation tissue which is comprised of fibroblasts, plasma cells and lymphocytes.



Drawing of histological appearances of a subcutaneous nodule in rheumatoid arthritis. Note the three separate elements: the central zone of necrosis with fibrinoid change, enclosed in a palisade of radially-arranged elongated cells, and a peripheral layer of chronic inflammatory granulation tissue.

Figure 1 From ref. (1)

It is of interest that rheumatoid nodules of the palmar surfaces of the hands and fingers often immediately follow the development of 1 to 2 mm, slightly raised areas of cutaneous vasculitis (2). These lesions persist for two to three weeks and are then followed by development of typical subcutaneous nodules.

Both arteritis (3-5) and venulitis (6) have been noted in the early nodule. Heterologous and homologous fibrin implants in experimental animals will produce nodule formation.

Approximately one third of patients have nodules if they are carefully examined (7). The most commonly recognized sites for rheumatoid nodules are the extensor surfaces of the arms and elbows, especially the olecranon process. However, they may be found anywhere in the subcutaneous tissue but particularly on contact or pressure points over tendons and bone, on feet and knees, knuckles, buttocks, scalp or back (8). They may also be found systemically in the abdominal wall (9), heart (10-12), larynx (12), lungs and pleura (9,12,13), splenic capsule, peritoneum, eye, bridge of the nose (14,15) and pinna of the ear (15). They may also be seen over the ischial tuberosity and Achilles tendon. See Table 1.

Table 1

LOCATION OF RHEUMATOID NODULES

Extensor Surfaces

- Feet and Achilles Tendon
- Knees
- Knuckles
- Buttocks and Ischial Tuberosity
- Scalp (occiput)
- Back

Systemic

- Abdominal wall
- Heart
- Larynx
- Lungs and pleura
- Splenic capsule
- Peritoneum
- Eye
- Bridge of nose
- Pinna of ear

The major complication is breakdown of the overlying skin with discharge of the contents. This may result in "fistulous rheumatism" and may require excision. A number of nodular lesions may be confused

with rheumatoid nodules. Over the olecranon process, the major considerations would probably be gouty tophi and amyloid nodules. Tophi would also be a major consideration in the pinna of the ear. Other lesions that might be mistaken include ganglions of the hand or wrist, sebaceous cysts, xanthomatous tendon nodules (16), basal cell carcinoma (15) and nodules of multicentric reticulohistiocytosis or granuloma annulare (17).

In patients with small rheumatoid nodules on the bridge of the nose, it was believed that the nodules were induced in this location by pressure from spectacle frames (15). Several of these patients also had small rheumatoid nodules on the antihelix of the ear. Both the location and appearance of these lesions suggested basal cell carcinoma of the skin.

Lipoid nodules are unusual lesions occurring in patients with chronic rheumatoid arthritis (18). These masses are large, cystic, and contain yellow fat-like material containing calcium, lipids, and cholesterol. Thus these lesions are not really rheumatoid nodules. According to these authors, the rapid development of a large cystic mass in a patient with chronic rheumatoid arthritis should be suspected of being a lipoid nodule. These are usually in the vicinity of a joint and are frequently in the groin. Draining the mass satisfactorily eradicates the lesion.

In one patient (19) a large rheumatoid granulomatous lesion was present in the head and neck of the femur and mimicked a lytic bone tumor.

Perhaps the most unusual form of rheumatoid granuloma reported in a few patients, is the linear subcutaneous band (20). These bands were manifested as elevated and elongated cordlike subcutaneous lesions which histologically were compatible with rheumatoid nodules. They were associated with numerous subcutaneous nodules.

Although rheumatoid nodules usually occur in patients with rheumatoid arthritis, patients with severe joint involvement and positive tests for rheumatoid factor, exceptions may occur. In one patient (21) subcutaneous rheumatoid nodules and presence of serum rheumatoid factor occurred in a patient without arthritis. In another patient, polyarthritis and subcutaneous nodules were present with agammaglobulinemia (22). Rarely, subcutaneous nodules may be an early manifestation of RA.

Treatment with oral steroids or injection directly into the nodule with steroids can decrease the size of the nodule (23). However, older and larger nodules may be unaffected. Treatment is usually unnecessary but, if it becomes extremely large or infected, then surgical excision may be necessary.

REFERENCES (Nodules)

1. Boyle JA and Buchanan WW: Clinical Rheumatology. FA Davis Co. Philadelphia, Pa, p. 89, 1971.

2. Williams RC: Rheumatoid arthritis as a systemic disease. Major Problems in Internal Medicine IV, p. 32, W.B. Saunders Co. Philadelphia, London Toronto, 1974.

3. Sokoloff L: The pathophysiology of peripheral blood vessels in collagen diseases, chap. 13, The Peripheral Blood Vessels, edited by JL Orbison and D Smith, Williams & Wilkins, Baltimore, 1963.

4. Sokoloff L, McCluskey RT and Bunim JJ: Vascularity of the early subcutaneous nodule in RA. Arch Path 55:475, 1953.

5. Sokoloff L, Wilens SL and Bunim JJ: Arteritis of striated muscle in RA. Am J Path 27:157, 1953.

6. Kulka JP: The vascular lesions associated with RA. Bull Rheum Dis 10:201, 1959.

7. Kellgren JH and Ball J: Clinical significance of the rheumatoid serum factor. Brit Med J 1:523, 1959.

8. Williams RC: RA as a systemic disease V in Major Problems in Int Med, W.B. Saunders Co., Philadelphia, Pa., 1974.

9. Gruenwald P: Visceral lesions in a case of RA. Arch Path 46: 59, 1948.

10. Baggenstross AH and Rosenberg EF: Visceral lesions associated with chronic infectious (rheumatoid) arthritis. Arch Path (Chicago) 35:503, 1943.

11. Baggenstross AH and Rosenberg EF: Unusual cardiac lesions associated with chronic multiple rheumatoid arthritis. Arch Path 37:54, 1944.

12. Raven RW, Weber FP and Price LW: The necrobiotic nodules of RA: case in which the scalp, abdominal wall (involving striped muscle), larynx, pericardium (involving myocardium), pleurae (involving lungs) and peritoneum were affected. Ann Rheum Dis 7:63, 1948.

13. Robertson JL and Brinkman GL: Nodular rheumatoid lung disease. Amer J Med 31:483, 1961.

14. Bunim JJ, Sokoloff L, Williams RR and Black RL: RA: a review of recent advances in our knowledge concerning pathology, diagnosis and treatment. J Chron Dis 1:168, 1955.

15. Healey LA, Wilshe KR and Sagebiel RW: Rheumatoid nodules simulating basal cell carcinoma. New Eng J Med 277:7-9, 1967.

16. Kellgren JH and Ball J: Tendon lesions in RA: a clinicopathological study. Ann Rheum Dis 9:48, 1950.

17. Keil H: The rheumatic subcutaneous nodules and simulating lesions. Med 17:261-380, 1938.

18. Mittal A, Block MA and Wylie JH: Lipoid nodules of chronic RA presenting in the groin. Am Surgeon 34:309-310, 1968.

19. Hunder GG, Ward LM and Ivins JC: Rheumatoid granulomatous lesion simulating malignancy in the head and neck of the femur. Mayo Clin Proc 40:766-770, 1965.

20. Dykman CJ, Golens GJ and Good AE: Linear subcutaneous bands in RA an unusual form of rheumatoid granuloma. Ann Int Med 63:134-140, 1965.

21. Askari A, Moskowitz RW and Goldberg VM: Subcutaneous rheumatoid nodules and serum rheumatoid factor without arthritis. JAMA 229: 319-320, 1974.

22. Barnett EV, Winkelstein A and Weinberger HJ: Agammaglobulinemia with polyarthritis and subcutaneous nodules. Am J Med 48:40-47, 1969.

23. Bunim ML, Ziff M, McEwen C: Evaluation of prolonged cortisone therapy in RA: a four year study. Am J Med 18:27, 1955.

B. *Ocular Involvement*

1) Associated with disease

The major types of eye involvement are shown in Table 2. These are episcleritis, scleritis and scleromalacia perforans.

Table 2

OCULAR INVOLVEMENT

Episcleritis

Scleritis

Scleromalacia perforans

Marginal furrows of the cornea

Retinopathy

Sicca syndrome of Sjögren

The most common ophthalmologic symptoms of rheumatoid arthritis, however, are associated with the sicca syndrome of Sjögren i.e. keratoconjunctivitis sicca which produces dry eyes.

If one does not include Sjögren's Syndrome which is discussed elsewhere, then the most frequent type of eye involvement in rheumatoid arthritis is probably episcleritis and/or scleritis. Differentiation between these is shown in Table 3 (1). Episcleritis is caused by in-

Table 3

Characteristics	*Episcleritis*	*Scleritis*
Definition	Inflammation of the episcleral (subconjunctival) tissues	Inflammation of the scleral coat of the eye
Course	Usually fairly acute in onset and resolves within 3 weeks	Acute or slow in onset; may resolve in a few weeks or last 1 to 2 years
Symptoms	Discomfort only, vision not affected	May cause severe pain and general malaise, vision may be blurred
Types	Simple or nodular	Simple, diffuse, nodular, or necrotizing
Signs	Conjunctival and superficial episcleral vascular plexuses affected, nodules are superficial and can be moved Cornea not affected	Deep episcleral vascular plexus affected, superficial vessels may also be affected, nodules are deep and fixed to the sclera Cornea may be affected (sclerokeratitis)
Outcome	No residual physical signs	Followed by scleral thinning; may have serious complications, including perforation

from ref. (1)

flammation of the episcleral tissues. It usually subsides spontaneously and does not impair visual acuity.

Scleritis is caused by inflammation of the deeper layer, the sclera. The inflammation can be so severe or recurrent that severe scleral thinning may result with possible eventual perforation. Such weakening of the sclera is most noticeable in the superior scleral segments. Scleritis is usually related to the severity of the rheumatoid disease, particularly with the presence of systemic manifestations (2). See Table 4. The sites of scleral inflammation in 14 rheumatoid patients

Table 4

ASSOCIATION OF SCLERITIS WITH RHEUMATOID ARTHRITIS IN 147 PATIENTS

	No. with scleritis	No. with no scleritis	Significance
Rheumatoid nodules	10	34	$P < 0.01$
No rheumatoid nodules	4	99	
Pericarditis/pleurisy	2	1	$P < 0.05$
No pericarditis/pleurisy	12	132	
Arteritis	10	16	$P < 0.001$
No arteritis	4	117	
Systemic complications	11	18	$P < 0.001$
No systemic complications	3	115	

from ref. (2)

are shown in figure 2.

Right (14) Left (10)

Figure 2

Sites of scleral inflammation in 14 rheumatoid patients (1)

When the scleritis is severe, a rheumatoid granuloma may form in the scleral tissue. These lesions grossly and microscopically resemble rheumatoid nodules. When such lesions are present the sclera is markedly thinned and scleromalacia perforans may result.

Van der Hoeve (3) was the first to describe scleromalacia perforans. By 1938 fourteen cases had been reported and some of them had been studied microscopically (4). These workers first noted the pathologic similarities between the subcutaneous nodules of rheumatoid arthritis and the nodules of scleromalacia perforans. However, they are also different in certain respects e.g. trauma undoubtedly is an important contributory cause of the subcutaneous, but apparently not of the scleral nodules. In addition, the scleral nodules tend to become densely infiltrated with pus cells and cause marked chronic inflammatory reaction while subcutaneous nodules tend to remain relatively free from infiltration. The scleral nodules consist of a sharply defined area of necrotic scleral tissue which is surrounded by a wall of epithelial cells which becomes infiltrated with pus cells. This process results in a sequestrum, which becomes disintegrated and densely infiltrated with necrotic pus cells. These abscesses form cavities in the sclera. In a few nodules there may be infiltrates of lymphocytes and plasma cells. Replacement of the damaged sclera and uvea by fibrous tissue takes place and new epithelium forms an external covering (5). Because the sclera is a fibrous and almost avascular structure, pathologic processes affecting it are chronic in character and very resistant to therapy (6). When the sclera becomes involved, the adjacent tissues take over the role of a vascular system but often they are too far away from the damaged scleral fibers, which then rapidly become necrotic, with no chance for organization or repair. If the lesion is near the episclera or uvea the chances for replacement by fibroblastic tissue are correspondingly greater.

In some cases the episclera is rich in lymphocytes, forming follicle-like structures (7). In severe cases, perforation of the sclera with resultant collapse of the globe occurs.

Scleritis and episcleritis can be, but are not necessarily, exclusively precursors of the scleromalacia (8).

A necrotizing nodular scleritis proceeding to scleromalacia perforans may be seen in systemic lupus erythematosus, periarteritis nodosa, Wegener's granulomatosis, porphyria, herpes zoster (9) and Crohn's Disease (10). Thus scleromalacia is not specific for rheumatoid arthritis. This complication is very difficult to treat and perforation with an endophthalmitis with rapid loss of vision may occur. Unless topical or systemic steroids or surgery e.g. fascia lata grafting is helpful, perforation will occur and enucleation may be necessary.

In one patient with scleromalacia perforans (11) the treatment included the combined administration of d-penicillamine and fluoprednisolone for the control of the inflammatory process. Subsequently, a fascia lata autograft was used to repair the scleral defect. After 12 months of followup the examination revealed a well-integrated graft with good vision and no relapse of the eye disorder. There was also improvement in the underlying systemic condition. They concluded that treatment of the underlying disease to suppress the inflammatory process is mandatory prior to surgical intervention. Fascia lata autografts are preferable to donor homografts in these cases since homografts have generally produced poor results (12-14).

In one case of scleromalacia the topical application of sodium versenate (EDTA), used as an anticollagenase, was believed to be beneficial (10).

A very unusual case of unilateral exophthalmos resulting from diffuse scleritis has recently been reported. There was a good response to topical corticosteroid therapy (15).

A fairly characteristic corneal lesion of rheumatoid arthritis has also been described (16). Such lesions are marginal furrows at the edge of the cornea which can become quite thin to the point of perforation or leakage. In such patients, corneal grafts have been of value.

A similar lesion consisting of partial opacity of the peripheral areas of the cornea involving all or part of its circumference has been described (17). It has been known as "contact lens" cornea because the cornea may be thinned and slightly opaque, and the appearance is that of an eye wearing a contact lens. Impairment of the arteriolar vascular supply at the corneal limbic areas may be the cause of this lesion.

Uveitis and iritis are seen in patients with rheumatoid arthritis but the incidence is probably no higher than in the general population (18,19).

Other workers have reported a variety of retinal lesions found in patients with rheumatoid arthritis not treated with chloroquine (Table 5). How many of these lesions were related to the disease, the patient's age or other types of treatment e.g. gold salts, was not known.

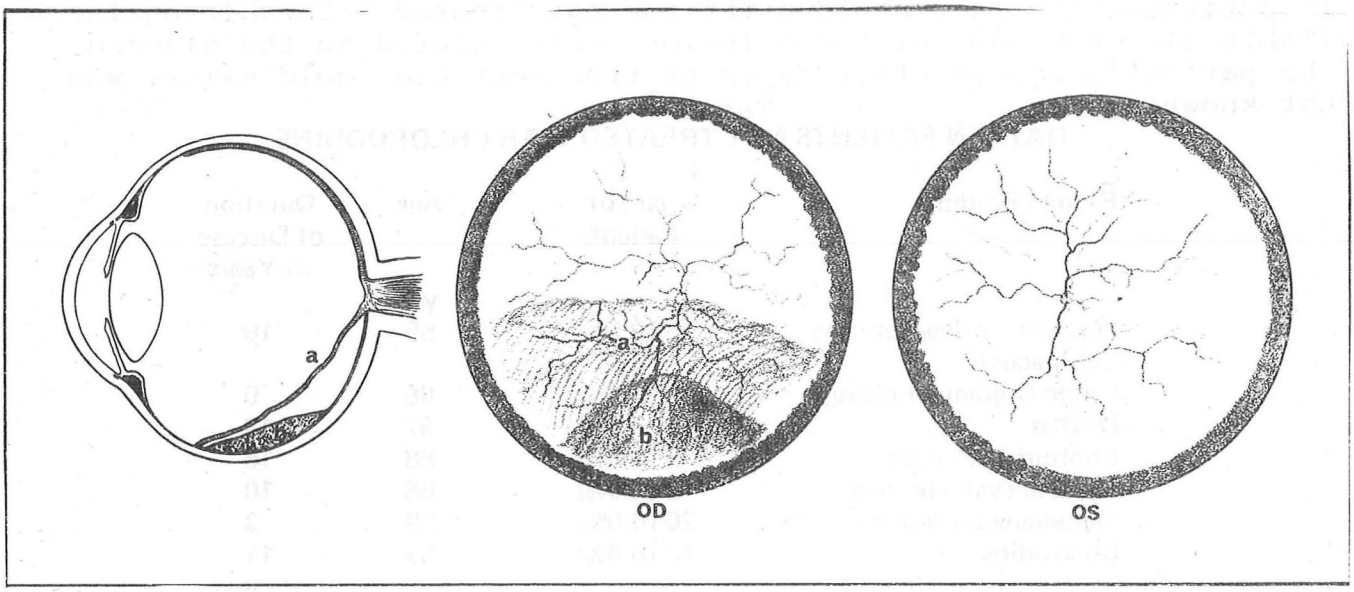
Table 5

DATA IN PATIENTS NOT TREATED WITH CHLOROQUINE

Retinal Findings	No. of Patients	Age	Duration of Disease in Years
		yr.	
Pigmentary degeneration of macula	3 (0.9%)	65	18
Senile & granular changes	10 (3.0%)	66	9
Drusen	11 (3.3%)	67	18
Choroidal selerosis	5 (1.5%)	68	18
Hyaline cystic lesions	3 (0.9%)	68	10
Miscellaneous lesions	20 (6.0%)	59	13
Choroiditis	18 (5.4%)	57	11
Total retinal lesions	70 (21.0%)	64	14.3
All untreated patients	333 (100.0%)	54.6	10

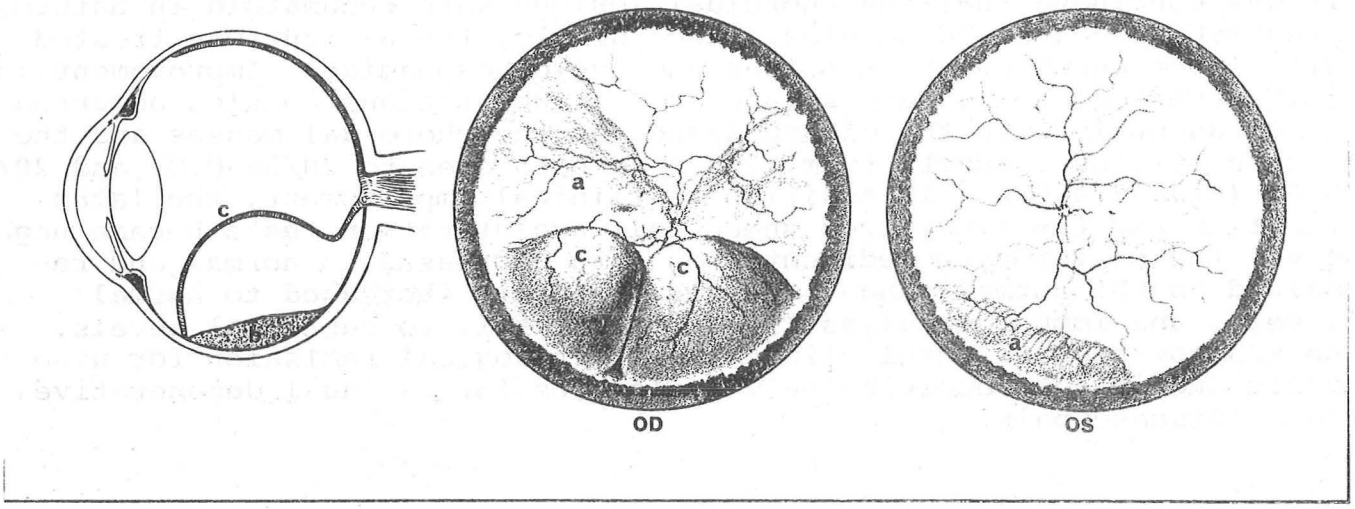
from ref. (20)

In a fascinating case which we have previously reported (21), a patient with severe rheumatoid arthritis and a history of vascular abnormalities, iritis and scleromalacia perforans, developed bilateral choroidal lesions and secondary retinal detachments. The changes in the eyes were coincidental with an exacerbation of joint involvement and an extraordinary eruption of rheumatoid subcutaneous nodules. Because of this association, and because the ocular lesions were bilateral, it was concluded that the choroidal lesions were rheumatoid in nature, presumably rheumatoid nodules. Accordingly, the patient was treated with large doses of prednisolone and cyclophosphamide. Improvement in joint symptoms and disappearance of the subcutaneous nodules occurred simultaneously with the disappearance of the choroidal masses and the return of visual acuity from 20/300 in both eyes to 20/50 O.D. and 20/30 O.S. (Fig. 3,4,5). In addition to clinical improvement, the latex fixation and the sensitized sheep cell agglutination tests became negative, the erythrocyte sedimentation rate decreased to normal and remained in the normal range, the serum albumin increased to normal levels, and immunoglobulins (IgG and IgM) fell to subnormal levels. He has now been in total clinical and serological remission for nine years and is now receiving only analgesics for residual degenerative joint disease pain.



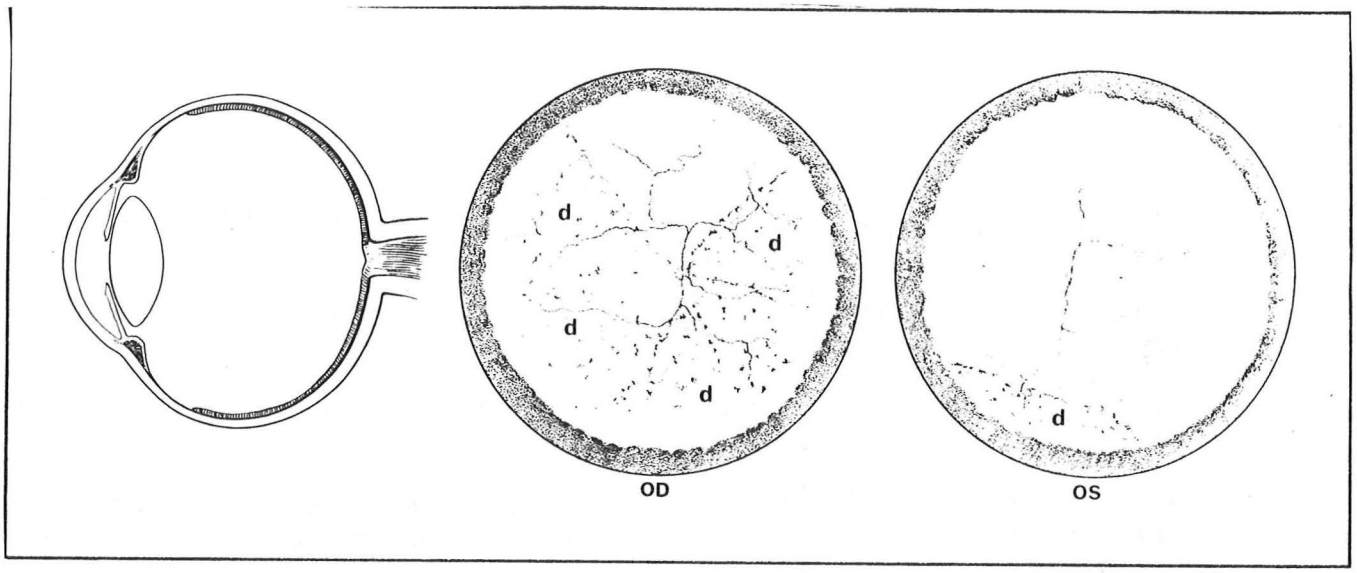
The appearance of the fundi of both eyes in October 1966. In the right eye, an inferior retinal detachment (a) can be seen overlying a mass (b) in the choroid. The left fundus was completely normal at this time. Visual acuity was 20/80 (OD) and 20/50 (OS).

Figure 3 from ref. (21)



Appearance of both fundi in December 1966. In the right eye, the retinal detachment (a) has extended and is seen inferiorly as a bullous uveal effusion (c) with the underlying mass (b) still present. A small inferior retinal detachment (a) is also present in the left eye. Visual acuity was 20/300 (OD) and 20/40 (OS).

Figure 4 from ref. (21)



Appearance of both fundi in April 1967. Clumping and dispersion of subretinal pigment (d) are seen OD and OS.

Figure 5 from ref. (21)

2) Ocular Side Effects of Drugs used for Treatment of Rheumatoid Arthritis

Corticosteroids, gold salts and anti-malarial drugs can all produce eye lesions.

Corticosteroids can increase intraocular pressure (22), precipitate glaucoma (22), and with chronic use, can cause posterior subcapsular cataracts (23-26). They may progress to the point that visual acuity is impaired, necessitating surgical removal.

Gold may be deposited in the cornea or conjunctivae after prolonged use and rarely may produce a pseudomembranous conjunctivitis (27).

Antimalarial drugs may cause retinopathy or keratopathy. The types of retinal damage caused by chloroquine are shown in Table 6.

Table 6
DATA IN CHLOROQUINE–TREATED PATIENTS

Retinal Findings	No. of Patients	Age	Duration of Disease	Drug Exposure
		yr.	yr.	mo.
Pigmentary degeneration of macula	2 (0.5%)	50	11 1/2	40
Sinile & granular changes	8 (2.0%)	65	15	36
Drusen	6 (1.5%)	62	15 2/10	46
Choroidal selerosis	3 (0.7%)	62	7 7/10	38
Hyaline cystic lesions	2 (0.5%)	70	17	50
Miscellaneous lesions	7 (1.8%)	69	14	48
Choroiditis	2 (0.5%)	54	10	38
Total retinal lesions	30 (7.4%)	60	13	40
All treated patients	408 (100.0%)	42	8 6/10	40 3/10

from ref. (20)

REFERENCES (Ocular)

1. Jayson MIV and Jones DEP: Scleritis and rheumatoid arthritis. Ann Rheum Dis 30:344, 1971.

2. Jones P and Jayson MIV: Rheumatoid arthritis of the eye. Proc Roy Soc Med 66:1161-1163, 1973.

3. Van der Hoeve J: Scleromalacia perforans. Arch Ophth 11:111-118, 1934.

4. Verhoeff FH and King MJ: Scleromalacia perforans report of a case in which the eye was examined microscopically. Arch Ophth 20:1013-1035, 1938.

5. Eggers H: Necroscleritis nodosa associated with chronic rheumatoid polyarthritis report of case. Arch Ophth 23:501-506, 1940.

6. Smoleroff JW: Scleral disease in RA report of 3 cases in one of which both eyes were studied post mortem. Arch Opth 29:98-108, 1943.

7. Goar EL and Smith LS: Rheumatoid nodules of the eye. JAMA 148: 889-892, 1952.

8. Anderson B and Margolis G: Scleromalacia. Clinical and pathological study of a case with consideration of differential diagnosis, relationship of collagen disease and effect of ACTH and cortisone therapy. Am J Ophth 35:917-931, 1952.

9. Duke-Elder S and Leigh AG: System of Ophthalmology. 8 pt 2 p. 1098 Kimpton London, 1965.

10. Evans PJ and Eustace P: Scleromalacia perforans associated with Crohn's disease treated with sodium versenate EDTA. Brit J Ophth 57:330-335, 1973.

11. Zee I. Machtey I and Kurz O: Combined treatment of scleromalacia perforans in RA with penicillamine and plastic surgery. Ophth 166:293-300, 1973.

12. Armstrong K and McGovern VJ: Scleromalacia perforans with repair grafting. Trans Ophthal Soc Austr 15:110, 1955.

13. Rosenthal JW and Williams GT: Scleromalacia perforans as a complication of RA. Amer J Ophth 54:862, 1962.

14. Torchia RT, Dunn RE and Pease PJ: Fascia lata grafting in scleromalacia perforans. Am J Ophth 66:705-1968.

15. Kennedy AC and McGavin DD: Rheumatoid scleritis producing exophthalmos. Brit J Clin Pract 29:73-75, 1975.

16. Brown SI and Grayson M: Marginal furrows: a characteristic corneal lesion of RA. Arch Ophth 79:563-567, 1968

17. Lyne AJ: "Contact lens" cornea in RA. Brit J Ophth 54:410-415, 1970.

18. Kimura SJ, Hogan MJ, O'Connor GR and Epstein WV: Uveitis and joint diseases. Clinical findings in 191 cases. Arch Ophth 71:309-316, 1967.

19. Stanworth A and Sharp J: Uveitis and rheumatic diseases. Ann Rheum Dis 15:140-150, 1956.

20. Scherbel AI, MacKenzie AH, Nousek JE and Atdjian M: Ocular lesions in RA and related disorders with particular reference to retinopathy. A study of 741 patients treated with and without Chloroquine drugs. NE J Med 273:360-365, 1965.

21. Hurd ER, Snyder WB, Ziff M: Choroidal nodules and retinal detachments in RA.Improvement with fall in immunoglobulin levels follow-in prednisolone and cyclophosphamide therapy. Am J Med 48:273, 1970

22. Becker B and Milles DW: Corticosteroids and intraocular pressure. Arch Ophthal 70:500-507, 1963.

23. Black RL, Oglesby RB, Van Sallman L and Bunim JJ: Posterior subcapsular cataracts induced by corticosteroids in patients with RA. JAMA 174:166-171, 1960.

24. Giles CL, Mason GL, Duff FF and McLean J: The association of cataract formation and systemic corticosteroid therapy. JAMA 182: 719-722, 1962.

25. Oglesby RB, Black RL, von Sallmann L and Bunim JJ: Cataracts in patients with rheumatic disease treated with corticosteroids. Arch Ophth 66:625-630, 1961.

26. Hart FD, Casey TA and O'Riordan MD: Cataract and steroids. Brit Med J 1:1680-1681, 1961.

27. Henkind P: Ocular complications of drug treatment of rheumatic disorders. Ann Phys Med 7:258-262, 1963.

C. *Cardiac*

Cardiac lesions occur in rheumatoid arthritis but are noted more frequently at necropsy than on clinical examination and study. The major types of cardiac involvement are shown in Table 7.

Table 7

MAJOR TYPES OF CARDIAC INVOLVEMENT

Pericarditis

Rheumatoid Granulomas

1) epicardial fat
2) epicardium
3) myocardium
4) interventricular septum
5) chordae tendineae
6) aorta
7) valves

Arteritis

Myocarditis

Chronic pericarditis is probably the most common rheumatoid lesion of the heart, at least at time of autopsy (1). A recent echocardiographic study of 30 patients with classic rheumatoid arthritis demonstrated pericardial effusion, thickening, or both in 14 patients (46.6%) and mitral valve abnormalities in 9 patients (30%)(2). Another echocardiographic study (3) found that 44% of patients had evidence of posterior pericardial effusion that could not be detected on electrocardiogram and chest x-ray study. A reduced E to F slope of the anterior leaflet of the mitral valve was present in 25% of patients. All of these patients were free of cardiac symptoms. A third study (4) demonstrated a pericardial effusion in 34% of 44 rheumatoid arthritis patients and 50% of the subgroup with subcutaneous nodules. These authors also demonstrated slowing of mitral valve movement which they suggested was caused by granulomata involving the mitral valve.

The most recent echocardiographic study (5), however, claimed that echocardiographic abnormalities of the anterior mitral valve leaflet rarely, if ever, occur in patients with rheumatoid arthritis. All of their 31 patients showed normal valve motion and a normal E to F slope. They believed that the earlier studies were not meticulously done.

Pericarditis has been observed in patients with rheumatoid arthritis since 1881, when Charcot (6) found evidence of previous pericardial inflammation in four of nine rheumatoid patients at autopsy. Since then the incidence has ranged between 30% and 50% in several autopsy series (1,7-11).

While the post-mortem incidence of pericarditis is approximately 40%, (11) the clinical incidence is much lower. In a study of 100 consecutive patients with rheumatoid arthritis of sufficient severity to require hospitalization for articular problems, (12) 10 patients (10%) had some clinical evidence of pericarditis. While all 10 patients had pericardial friction rubs, only one had chest pain, and seven were entirely asymptomatic.

In a recent study of 17 patients with rheumatoid pericarditis (13), all had definite or classical rheumatoid arthritis. Rheumatoid factor was present in 93% of the patients tested and subcutaneous nodules were present in 47%.

The presenting complaints were left-sided chest pain (59%) and symptoms of congestive heart failure (18%). A pericardial friction rub was detected in 65%. All patients had cardiomegaly by x-ray and 65% had an accompanying pleural effusion.

In the pericardial fluid, the diagnostic triad of markedly reduced pericardial fluid sugar, increased gamma globulins and increased concentrations of LDH may help to establish rheumatoid arthritis as the cause for the effusion.

The most common findings in rheumatoid pericardial effusions are shown in Table 8.

Table 8

RHEUMATOID PERICARDIAL EFFUSION

WBC = 950 - 28,000/mm^3

Protein = 6.4 gm/100 ml (range 5.1-9.7)

↑ percentage of gamma globulin

↓ CH50

↓ Glucose

Rheumatoid factor may be present

Immune complexes present in some

Lymphokines predominate in others

The WBC counts were 950, 2000, 2600 and 28,000 per mm^3 in 4 patients recently reported (13). Protein levels averaged 6.4 gm/100 ml. The levels of gamma globulin were increased and complement levels were decreased.

Glucose levels in 3 patients were 17.6%, 26.5% and 65.6% of the serum glucose values. In a fourth patient, the pericardial fluid glucose was only 2 mg.%. Low glucose levels are believed to be due to decreased glucose transport across the pericardial membrane. Cholesterol may be increased (14) to such an extent that the crystals produce a "gold paint" appearance (15). A recent study (16) of a patient with cardiac tamponade due to pericarditis reported IgG-IgG immune complexes of 19S size in the ultracentrifuge. These complexes dissociated into 7S IgG molecules in acidic buffers. We (17) have recently, however, studied the pericardial fluid in one patient and found no evidence of immune complexes. In this fluid, we found evidence of MIF, migration inhibitory factor, which is a manifestation of cellular immunity.

While most effusions are transient and disappear spontaneously with rest and an increase in analgesics, steroid treatment or pericardiocentesis or pericardiectomy may be necessary in a few cases. According to Franco et al (13), steroids in a dosage of 30 to 40 mg of prednisone daily will predictably reverse signs and symptoms of rheumatoid pericarditis in a mean period of 3 weeks (2 to 4 weeks).

Pericardiocentesis should be performed for diagnostic purposes and, promptly, as a therapeutic measure if early tamponade is suspected. Pericardiectomy should be done if the pericardial effusion reaccumulates or signs of constriction appear. In the series by Franco et al (13), 34% of the patients with pericarditis eventually required pericardiectomy or died of their disease.

Cardiac tamponade has been reported in 20 cases of rheumatoid arthritis (18) (See Table 9). The male to female ratio was 11:8 which is similar to that found with rheumatoid pleural effusions (19) but is different from the normal rheumatoid arthritis population. The age range was from 4 to 62 years. The majority of patients (84%) had moderate or severe rheumatoid arthritis. Rheumatoid factor was positive in 12 of the 13 patients where it was obtained, and subcutaneous nodules in 9. A pericardial type of pain or pericardial friction rub preceded the cardiac tamponade in 63% of the patients.

Table 9

Cardiac Tamponade in Rheumatoid Arthritis

Case No.	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20
Age (years)	44	52	16	4	50	49	53	49	51	60	62	61	44	38	41	43	42	36	59	49
Sex	M	F	F	NR	F	M	M	M	F	M	M	M	F	M	M	F	M	M	F	F
Duration of Arthritis (years)	2	10	6	NR	19	9	3	4	5	13	1	16	1½	2	22	NR	54	7	17	9
Severity of Arthritis	MD	SV	SV	NR	SV	MD	ML	ML	MD	SV	MD	MD	SV	SV	MD	NR	ML	MD	MD	SV
Subcutaneous Nodules	NR	+	NR	NR	+	+	NR	+	+	+	−	NR	−	+	NR	NR	NR	−	+	+
Rheumatoid Factor	NR	NR	NR	NR	NR	+	+	NR	+	+	+	−	+	+	+	NR	+	+	+	+
Duration of Tamponade (weeks)	SH	24	SH	NR	SH	SH	12	SH	16	1	SH	12	NR	SH	28	NR	4	SH	41	216
Preceding Pericardial Pain	+	+	−	+	−	+	−	−	−	+	−	−	−	−	−	NR	+	+	−	−
Pericardial Rub	−	−	−	+	+	+	+	−	−	−	−	−	−	−	+	NR	−	+	+	+
Associated Pleural Effusion	+	+	+	+	−	+	+	+	−	+	−	−	−	−	+	+	NR	+	+	+
Pericardial Fluid																				
Amount (liters)	1	.35	.45	.30	.35	.70	.40	.90	.11	.38	.80	NR	.30	.50	NR	NR	.67	.20	.76	.46
Color	T	BS	BS	BS	BS	BS	T	BS	BS	T	NR	YE	SS	T	BS	NR	SS	BS	BS	BS
Sugar Content 100(mg/ml)	NR	NR	NR	NR	NR	NR	NR	NR	NR	15	NR	NR	NR	5	NR	NR	NR	0	0	0
Response to Corticosteroids	NR	−	−	NR	−	NR	−	−	NR	−	NR	NR	−	−	NR	NR	−	−	−	−
Pericardial Resection	NP	NP	NP	NP	NP	P	P	P	P	NP	P	P	P	NP	NP	P	P	NP	P	NP
Outcome	S	D	D	D	D	S	S	S	S	D	S	S	S	D	D	S	S	D	S	D

Abbreviations:- + = Present; − = Absent; B.S. = Blood Stained; D = Death; F = Female; M = Male; MD = Moderate; ML = Mild; NP = Not Performed; NR = Not Recorded; P = Performed; S = Survived; SH = Short; S.S. = sero sanguinous; SV = Severe; T = Turbid; YE = Yellow.

Key to Case No:-

1. Granirer—1946.
2. Bevans et al—1954.
3. Handforth & Woodbury—1959. Case—1.
4. Nadas & Levy—1961. Case—14.
5. Stern & Sobel—1966. Case—2.
6. Patridge & Duthie—1963.
7. Szatkowski & Inoue—1966.
8. Kennedy et al—1966. Case—1.
9. Kennedy et al—1966. Case—2.
10. Latham—1966. Case—1.
11. Sutton—1967.
12. Pitt et al—1969. Case—2.
13. Romanoff et al—1970.
14. Metzger—1970.
15. Clark et al—1972.
16. Franco et al—1972.
17. Smaha & Winston—1973.
18. Thomas & Hare—1974.
19. Present Series, Case—1.
20. Present Series, Case—6.

from ref. (18)

The pericardial effusions in the patients with tamponade was blood-stained or sero-sanguinous in 13, turbid in 4 and straw colored in one. The glucose level was either very low or absent in the five patients in which it was obtained.

Treatment with corticosteroids is not of much benefit for cardiac tamponade (18,20). Occasionally aspiration of the pericardial fluid may be of therapeutic benefit (21) but this may be difficult because the fluid is frequently thick and loculated (18).

Once the diagnosis of cardiac tamponade has been established, pericardial resection is usually necessary. In Table 9 it can be seen that all 10 patients who underwent pericardial resection survived but 9 of the 10 patients who were not operated died.

Constrictive pericarditis is more common than tamponade. At least 42 cases have been recorded. As with pericardial tamponade, treatment of constrictive pericarditis with steroids is not beneficial. The only effective treatment is surgical (18). Of a total of 38 pericardiectomies, only 2 patients died, postoperatively. Of 21 of these patients who were followed for 3 months to 10 years, 19 remained well.

In the majority of cases, the tissue histology is non-specific. In a few cases typical granulomatous lesions have been observed (18). Calcium deposits (22-24) and cholesterol crystals are sometimes seen (14,20,25,26).

In a controlled autopsy study of 47 rheumatoid arthritis patients and 47 age and sex-matched controls (Table 10), it is apparent that pericarditis was significantly higher in the rheumatoid group. Myocarditis was higher in the rheumatoid group, but this was not statistically significant. It is of interest that atherosclerosis was significantly less common in the rheumatoid arthritis patients.

Table 10

	47 RA Patients (No.)	47 Control Patients (No.)	X^2	P
Pulmonary edema	15	17	...	...
Cardiac hypertrophy (400 gm or more)	23	21	...	...
Atherosclerosis	26	37	4.81	0.05
Myocardial infarction (old or new)	14	14	...	...
Valvulitis	33	35	...	...
Stenotic valvular disease	2	8	2.80	0.10
Pericarditis	17	7	4.53	0.05
Fibrinous	4	4	...	...
Fibrous	7	2	6.80	0.01
Combination of fibrous and fibrinous	5	0		
Suppurative	1	1	...	...
Myocarditis	7	2	1.97	...
Bronchopneumonia	17	19	...	...
Bronchitis	9	5	...	...
Bronchiectasis	2	1	...	...
Pleuritis (old or new)	17	11	...	...
Pleural effusion	11	18	...	...
Pulmonary emphysema	19	23	...	...
Pulmonary fibrosis	17	8	3.49	0.10
Peptic ulcer, duodenal	2	1	...	...
Peptic ulcer, gastric	3	3	...	...
Cirrhosis	3	4	...	...
Hepatic necrosis, inflammatory	2	5	...	...
Pyelonephritis	9	6	...	...
Glomerulitis	2	3	...	...
Adrenal atrophy	4	0	...	...
Osteoporosis	23	11	5.58	0.05

from ref. (1)

The classical three-layered fibrinoid granuloma is considered to be quite specific for rheumatoid disease. These granulomas have been reported in all parts of the heart: the pericardium (9), epicardial fat and epicardium (27), myocardium (28,29), atrium (27), interventricular septum (30), endocardium (31), aorta (32), and chordae tendineae and all valve cusps and rings (predominantly mitral and aortic (27-29,32,33). In addition, nodules in the conduction system have produced lethal arrhythmias (34,35). The reported incidence of granulomas in the heart is 3% (34,36) (see Table 11). One group has reported two rheumatoid patients, each

Table 11

RHEUMATOID HEART DISEASE

Rheumatoid granulomas (3%)
- **Valve rings and valve leaflets**
- **Myocardium**
- **Ventricular septum** → **Complete heart block**; → **Left bundle branch block**
- **Pericardium**

Nonspecific inflammatory lesions
- **Pericarditis (40%) – Fibrous**
- **Myocarditis (20%)**
- **Coronary arteritis (20%)**
- **Acute and chronic valvulitis (5%)**

Percentages from Sokoloff 1953 ref. (36)

with quadrivalvular heart disease (34). One patient was a 65 year old woman with rheumatoid arthritis and rheumatoid nodules in the heart, lungs, joints and subcutaneous tissue. Signs of aortic and mitral regurgitation, congestive heart failure and left bundle branch block were observed clinically and necropsy revealed numerous rheumatoid nodules in all four cardiac valves as well as in the adjacent myocardium and in the pericardium. The left bundle branch block was the result of disruption by rheumatoid granulomas of the left bundle branch as it emerged from the atrioventricular bundle.

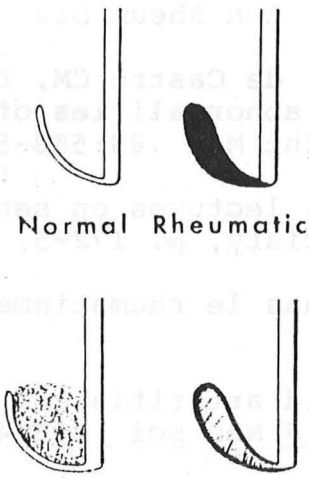
The second patient (35) was a 72-year-old man with severe deforming rheumatoid arthritis and rheumatoid cardiac nodules (Fig. 6).

The nodules, when present in a cardiac valve, are located in the "core" or central portions of the leaflets, and may cause them to be incompetent (see Fig. 6).

Involvement of the conduction system apparently can be produced by the granuloma itself, or by extension of the granulomatous inflammation from the base of the aortic or mitral valves (37). In some reported cases (37), no active granulomas are present in the conduction system, but fibrotic patches are present in the spot where active granulomas have presumably been present.

Coronary arteritis in patients with rheumatoid arthritis has been found at autopsy in as many as 20% of the cases (38). However, this complication is rarely diagnosed during life.

Figure 6



—Similunar valvular cusp in various cardiac diseases. A normal cusp is on top left for comparison. Normal components of rheumatically diseased cusp are replaced by uniform dense fibrous tissue. In carcinoid heart disease, valve cusp remains normal, and atypical fibrous tissue is simply superimposed on it. In rheumatoid heart disease, peripheral portions of original cusp remain, but central portions are replaced by rheumatoid granulomas.

from ref. (35)

Weintraub and Zvaifler (39-41) have reported an interesting group of patients with widespread rheumatoid granulomas, either scleromalacia perforans or nodular episcleritis, rheumatoid heart disease and, in two instances, aortitis with dilatation of the aortic root. A murmur of aortic insufficiency was present in 5 patients. At autopsy, systemic vasculitis, pericarditis and cardiomyopathy were noted. In addition, dilatation of the aortic root with aortitis, chronic inflammatory perivascular cuffing in the aortic vasa vasorum and rheumatoid granulomas in the adventitia of the aortic root were observed.

REFERENCES (Cardiac)

1. Bonfiglio T and Atwater EC: Heart disease in patients with seropositive RA. Arch Int Med 124:714-718, 1969.

2. Nomier AM, Turner R, Watts E, Smith D, West G and Edmonds J: Cardiac involvement in RA. Ann Int Med 74:800-806, 1973.

3. Prakash R, Atassi A, Poske R, Rosen KM: Prevalence of pericardial effusion and mitral valve involvement in patients with RA without cardiac symptoms. New Eng J Med 289:597-600, 1973.

4. Bacon PA and Gibson DG: Cardiac involvement in RA. An echocardiographic study. Ann Rheum Dis 33:20-24, 1974.

5. Davia JE, Chitlin MD, de Castro CM, Lawless O, Niemi L: Absence of echocardiographic abnormalities of the anterior mitral valve leaflet in RA. Ann Int Med 83:500-502, 1975.

6. Charcot JL: Clinical lectures on senile and chronic diseases. London, Synderham Society, p. 172-5, 1881.

7. Barie E: Le coeur dans le rhumatisme chronique. Arch Gen Med 2: 2881-2886, 1904.

8. Bayles TB: Rheumatoid arthritis and rheumatic heart disease in autopsied cases. Am J Med Sci 205:42-48, 1943.

9. Graef T, Hickey DV, Altman V: Cardiac lesions in rheumatoid arthritis (abstract). Am Heart J 37:635, 1949.

10. Egelius N, Gohle O, Jansson E, Wahlgren F: Cardiac changes in RA. Ann Rheum Dis 14:11-17, 1955.

11. Cathcart ES, Spodick D: The heart in RA. N Eng J Med 266:959-964, 1962.

12. Kirk J and Cash J: The pericarditis of RA. Quart J Med 38:297, 1969.

13. Franco AE, Levine HD and Hall AP: Rheumatoid pericarditis. Report of 17 cases diagnosed clinically. Ann Int Med 77:837-844, 1972.

14. Kindred LH, Heilbrunn A and Dunn M: Cholesterol pericarditis associated with RA treated by pericardiectomy. Am J Cardiol 23:464,1969.

15. Alexander JS: A pericardial effusion of "Gold-Paint" appearance due to the presence of cholesterin. Brit Med J, Oct. 11, 1919.

16. Ball GW, Schrohenloker R and Hester R: Gamma globulin complexes in rheumatoid pericardial fluid. Am J Med 58:123-128, 1975.

17. Andreis M, Hurd E and Ziff M: Unpublished observations.

18. Thadani U, Iveson JMI and Wright V: Cardiac tamponade, constrictive pericarditis and pericardial resection in RA. Med 54:261-270, 1975.

19. Walker WC and Wright V: Rheumatoid pleuritis. Ann Rheum Dis 26: 467, 1967.

20. Kennedy WPU, Partridge REH and Matthews MB: Rheumatoid pericarditis with cardiac failure treated by pericardiectomy. Br Heart J 28:602, 1966.

21. Granirer LW: Pericardial effusion in RA. Med Clin N Am 30:562, 1946.

22. Baggenstoss AH and Rosenberg E: Visceral lesions associated with chronic infections (rheumatoid) arthritis. Arch Pathol 35:503,1943.

23. Baggenstoss AH and Rosenberg E: Unusual cardiac lesions associated with chronic multiple RA. Arch Path 37:54, 1944.

24. Batley WJ, Uddin J and Kelly HG: RA complicated by constrictive pericarditis. Can Med Assoc J 100:863,1969.

25. Szatkowski J and Inoue T: Cholesterol pericarditis. An unusual case of probable tuberculous origin in a patient with rheumatoid arthritis. Am J Cardiol 12:730, 1963.

26. Tubbs OS, Slade PRH and Turner WM: Constrictive pericarditis in association with RA. Thorax 19:555, 1964.

27. Goehers HR,Baggenstoss AH and Slocumb CH: Cardiac lesions in RA. Arth Rheum 3:298-308, 1960.

28. Cruickshank B: Heart lesions in rheumatoid disease. J Path Bact 76:223-240, 1958.

29. Lebowitz WB: The heart in RA. Ann Int Med 58:102-123, 1963.

30. Gowans JDC: Complete heart block with Stokes-Adams syndrome due to rheumatoid heart disease. New Eng J Med 262:1012-1014, 1960.

31. Schoene RH and Risse GB: Rheumatoid heart disease. Ohio Med J 60:377-379, 1964.

32. Baggenstoss AH and Rosenberg EF: Unusual cardiac lesions associated with chronic multiple RA. Arch Pathol 37:54, 1944.

33. Lassiter GS and Tassy FT: Malignant rheumatoid disease with aortic stenosis. Arch Int Med 116:930-936, 1965.

34. Carpenter DF, Golden A and Roberts WC: Quadrivalvular rheumatoid heart disease associated with left bundle branch block. Am J Med 43:922-929, 1967.

35. Roberts WC, Kekoe JA, Carpenter DF and Golden A: Cardiac valvular lesions in RA. Arch Int Med 122:141-146, 1968.

36. Sokoloff L: The heart in RA. Am Heart J 45:635, 1953.

37. Lev M, Bharati S, Hoffman FG, Leight L: The conduction system in RA with complete atrioventricular block. Am Heart J 90:78-83,1975.

38. Lebowitz WB: The heart in RA (rheumatoid disease). A clinical and pathological study of 62 cases. Ann Int Med 58:102-123, 1963.

39. Weintraub AM and Zvaifler NJ: Rheumatoid heart disease. A clinical as well as pathologic entity. Arth Rheum 5:328, 1962.

40. Zvaifler NJ and Weintraub AM: Aortitis and aortic insufficiency in the chronic rheumatic disorders: a reappraisal. Arth Rheum 6:241-245, 1963.

41. Weintraub HM and Zvaifler NJ: The occurrence of valvular and myocardial disease in patients with chronic joint deformity. Am J Med 35:145-162, 1963.

D. *Pulmonary Involvement*

While the overall incidence of pulmonary involvement in rheumatoid arthritis patients is small, certain types of involvement are generally accepted as being part of the rheumatoid process. These are shown in Table 12.

Table 12

PULMONARY INVOLVEMENT

Pleural Effusion

Nodules

Cavitary Lesions

Caplan's Syndrome

Diffuse Interstitial Fibrosis

Pleural involvement is probably the most common pulmonary complication of rheumatoid arthritis. At postmortem, more than 40 per cent of patients with rheumatoid arthritis had chronic pleural adhesions, some of which were extensive (1,2). Pleural effusions tend to occur in men more than women (3) and mostly in males over 45 years of age (3,4). While most patients with pleuritis have had severe, longstanding arthritis, pleural effusion may develop early in the disease (3,4). The pleural involvement is usually asymptomatic. The effusion is usually moderate in size and may be bilateral.

In a series of 516 patients with rheumatoid arthritis 21% gave a history of pleurisy as compared with 12% of 301 control patients with degenerative joint disease (3). Pleural effusions were present in 17 rheumatoid patients (3.3%) but only 1 of the 301 patients in the control series. The most common findings in the pleural fluid are shown in Table 13.

Table 13

RHEUMATOID PLEURAL EFFUSION

Glucose <40 mg/100 ml in most
<10 mg/100 ml in many
Proteins >3 gm/100 ml
Cells = 1000 - 3000/mm^3
(Mostly T-lymphocytes)

(from ref. 5)

A comparison of the findings in patients with rheumatoid arthritis as compared with other conditions is shown in Table 14.

Table 14

Differential Diagnostic Features of Pleural Effusions in Patients with Rheumatoid Arthritis and Other Conditions

Disease State	Age (yr.)	Sex	Protein Content of Pleural Effusion (gm./100 ml.)	Total Cell Count (WBC/cu. mm.)	Pleural Biopsy	Pleural Fluid Sugar Content
Carcinoma of lung	40–70	M > F	2.0–5.5	2.5–10,000	+ in ≈ 60% with 3 quadrant biopsy	Consistent with peripheral blood sugar and pleural fluid cell count but 15% below 60 mg./100 ml.
Tuberculosis	15–40	M = F	3.8–6.5	2.5–10,000	+ in 65% with 3 quadrant biopsy	Same
Parapneumonic effusion	20–80	M = F	2.0–5.0	2.0–20,000	–	–
Pulmonary infarction	50–80	M = F	2.0–5.5	2.5–10,000	–	Same
Congestive failure	40–80	M = F	0.8–3.5	0– 500	–	Same
Rheumatoid arthritis	> 45	M > F	3.0–5.0	1– 3000	May show RA granulomata but usually nondiagnostic	70–80% show pleural fluid sugar < 40 mg./100 ml.

(from ref. 5)

The most important feature of the rheumatoid pleural effusion is that the glucose level is frequently very low, sometimes zero. In one study (6), low glucose concentrations were observed in the pleural effusions of 6 patients with rheumatoid arthritis. In a more recent study the same investigators (7) found that in all except 3 of 18 rheumatoid pleural effusions the glucose concentration was less than 37 mg per 100 ml. The major problem is that the glucose is not invariably low and occasionally will be normal. About 17% of patients had glucose concentrations of more than 50 mg per ml (7). In one study (3), only 2 of 8 patients had glucose concentrations of less than 30 mg per 100 ml. Glucose levels may also be low in malignant or tuberculous serous effusions (see Table 14) but in these conditions bacteriological or cytological diagnosis can be made. Thus some feel that a low glucose level in pleural fluid that is nonpurulent, negative for bacteria on smear and culture, and negative for malignant cells on cytologic examination almost invariably indicates that the effusion is due to rheumatoid pleuritis unless pleural biopsy reveals tuberculosis (7). Studies of patients with pleural effusions have concluded that the glucose levels are decreased because of impaired transport of glucose into the pleural fluid from the blood (8). In these studies intravenous glucose infusion failed to raise intrapleural glucose concentration but glucose injected directly into the pleural effusion was not utilized rapidly.

Other findings reported in some pleural effusions include positive tests for rheumatoid factor (9), elevated lipid levels (10,11), elevated lactic dehydrogenase levels (9,10) and presence of rheumatoid arthritis cells (9,12) (phagocytic leukocytes containing inclusion bodies). Cholesterol crystals are also occasionally seen. The presence of rheumatoid

factor in the fluid is not of diagnostic value since it may be absent in rheumatoid effusions, and may be present in effusions of non-rheumatoid patients (13).

The predominant cell type present usually is the lymphocyte although polymorphonuclear leucocytes may predominate (14). Occasionally large numbers of eosinophils may be present (15). Williams et al (16) have shown that the majority of these pleural fluid lymphocytes are T-lymphocytes using either anti-T-cell antisera or the sheep cell rosette technique.

Biopsy of the pleura usually shows only non-specific granulomatous or fibrotic changes. Only rarely are rheumatoid nodules present.

The pleural effusions usually resolve spontaneously within three months. However, some require repeated aspiration if symptoms are present. Corticosteroids may be of value if the effusion is associated with early active rheumatoid arthritis (17). Decortication of the lung may be infrequently necessary if gross thickening of the pleura causes disability.

One of the most common pulmonary manifestations of rheumatoid arthritis is the subpleural or intraparenchymal rheumatoid nodule. It has been suggested that movement of the pleura may favor their predilection for a subpleural location (18). The pulmonary nodules usually occur in patients with severe disease with subcutaneous nodules and high titers of rheumatoid factor. The lung nodules are usually round and discrete, subpleural, and sometimes slightly lobulated (19). They vary in size from several millimeters to a few centimeters. They may cavitate and spontaneous pneumothorax may rarely occur. As with subcutaneous nodules, pulmonary nodules may regress spontaneously. Although nodules may be solitary, they tend to be multiple (19,20). The nodule may be associated with a pleural effusion and may thus suggest the possibility of carcinoma. The distinction from carcinoma cannot usually be established without removal of the lesion.

In one reported case (21) of a young woman with rheumatoid arthritis, a solitary pulmonary lesion was composed of an alveolar cell carcinoma in intimate association with a rheumatoid nodule. There are several reports of lung carcinoma and coexisting rheumatoid nodules (22). According to these investigators, the finding of a solitary pulmonary nodule, particularly a recent or enlarging one, in a patient with rheumatoid arthritis carries no assurance that the process is benign. They recommend that such nodules should be excised for diagnosis.

Cavitation of nodules occurs when they shell out or erode their centers. These may be very difficult to differentiate from tuberculous, mycotic or tumor lesions. In two unusual cases (23), the triad of cavitary pulmonary nodules, spontaneous pneumothorax and peripheral eosinophilia was seen.

In 1953, Caplan (24) reported a close association between nodular lung disease and rheumatoid arthritis in Welsh coal miners. The lung disease often preceded the development of active arthritis. In fact, systemic rheumatoid arthritis is absent in 40% of patients with typical Caplan nodules, although these patients usually have rheumatoid factors present in their serum (25). The characteristic roentgenographic appearance con-

sists of multiple well defined nodular opacities from 0.3 to 5 cm in diameter, distributed throughout both lung fields, but predominantly in the periphery (26,27). There is a tendency for calcification and cavitation of the opacities to occur. The lesions may become confluent and may be indistinguishable radiographically from progressive massive fibrosis (28) hence the term nodular fibrosis. The smaller nodules may be few in number and confined to the upper zones or may present a "snowstorm" appearance widely scattered throughout the chest (29). These nodules have also been reported in workers exposed to other types of dust e.g. carbon electrode workers (30), boiler scalers (31), asbestos workers (32), gold miners (33), chalk workers (34) and foundry workers (35). The great majority of reports of this syndrome have come from Europe and this syndrome appears to be quite rare in the United States. Of 100 bituminous coal miners in the U.S. who had rheumatoid arthritis, two met the roentgenographic criteria of Caplan's syndrome (36). Benedek (36) has suggested that these pulmonary lesions are a manifestation of rheumatoid disease and that their development is facilitated by the presence of silica rather than that these patients have coincidental silicosis and rheumatoid arthritis. He also suggested that both tuberculoprotein and rheumatoid factor increase the granulomatous reaction to silica in the lungs. Neither the prevalence nor titer of rheumatoid factor is increased in persons with rheumatoid arthritis who have a history of exposure to silica (36).

At the Mayo Clinic (37) 16 patients with pneumoconiosis, consisting of nodular fibrosis of the lungs associated with rheumatoid arthritis were seen between 1955 and 1964. Twelve of these patients were foundry workers. The remainder included a coal miner, a granite polisher, a textile mill worker, and a rubber factory worker who had experienced prolonged exposure to rubber duse.

The characteristic lesion consists of fibrosing pneumonitis with necrobiotic foci and closely resembles the subcutaneous nodules of rheumatoid arthritis (38). Thus the Caplan nodules have features similar to rheumatoid nodules while pneumoconiotic nodules do not. It has been suggested (37) that the pulmonary nodules develop in the lung parenchyma because of antecedent damage from the irritating dust particles. Noonan and coworkers (39) described coarsely nodular pulmonary fibrosis in patients with rheumatoid arthritis who had no history of exposure to silica or other toxic inhalants. Careful examination of the lung tissue failed to reveal silica in the lesion. On this basis the classification shown in Table 15 has been suggested.

Table 15

PATHOLOGY OF LUNG IN RHEUMATOID ARTHRITIS

I. Pleuritis
II. Interstitial pneumonitis
III. Fibrosis
  A. Diffuse
  B. Coarsely nodular
    1. Pneumoconiosis (Caplan)
    2. Without pneumoconiosis (Noonan et al)
IV. Arteritis

(from ref. 40)

The production of rheumatoid factor may result from an immune response which results from antigenic stimulation of the respiratory mucosal system. That such a mechanism is possible is supported by the fact that high titers of rheumatoid factor developed in the sera of several patients who developed chronic hypersensitivity pneumonitis due to mold contamination in an air conditioner (41). The rheumatoid factor disappeared after inhalation exposure was stopped.

Diffuse interstitial fibrosis of the lungs is an unusual type of pulmonary involvement in patients with rheumatoid arthritis. X-rays usually show a diffuse bilateral reticular, or reticulo-nodular pattern. Interposed areas of translucency may give a "honeycomb" appearance (42).

There is some disagreement as to whether interstitial fibrosis is a specific manifestation of the rheumatoid process (1). However, most workers seem to accept it (43-46). One study reported that in 116 cases in which pulmonary interstitial fibrosis was an isolated finding, 25% were associated with joint disease (47). In a review of 702 patients with rheumatoid arthritis, 8 instances of moderate or severe diffuse pulmonary fibrosis were found (40). In a controlled study, Walker and Wright (48) found an incidence of 1.6% of diffuse interstitial lung disease in patients with rheumatoid arthritis. However, this incidence was no higher than that of the control group of osteoarthritis patients. Thus, unless pathognomonic rheumatoid nodules are found in association, it may be very difficult to definitely make the diagnosis of rheumatoid interstitial fibrosis. The pathology is similar to that seen in the Hamman-Rich syndrome with proliferation of the interstitial fibrous tissue around the small bronchioles and within the alveolar walls which become thickened. An infiltrate of lymphocytes and plasma cells may be present in the interstitial spaces (49). The fibrosis may be so intense that it distorts the bronchi. Because of these changes there is diminished vital capacity and impairment in the efficiency of alveolar-capillary gas transfer (50). The prognosis is poor with death due to respiratory failure and hypoxemia.

If pulmonary function tests are utilized in addition to radiology, one study reports that 47% of patients with rheumatoid arthritis have pulmonary involvement (51). A very recent study (51) selected 85 patients with rheumatoid arthritis and normal chest x-rays. Tests performed included spirometry lung volumes and gas transfer (DLco). Significantly lower values of DLco were found in patients with rheumatoid arthritis, compared with a control group.

Although the exact pathogenetic mechanism of rheumatoid lung disease is unknown, rheumatoid factors and/or intermediate complexes of 8S to 11S size may play an important role (52-54).

Immunofluorescent studies were done on lung tissues from patients with rheumatoid arthritis and pulmonary involvement (55). Striking immunofluorescence was noted with anti-IgM and heat aggregated γ-globulin to localize tissue deposition of IgM rheumatoid factor. Patchy fluorescence of IgG was also present. Positive lupus erythematosus (LE) cell preparations and serum levels of intermediate IgG complexes (11-15S) were found in a large proportion of the patients, although no correlation with the clinical or pathologic processes could be established.

The same investigators (56) demonstrated in animal lungs that IV injected IgM rheumatoid factors could accelerate or aggravate hemorrhagic or vasculitic lesions near or adjacent to established granulomata. These small parenchymatous pulmonary granulomata had been induced by prior intravenous inoculation of complete Freund's adjuvant. This work is similar to that previously done by Baum, Stastny and Ziff (57) in which the effect of rheumatoid factors on antigen-antibody complexes in the capillaries of living rat mesentery was studied. Thus the above studies suggest that IgM rheumatoid factor may be able to enhance potentially harmful immune reactions. Diffuse interstitial pulmonary fibrosis may therefore result from occlusion or damage to pulmonary vessels. Such damage may be caused by intermediate complexes which may either cause vascular damage (vasculitis) or occlusion.

REFERENCES (Pulmonary)

1. Aronoff A, Bywaters EGL and Fearnley GR: Lung lesions in RA. Brit Med J 2:228-232, 1955.

2. Cruickshank B: RA and rheumatoid disease. Proc Roy Soc Med 50: 462-465, 1957.

3. Walker WC and Wright V: Rheumatoid pleuritis. Ann Rheum Dis 26: 467-474, 1967.

4. Horler AR and Thompson M: The pleural and pulmonary complications of RA. Ann Int Med 51:1179-1203, 1959.

5. Williams RC: RA as a systemic disease. Major Problems in Internal Medicine IV, p. 37, W.B. Saunders Co., 1974.

6. Carr DT and Power MH: Pleural fluid glucose with special reference to its concentration in rheumatoid pleurisy with effusion. Chest 37:321-324, 1960.

7. Lillington GA, Carr DT, Mayne JG: Rheumatoid pleurisy with effusion. Arch Intern Med 128:764, 1971.

8. Dodson WH and Hollingsworth JW: Pleural effusions in RA. Impaired transport of glucose. New Eng J Med 275:1337-1342, 1966.

9. Berger HW, Seckler SG: Pleural and pericardial effusions in rheumatoid disease. Ann Int Med 64:1291-1297, 1966.

10. Stengel BF, Watson RR, Darling RJ: Pulmonary rheumatoid nodule with cavitation and chronic lipid effusion. JAMA 198:1263-1266, 1966.

11. Bower GC: Chyliform pleural effusion in rheumatoid arthritis. Am Rev Resp Dis 97:455-459, 1968.

12. Carmichael DS, Golding DN: Rheumatoid pleural effusion with "RA cells" in the pleural fluid. Brit Med J 2:814, 1967.

13. Levine H, Szanto M, Grieble HG, Bach GL, Anderson TO: Rheumatoid factor in nonrheumatoid pleural effusions. Ann Int Med 69:487,1968.

14. Dieppe PA: Empyema in RA. Ann Rheum Dis 34:181-185, 1975.

15. Campbell GD, Webb WR: Eosinophilic pleural effusion. Am Rev Resp Dis 90:194, 1964.

16. Williams RC,Jr, DeBord JR, Melbye OJ, Messner RP and Lindström FD: Studies of T & B lymphocytes in patients with connective tissue diseases. J Clin Invest 52:283-295, 1973.

17. Hollingsworth JW: Local and systemic complications of RA. Chapt.27 p. 139, WB Saunders Co., Philadelphia, Pa., 1968.

18. Williams RC: Rheumatoid arthritis as a systemic disease. p. 139, Major Problems in Internal Medicine IV, WB Saunders Co., Philadelphia, 1974.

19. Martel W, Abell MR, Mikkelsen WM, Whitehouse WM: Abstracts Mod Med 18 Nov, p. 99, 1968.

20. Schneider PJ and Ehrlich GE: Pulmonary lesions in RA. Chest 62, p. 747-749, Dec., 1972.

21. Blodgett RC, Cera PJ, Jr. and Iones FL: Aveolar cell carcinoma associated with rheumatoid nodules. Chest 62:625-627, 1972.

22. Stack BHR and Grant IWB: Rheumatoid interstitial lung diseases. Brit J Dis Chest 59:202-211, 1965.

23. Portner MM and Gracie WA: Rheumatoid lung disease with cavitary nodules, pneumothorax and eosinophilia. New Eng J Med 275:697-700, 1966.

24. Caplan A: Certain unusual radiological appearances in the chest of coal miners suffering from RA. Thorax 8:29-37, 1953.

25. Morgan WKC, Wolfe DA: The lungs and pleura in RA. Am J Roentgenology 98:334-41, 1966.

26. Caplan A: Certain radiological appearances in the chest of coal miners suffering from RA. Thorax 8:30, 1953.

27. Caplan A, Payne RB, Withey JL: A broader concept of Caplan's syndrome related to rheumatoid factors. Thorax 17:205, 1967.

28. Boyle JA and Buchanan WW: Clinical Rheumatology, Chap. 6, p. 144, FA Davis, Philadelphia, 1971.

29. Hollander JL and McCarty DJ: Arthritis and Allied Conditions. p. 349, Lea and Febiger, Philadelphia, 1972.

30. Watson AJ, Black J, Doig AT and Nagelschmidt G: Pneumoconiosis in carbon electrode workers. Brit J Indust Med 16:274,1959.

31. Campbell JA: A case of Caplan's syndrome in a boiler-scaler. Thorax 13:177-180, 1958.

32. Richards AG and Barnett GM: Rheumatoid lung changes associated with asbestos. Thorax 13:185-193, 1958.

33. Chatgidakis CB and Theron C: Rheumatoid pneumococcus (Caplan's syndrome). A discussion of the disease and a report of a case in a European Witwaterstand gold miner. Arch Environ Health 2:397-408, 1961.

34. Lamvik J: Rheumatoid pneumococcus. A case of Caplan's syndrome in a chalk mine worker. Acta Path Microbiol Scand 57:169-174, 1963.

35. Caplan A, Cowen EDH and Gough J: Rheumatoid pneumoconiosis in a foundry worker. Thorax 13:181-184, 1958.

36. Benedek TG:Rheumatoid pneumoconiosis. Documentation of onset and pathogenic considerations. Am J Med 55:515-524,1973.

37. Dines DE and Ward LE: Caplan's Syndrome. Minn Med 50:1707, 1967.

38. Gough J, Rivers D and Seal RME: Pathological studies of modified pneumonoconiosis in coal miners with RA (Caplan's Syndrome). Thorax 10:9, 1955.

39. Noonan CD, Taylor FB,Jr, and Engleman EP: Nodular rheumatoid disease of the lung with cavitation. Arth Rheum 6:232, 1963.

40. Patterson CD, Harville WE and Pierce JA: Rheumatoid lung disease. Ann Int Med 62:685-697, 1965.

41. Banaxzak EF, Thiede WA and Fink JN: Hypersensitivity pneumonitis. Direct contamination of an air conditioner. New Eng J Med 283:271-276, 1970.

42. Dixon A St.J and Ball J: Honeycomb lung and chronic RA: a case report. Ann Rheum Dis 16:241, 1957.

43. Sinclair RJG and Cruikshank B: Clinical and pathological study of 16 cases of RA with extensive visceral involvement. Quart J Med 25:313, 1956.

44. Ellman P and Ball RE: "Rheumatoid Disease" with joint and pulmonary manifestations. Brit Med J 2:816, 1948.

45. Rubin EH: Pulmonary lesions in "Rheumatoid Disease" with remarks on diffuse interstitial fibrosis. Am J Med 19:569, 1955.

46. Martel W, Murray RS, Middelsen WM, Whitehouse M: Pulmonary and pleural lesions in rheumatoid disease. Radiology 90:641-653, 1968.

47. Doctor L and Snider GL: Diffuse interstitial pulmonary fibrosis associated with arthritis: with comments on the definition of rheumatoid lung disease. Am Rev Resp Dis 85:413, 1962.

48. Walker WC and Wright V: Diffuse interstitial pulmonary fibrosis and RA. Ann Rheum Dis 28:252-259, 1969.

49. Boyle JA and Buchanan WW. Clinical Rheumatology, Chapt. 6, p. 148, FA Davis, Philadelphia, 1971.

50. Stack BHR and Grant IWB: Rheumatoid interstitial lung disease. Brit J Dis Chest 59:202, 1965.

51. Frank ST, Weg JG, Harkleroad LE and Fitch RF: Pulmonary dysfunction in rheumatoid disease. Chest 63:27-34, 1973.

52. Franklin EC, Holman HR, Muller-Eberhard HJ and Kunkel HG: An unusual protein component of high molecular weight in the serum of certain patients with RA. JEM 105:425-438, 1957.

53. Tomasi TB, Jr., Fudenberg HH and Finby N: Possible relationship of rheumatoid factors and pulmonary disease. Am J Med 33:243-248,1962.

54. Sievers K, Alo K,Schakir R,Ahlman K:Studies of rheumatoid pulmonary disease. II."Intermediate" protein components in the sera of patients with RA with simultaneous pleuropulmonary lesions. Acta Tuberc Scand 46:101-108, 1965.

55. DeHoratius RJ, Abruzzo JL and Williams RC: Immunofluorescent and immunologic studies of rheumatoid lung. Arch Int Med 129:441-446, 1972.

56. DeHoratius RJ and Williams RC, Jr: Rheumatoid factor accentuation of pulmonary lesions associated with experimental diffuse proliferative lung disease. Arth Rheum 15:293-301, 1972.

57. Baum J, Stastny P and Ziff M: Effects of the rheumatoid factor and antigen antibody complexes on the vessels of the rat mesentery. J Immunol 93:985-992, 1964.

E. *Felty's Syndrome*

In 1924 Dr. A.R. Felty summarized 5 cases in the Johns Hopkins Bulletin as follows: "Five cases, strikingly similar in their essential features, are described, presenting an unusual, but unmistakable clinical picture, characterized by arthritis, splenomegaly, and leukopenia. The etiology is entirely obscure, though the various findings seem best accounted for as manifestations of a single disease process" (1).

Since that time considerable new insight has been gained regarding pathogenesis of the disease but the etiology is still obscure.

The major components of Felty's syndrome, as originally described by Felty are shown in Table 16.

Table 16

MAJOR COMPONENTS OF FELTY'S SYNDROME

Rheumatoid Arthritis

Splenomegaly

Leukopenia, especially granulocytopenia

Other features which are commonly seen in patients with Felty's syndrome are shown in Table 17.

Table 17

FINDINGS COMMON IN FELTY'S SYNDROME

Infection

Rheumatoid Vasculitis

Rheumatoid Nodules

High Titer IgM Rheumatoid Factor, Positive ANA and LE Prep and Cryoglobulins

Intermediate Complexes (11S-15S) in 100%

Such patients have a high incidence of infections and systemic extra-articular manifestations of the disease process such as vasculitis and peripheral neuropathy and serologic abnormalities such as positive LE cell tests, positive anti-nuclear antibody tests, both organ non-specific and granulocyte reactive, high titers of rheumatoid factor and an increased incidence of cryoglobulinemia.

Immune Complexes in Rheumatoid Arthritis (RA) and Felty's Syndrome (FS)

The presence of immunoglobulin (Ig) complexes which will react with purified IgM rheumatoid factor (RF) was first demonstrated by Hannestad (2) in 1967. Winchester, Agnello and Kunkel (3) confirmed this finding, and, in addition, described the presence of IgG rheumatoid factors in certain RA synovial fluids.

The presence of 22S complexes in the sera of certain RA patients, including some with Felty's syndrome was described by Franklin, Kunkel and Ward in 1958 (4). An association of the presence of IgG-RF and low molecular weight IgM with RA patients with vasculitis has been reported by several groups. Norberg (5) has recently reported that 54% of RA sera contain IgG complexes using a platelet agglutination technique.

We recently have described the presence of intermediate-sized complexes (11S-15S) in 100% of our patients with Felty's syndrome as compared with RA patients without leukopenia or splenomegaly (6). Weisman and Zvaifler (7)

have shown the presence of cryoglobulins in the majority of FS sera.

Thus, the presence of immune complexes in RA and FS is well established.

Chemotaxis of Neutrophils by Immune Complexes

It has been demonstrated by several workers that both aggregated Igs and IgG-IgM RF complexes are chemotaxic for neutrophils (8).

Phagocytosis of Immune Complexes by Neutrophils

Parker and Schmid (9) in 1962 demonstrated that complexes consisting of aggregated IgG and IgM RF were phagocytosed by neutrophils. We have demonstrated that normal neutrophils can phagocytose immune complexes from IgM-RF positive RA fluids after incubation for 90 minutes at 37°C *in vitro* (10). IgM RF negative fluids produced phagocytosable inclusions if purified IgM RF was added to the synovial fluid prior to incubation. Added Waldenström IgM did not produce such an effect. Cats and coworkers (11) have produced formation of intracytoplasmic inclusions in normal neutrophils which have been incubated in RA sera.

The presence of such intracytoplasmic inclusions or "RA cells" in synovial fluid neutrophils was first observed by Hollander and coworkers (12). A number of investigators have confirmed these observations and also reported the presence of the inclusions in circulating peripheral blood neutrophils (13) and in synovial lining cells from RA patients (14).

Effects of Ingestion of Immune Complexes by Neutrophils

The release of lysosomal enzymes from neutrophils which have been exposed to immune complexes has been shown (15,16).

Increased nitroblue tetrazolium dye reduction after exposure to IgG-IgM-RF complexes has also been demonstrated (17). Increased dye reduction in RA synovial fluid (SF) cells and in normal cells incubated in RA-SF has been shown. Similarly, decreased phagocytic ability (18) in these cells as well as decreased chemotaxis (8) in both SF and peripheral blood neutrophils has been demonstrated in RA and Felty patients.

Abnormalities in Patients with Felty's Syndrome

As mentioned previously, Felty in 1924 (1), described the association of leukopenia, splenomegaly and rheumatoid arthritis. In these patients there is an increased incidence of bacterial infection, vasculitis, peripheral neuropathy and other manifestations of systemic disease. Serologically, there is a high incidence of positive LE preps, ANA's, hypocomplementemia, cryoglobulinemia, high titers of rheumatoid factor and granulocyte reactive ANA's (19-23). Some of the patients have granulocyte-specific ANA's which have been shown to be complement fixing (24).

The leukopenia appears to be primarily peripheral since the bone marrows are usually hyperplastic (19). Granulocytes are mostly involved. It has recently been shown that there is increased margination of the granulocytes in Felty's patients, i.e. the circulating granulocyte pool is decreased but the total body granulocyte number is normal (25).

It has been shown that there is a high incidence of 22S complexes in Felty sera (4). We have recently found, in addition to 22S complexes, intermediate (11S-15S) sized immune complexes in the sera of 100% of patients with Felty's syndrome (6).

We have also demonstrated that normal leukocytes can phagocytose large intracytoplasmic inclusions from the majority of Felty patients' sera as compared with RA patients without Felty's syndrome (10). There is also good correlation between presence of intermediate complexes and phagocytosable inclusions. We would suggest that the explanation for the above findings is that the granulocytes phagocytose immune complexes and are immediately removed from circulation by margination or trapping by the spleen or other lymphoid organs. This would explain the fact that the majority of circulating neutrophils do not have large intracytoplasmic inclusions. We would explain the existence of the granulocyte ANA's as a secondary event which takes place as a result of the continual breakdown and release of granulocyte nuclear material against which the body then develops an antibody. An alternative explanation for the ANA is that the ANA is produced nonspecifically by the immune complexes sticking to the damaged neutrophil nucleus. It has recently been shown by Weisman and Zvaifler (7) that most of the granulocyte ANA activity is concentrated in the cryoglobulin portion of a Felty serum.

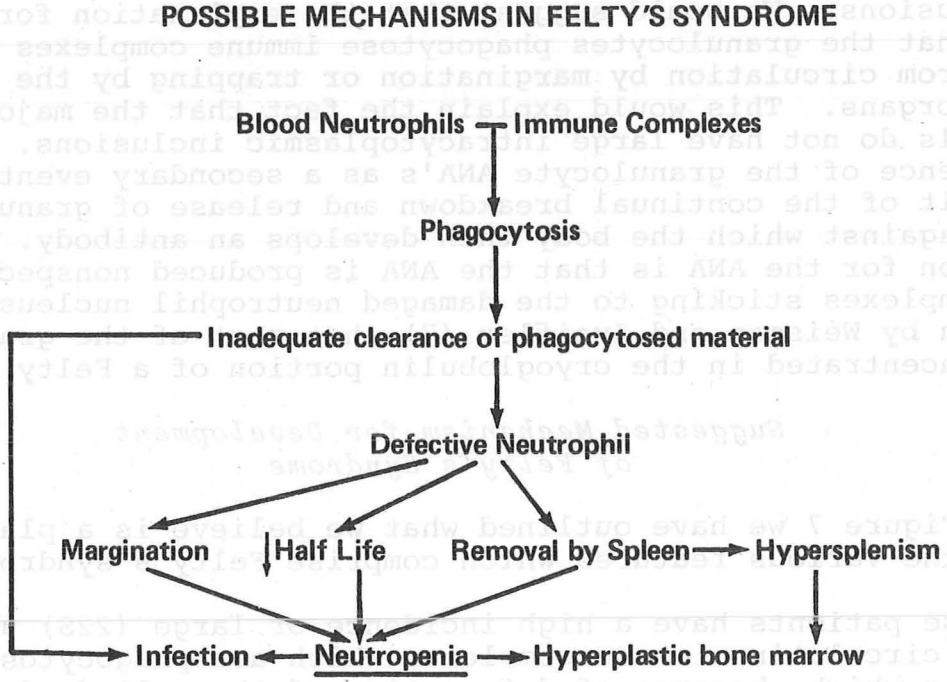
Suggested Mechanism for Development of Felty's Syndrome

In Figure 7 we have outlined what we believe is a plausible explanation for the various features which comprise Felty's syndrome.

These patients have a high incidence of large (22S) and intermediate (11S-15S) circulating immune complexes which are phagocytosed by the patient's neutrophils which, because of deformation of the cell (and possibly because of complexes sticking to the cell surface), the neutrophils are immediately marginated and/or sequestered in the spleen and, perhaps, in other sites. This produces enlargement of the spleen. The chronic intermittent peripheral margination and sequestration of neutrophils is responsible for the hyperplastic bone marrow response. Following enlargement of the spleen, a hypersplenia state may also contribute to further sequestration of granulocytes.

While the increased incidence of infection may result primarily from the neutropenia, an additional factor may be important i.e. a defective neutrophil may result from phagocytosis of the immune complexes. The half life of the cell may be decreased and, in addition, such cells may be degranulated. Decreased ability to kill bacteria may occur, thus contributing to the problem of infection. This would perhaps explain why Felty patients may have infections and neutropenia post-splenectomy. We also suggest the immune complexes are also responsible for the vasculitis which may occur in these patients.

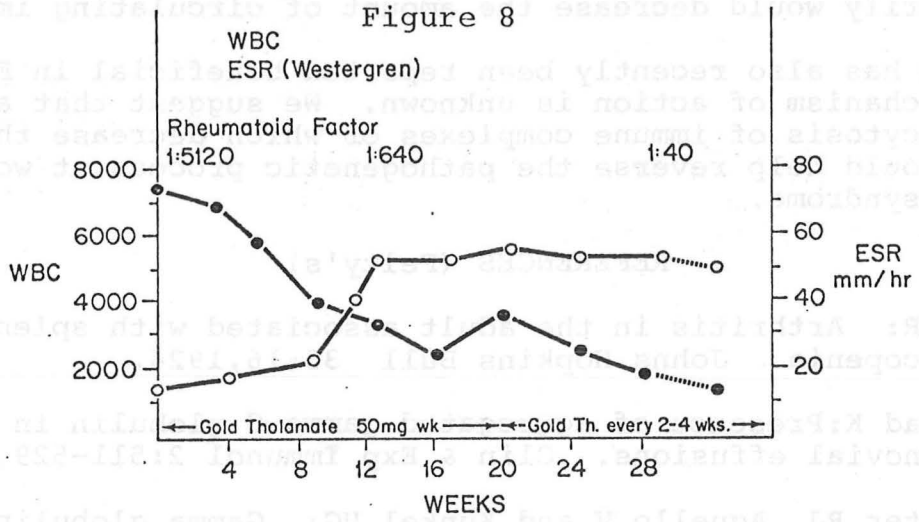
Figure 7


POSSIBLE MECHANISMS IN FELTY'S SYNDROME
Blood Neutrophils
Immune Complexes
Phagocytosis
Inadequate clearance of phagocytosed material
Defective Neutrophil
Margination
Half Life
Removal by Spleen
Hypersplenism
Infection
Neutropenia
Hyperplastic bone marrow

Speculation Concerning Therapy

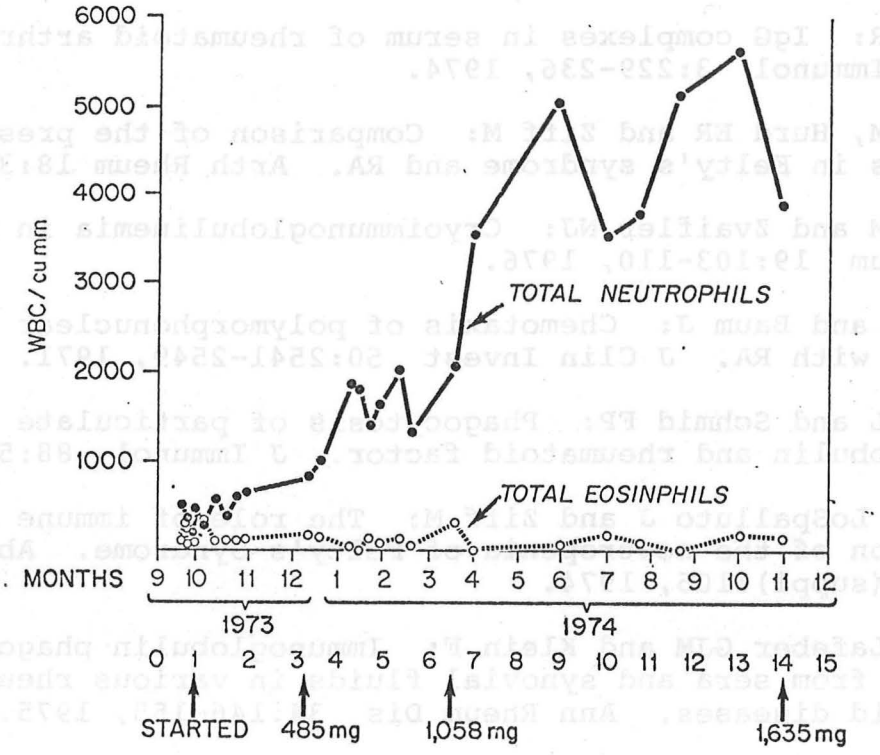
Gowans and Salami (26) demonstrated an increase in numbers of blood neutrophils in gold salt-treated Felty patients (Fig. 8). We have recently

Figure 8



observed not only an increase in blood neutrophils but decreased spleen size after gold salt therapy (27)(Fig. 9). There is evidence that gold

Figure 9



treatment decreases phagocytosis (28). We would postulate that the beneficial effect of gold treatment is due to impairment of the uptake of the immune complexes by the neutrophil. It is also possible that gold treatment may decrease the amount of circulating immune complexes either as a direct effect or indirectly by producing improvement in the disease process which secondarily would decrease the amount of circulating immune complexes.

Lithium has also recently been reported beneficial in Felty's syndrome (29). Its mechanism of action is unknown. We suggest that agents which inhibit phagocytosis of immune complexes or which decrease their amount in the blood, should help reverse the pathogenetic process at work in patients with Felty's syndrome.

REFERENCES (Felty's)

1. Felty AR: Arthritis in the adult associated with splenomegaly and and leucopenia. Johns Hopkins Bull 35:16,1924.

2. Hannestad K:Presence of aggregated gamma-G globulin in certain rheumatoid synovial effusions. Clin & Exp Immunol 2:511-529, 1967.

3. Winchester RJ, Agnello V and Kunkel HG: Gamma globulin complexes in synovial fluids of patients with RA. Partial characterization and relationship to lowered complement levels. Clin Exp Immunol 6:687-706, 1970.

4. Franklin EC, Kunkel HG and Ward JR: Clinical studies of seven patients with RA and uniquely large amounts of rheumatoid factor. Arth Rheum 1:400-409, 1958.

5. Norberg R: IgG complexes in serum of rheumatoid arthritis patients. Scand J Immunol 3:229-236, 1974.

6. Andreis M, Hurd ER and Ziff M: Comparison of the presence of immune complexes in Felty's syndrome and RA. Arth Rheum 18:383, 1975.

7. Weisman M and Zvaifler NJ: Cryoimmunoglobulinemia in Felty's syndrome. Arth Rheum 19:103-110, 1976.

8. Mowat AG and Baum J: Chemotaxis of polymorphonuclear leukocytes from patients with RA. J Clin Invest 50:2541-2549, 1971.

9. Parker RL and Schmid FP: Phagocytosis of particulate complexes of gamma globulin and rheumatoid factor. J Immunol 88:519, 1962.

10. Hurd ER, LoSpalluto J and Ziff M: The role of immune complexes in production of the neutropenia of Felty's Syndrome. Abstracted J Rheum 1 (suppl):105, 1974.

11. Cats A, Lafeber GJM and Klein F: Immunoglobulin phagocytosis by granulocytes from sera and synovial fluids in various rheumatoid and non-rheumatoid diseases. Ann Rheum Dis 34:146-155, 1975.

12. Hollander JL, McCarty DJ, Astorga G and Castro-Murillo E: Studies on the pathogenesis of rheumatoid joint inflammation. I. The "RA Cell" and a working hypothesis. Ann Int Med 62:271-280, 1965.

13. Vaughn JH, Barnett EV, Sobel MV and Jacox RF: Intracytoplasmic inclusions of immunoglobulins in RA and other diseases. Arth Rheum 11:125-134, 1968.

14. Kinsella TD, Baum J and Ziff M: Immunofluorescent demonstration of an IgG complex in synovial lining cells of rheumatoid synovial membrane. Clin Exp Immunol 4:265-271, 1969.

15. Weismann G, Zurier RB,Spieler PJ and Goldstein IM: Mechanisms of lysosomal enzyme release from leukocytes exposed to immune complexes and other particles. JEM 134:149S-165S, 1971.

16. Taichman NS, Pryzanski W and Ranadive NS: Release of intracellular constituents from rabbit polymorphonuclear leukocytes exposed to soluble and insoluble immune complexes. Int Arch Allergy Appl Imm 43:182-195, 1972.

17. Pachman LM, Jayanetra P and Rothberg RM: Rheumatoid sera and soluble complexes: nitroblue tetrazolium dye test and hexose monophosphate shunt activation. Ped 52:823-830, 1973.

18. Turner RA, Schumacher HR and Myers AR: Phagocytic function of polymorphonuclear leukocytes in rheumatic diseases. J Clin Invest 52:1632-1635, 1973.

19. DeGruchy GC, Langley GR: Felty's syndrome. Australasian Ann Med 10: 292-303, 1961.

20. Barnes GG, Turnbill AL and Vernon-Roberts B: Felty's Syndrome. A clinical and pathological survey of 21 patients and their response to treatment. Ann Rheum Dis 30:359-374, 1971.

21. Denko CW and Zumpft CW: Chronic arthritis with splenomegaly and leukopenia. Arth Rheum 5:478-491, 1962).

22. Ruderman M, Miller LM and Pinals RS: Clinical and serologic observations on 27 patients with Felty's syndrome. Arth Rheum 11:377-384, 1968.

23. Hahn RG, Mayne JG and Kiely JM: Clinical and hematologic study of Felty's Syndrome. Arth Rheum 6:275, 1963 (abstract).

24. Faber V and Elling P: Leukocyte-specific antinuclear factors in patients with rheumatoid arthritis, Felty's syndrome, systemic lupus erythematosus and other diseases. Acta Med Scand 179:257-267,1966.

25. Vincent PC, Levi JA, Macqueen A: The mechanism of neutropenia in Felty's Syndrome. Brit J Haem 27:463-475, 1974.

26. Gowans JDC and Salami M: Response of rheumatoid arthritis with leukopenia to gold salts. New Eng J Med 288:1007-1008, 1973.

27. Hurd ER, Cheatum DE: Decreased spleen size and increased neutrophils in patients with Felty's syndrome. JAMA 235:2215-2217, 1976.

28. Jessop JD, Vernon-Roberts B, Harris J: Efficacy of gold salts and prednisolone on inflammatory cells. I. Phagocytic activity of macrophages and polymorphs in inflammatory exudates studied by skin window technique in rheumatoid and control patients. Ann Rheum Dis 32:294, 1973.

29. Gupta RC, Robinson WA and Smyth CJ: Efficacy of Lithium in rheumatoid arthritis with granulocytopenia (Felty's syndrome). Arth Rheum 18: 179-184, 1975.

F. *Lymphadenopathy*

Lymphadenopathy is generally accepted as part of the rheumatoid process. In one of the earliest studies (1) of 86 patients with rheumatoid arthritis, 29.4% had significant lymph node enlargement compared with 8.9% of 26 control subjects. There was a higher incidence in males but there was no correlation between amount or degree of lymphadenopathy and disease activity, course of disease or type of onset.

A very nice controlled study was done by Robertson et al (2) in which they compared 100 patients with active rheumatoid arthritis with 100 patients with a variety of other conditions. They found that lymph node enlargement was significantly more common and more marked in rheumatoid patients in axillary, epitrochlear and inguinal regions, but not above the clavicles. Although in a few cases there was a generalized lymph node enlargement, the majority of patients had lymphadenopathy near actively inflamed joints. They also noted that lymph node enlargement was significantly greater in males than females in both the rheumatoid and control groups of patients. The amount of lymph node enlargement was greater in rheumatoid-factor positive patients and in those with active disease with erythrocyte sedimentation rates over 30 mm in one hour (2). By lymphangiography, only non-specific inflammatory changes were noted with no evidence of lymphangiectasis or lymphatic blockage. A coarse granular appearance has been noted (2,3).

Generalized lymph node enlargement should raise the possibility of a reticulosis which apparently occurs slightly more often in patients with rheumatoid arthritis than in the general population (4).

Generalized lymph node enlargement may also raise the possibility of a reticulosis which apparently occurs slightly more often in patients with rheumatoid arthritis than in the general population (4).

Generalized lymph node enlargement may also raise the possibility of a malignant lymphoma. Rheumatoid follicular hyperplasia may simulate malignant nodular (follicular) lymphoma (5,6). These investigators point out that the presence of discrete follicles with active germinal centers surrounded by a well-demarcated cuff of lymphocytes, the presence of numerous plasma cells in the interfollicular areas, and proliferation of vascular endothelium are features of a benign rather than malignant process.

REFERENCES (Lymphadenopathy)

1. Short CL, Bauer W and Reynolds WE: "Rheumatoid Arthritis". p. 311, Howard Univ Press, Cambridge, Mass., 1957.

2. Robertson MDJ, Hart FD, White WF, Nuki G and Boardman PL: Rheumatoid lymphadenopathy. Ann Rheum Dis 27:253-260, 1968.

3. Michotte LJ and Van Bogaert P: La lymphographie dans la polyarthrite rheumataede. Rev Rheum 33:100, 1966.

4. Lea AJ: An association between the rheumatic diseases and the reticuloses. Ann Rheum Dis 23:480, 1964.

5. Nasanchuk JS and Schnitzer B: Follicular hyperplasia in lymph nodes from patients with RA. Cancer 24:343-354, 1969.

6. Motulsky AG, Weinberg S, Saphir O and Rosenberg E: Lymph nodes in RA. Arch Int Med 90:660, 1952.

G. *Neurologic Involvement*

The major types of nervous system involvement are shown in Table 18.

Table 18

NEUROLOGIC INVOLVEMENT

Nodules in CNS

Cervical myelopathy due to Atlanto-Axial Subluxation

Entrapment or Compression Neuropathy
1) Carpal Tunnel Syndrome
2) Tarsal Tunnel Syndrome
3) Ulnar Nerve Entrapment
4) Posterior Interosseous Nerve Entrapment

Neuropathy due to Arteritis

A more complete list is shown in Table 19.

Table 19

THE NEUROLOGIC MANIFESTATIONS OF RHEUMATOID ARTHRITIS

I. Articular-cervical spine disease
   A. Cervical subluxations (four types)
      1. C1 moves anteriorly on C2
      2. C1 moves posteriorly on C2
      3. Vertical subluxation of odontoid
      4. "Staircase" or multiple lower level subluxations

   B. Radiologic findings often with clinical symptoms
      1. Double crush syndrome
      2. Narrowed disc spaces above C5

   C. Radiologic findings without clinical symptoms
      1. Vertebral plate erosion
      2. Apophyseal joint erosion
      3. Basilar impression of the skull

II. Extra-articular
   A. Peripheral neuropathies
      1. Compression leading to entrapment
      2. Mild sensory neuropathy with a good prognosis
      3. Diffuse sensorimotor neuropathy
      4. Fulminant sensorimotor neuropathy

   B. Vasculitis
      1. Mononeuritis complex
      2. Cerebral vasculitis

   C. Dural rheumatoid nodules causing brain and spinal cord compression

modified from ref. (1)

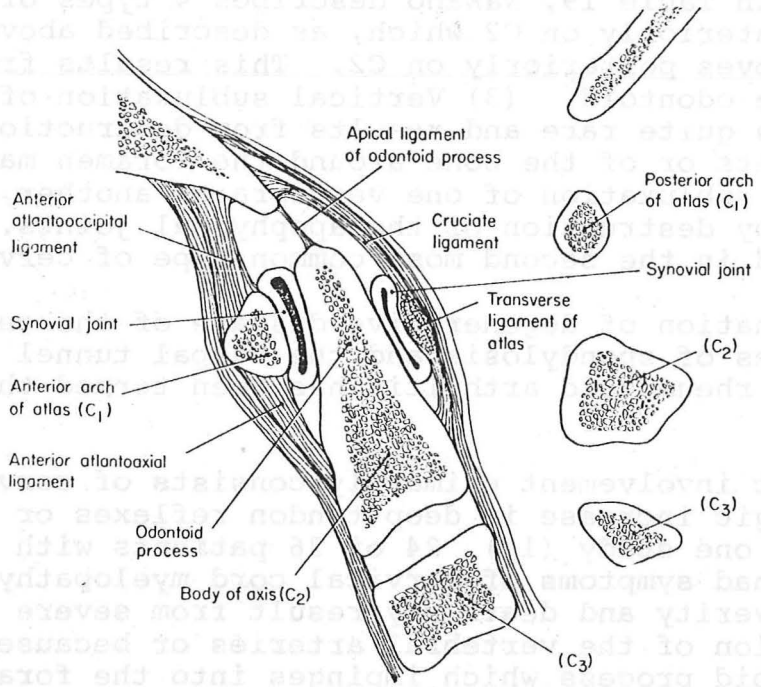
As with other organ systems, the central nervous system can be involved with rheumatoid nodules. Intracranial dural rheumatoid nodules have been infrequently reported (2,3).

A case in which unusually diffuse involvement of the CNS was present has been described (4). At autopsy this patient had diffuse lymphocytic and plasma cell infiltration of the subarachnoid space and perivascular spaces of the brain associated with focal deposition of granular or hyaline material in the leptomeninges, vascular changes compatible with rheumatoid disease in the pia-arachnoid and in the brain tissue and numerous typical rheumatoid nodules of the leptomeninges, especially over the temporal poles. A second report described meningeal involvement in a patient with chronic rheumatoid arthritis (4). Vertebral bodies may also be affected with eventual erosion and collapse (5-7). These lesions may be difficult to differentiate from tumor or infection.

Three other types of cervical spine involvement have been reported. One is known as rheumatoid discitis (8). In this condition the annulus fibrosus and normal intervertebral disc substance are replaced by rheumatoid pannus which arises directly in the middle of the neurocentral joints. The second is spinal cord injury and myelopathic disease resulting from thickening and fibrosis of the dura without bone compression (9).

The third and most common type of cervical spine involvement is atlanto-axial subluxation with secondary cervical myelopathy. The odontoid process forms two synovial joints, one anteriorly with the atlas and one posteriorly with the transverse ligament of the atlas. (Fig. 10) Thus both the odontoid

Figure 10



from ref. (10)

Anatomical relation of the odontoid process with synovial joints and with the anterior arch and transverse ligament of the atlas (C_1).

process itself and the transverse ligament are subject to erosion because of their proximity to synovial tissue. Laxity of the transverse ligament also may occur, allowing slippage of the odontoid process posteriorly, causing pressure on the spinal cord. In addition, vertebro-basilar insuf-

ficiency may result from torsion of the vertebral arteries caused by the subluxation.

By x-ray of the cervical spine using lateral tomography in flexion, subluxation is probably present if the distance between the posterior aspect of the anterior arch of the atlast and the anterior part of the odontoid process is greater than 2.5 mm in women and 3.0 mm in males. Subluxation can be detected clinically by gently rocking the head.

Using the 3 mm x-ray criterion as mentioned above, atlanto-axial subluxation was found in 36 of 100 successive rheumatoid patients (12). Other studies have found subluxation in 25% of 76 outpatients studied (13), 19% of hospitalized patients (14) and 71% of rheumatoid patients with neck symptoms (15).

As shown in Table 19, Nakano describes 4 types of cervical subluxations: (1) C1 moves anteriorly on C2 which, as described above is the most common form, (2) C1 moves posteriorly on C2. This results from severe erosion or fracture of the odontoid. (3) Vertical subluxation of the odontoid and body of C2: this is quite rare and results from destruction of the lateral atlantoaxial joints or of the bone around the foramen magnum. (4) "Staircase" subluxation or subluxation of one vertebra on another, often being multiple and is caused by destruction of the apophyseal joints. It occurs below the level of C2 and is the second most common type of cervical subluxation.

The combination of degenerative disease of the cervical spine with variable degrees of spondylosis and the carpal tunnel syndrome occurring in a patient with rheumatoid arthritis has been termed the "double crush" syndrome.

Neurologic involvement primarily consists of cervical cord myelopathy with a pathologic increase in deep tendon reflexes or positive plantar responses. In one study (12), 24 of 36 patients with atlanto-axial subluxation by x-ray had symptoms of cervical cord myelopathy. These symptoms may increase in severity and death may result from severe compression of the cord, obstruction of the vertebral arteries or because of snapping of the weakened odontoid process which impinges into the foramen magnum (16-18). Surgical fixation is necessary when there is severe head and neck pain, when neurological signs are severe or when there is gross vertebral displacement (19). However, conservative treatment such as attempting to immobilize the neck with a cervical collar is probably the best therapy (20). In fact, surgical therapy has not been ideal since relapse of neurological complaints frequently occurs (21). Studies of 130 patients' x-rays have shown that over a 5 to 14 year follow-up period 52 patients died. Four developed spinal cord involvement and 6 acquired symptoms of vertebral ischemia. In the 84 survivors, approximately 25% increased their degree of subluxation, less than 50% had remained the same and 25% had either improved or recovered completely (22).

Neck trauma should be avoided if at all possible in these patients. Automobile accidents with whiplash injury, intubation, extreme head positions under anesthesia or even at the hairdressers should all be avoided.

Entrapment or compression neuropathies may occur in patients with rheumatoid arthritis (see Tables 18 and 20). These include the carpal tunnel and tarsal tunnel syndromes, ulnar nerve entrapment syndrome, and entrapment of the posterior interosseous branch of the radial nerve.

Table 20

THE ENTRAPMENT SYNDROMES OF RHEUMATOID ARTHRITIS

A. Median Nerve

1. Carpal tunnel syndrome
2. "Double crush" syndrome of the median nerve

B. Ulnar Nerve

1. Cubital canal syndrome - at elbow
2. Canal of Guyon syndrome - at wrist
3. "Double crush" syndrome of ulnar nerve

C. Radial Nerve

Posterior interosseous syndrome

D. Sciatic Nerve

Tibial or common peroneal entrapment by a Baker (popliteal) cyst

E. Common Peroneal Nerve

Pressure palsy

F. Posterior Tibial Nerve

1. Tarsal tunnel syndrome
2. Medial plantar syndrome
3. Lateral plantar syndrome

from ref. (1)

Median Nerve

The carpal tunnel syndrome is by far the most common of these entrapment syndromes encountered in rheumatoid arthritis patients. In a study of 29 rheumatoid patients (23) over 40 years of age and 23 normal control individuals over the age of 40, the symptoms of numbness, tingling and burning in the median nerve distribution were found to be significantly increased in the rheumatoid patients. There was no relationship between symptoms and sex, duration of rheumatoid arthritis, erythrocyte sedimentation rate, rheumatoid factor, functional class, x-ray stage, limitation of wrist motion, swelling or wrist tenderness. Symptoms were related to a positive Tinel's test. By electromyography, symptomatic rheumatoid patients had significantly slower conduction across the carpal tunnel than the remaining rheumatoid patients. This study concluded that complaints of numbness, tingling and burning in the median nerve distribution plus a positive

Tinel's or Phalen's test suggests the diagnosis of carpal tunnel syndrome.

The diagnosis can be substantiated, however, by use of electromyography. Approximately two thirds of patients with verified carpal tunnel syndrome will have prolonged median motor latencies when the nerve is stimulated at the wrist (24,25). About 85% to 95% of affected hands will have prolongation of median distal sensory latencies (beyond 3.5 msec)(26).

In a group of 36 patients with early rheumatoid arthritis, the incidence of electrodiagnostic abnormalities was 5.5%. The incidence of carpal tunnel syndrome clinically diagnosed who underwent electrical tests was 17% and the overall incidence was 23% (27).

Splinting the wrist in slight extension or injecting a steroid preparation into the carpal tunnel provides prompt short-term relief in the majority of cases (26). However, patients with thenar atrophy or progression of numbness and weakness should have surgery (28). Sectioning the transverse carpal ligament will usually relieve the patient's symptoms.

The "double crush" syndrome is the combination of cervical spondylosis and carpal tunnel syndrome in a patient with rheumatoid arthritis.

Ulnar Nerve

Ulnar nerve neuropathy secondary to compression at the cubital fossa occurs uncommonly in the rheumatoid patient. Compression is due to synovitis extending extra-articularly (1). A large olecranon bursa may also compress the ulnar nerve. Decompression and excision of the synovial mass results in alleviation of symptoms. Elbow entrapment causes weakness of the flexi carpi ulnaris, flexor digitorum profundus of the fourth and fifth fingers, and intrinsic muscles. Sensory loss involves the dorsum of the ulnar aspect of the hand.

Rarely the synovium within the carpal tunnel can bulge and compress the ulnar nerve proximal to Guyon's canal, resulting in symptoms which simulate ulnar nerve neuropathy at the elbow.

If ulnar nerve entrapment and lower cervical spine disease (C8,T1) occur concomitantly, as with the median nerve, it is known as the "double crush" syndrome of the ulnar nerve.

Radial Nerve

A few patients have been reported with posterior interosseous nerve paralysis secondary to rheumatoid arthritis (29-31). Clinically there is an inability to extend the fingers and thumb. The condition is a compression neuritis of the posterior interosseous nerve secondary to elbow synovitis bulging anteriorly against the overlying supinator muscle. In many patients the diagnosis of extensor tendon rupture has erroneously been made (29). Treatment by injection of steroids may help. Synovectomy with radial head resection may also be of value.

Sciatic Nerve

Occasional patients with rheumatoid arthritis and synovitis of a knee will develop popliteal (Baker) cysts. These may dissect into the calf and sometimes rupture. When inflamed they may closely simulate thrombophlebitis, including a positive Homan sign. Such a cyst may involve the peroneal or tibial nerves, or both (1).

If the common peroneal nerve is involved, one will see paresis of the peroneal muscles, tibialis anterior, extensor hallucis longus, extensor digitorum longus, and extensor digitorum brevis. Sensory loss will occur over the lateral leg and dorsum of the foot.

When the tibial nerve is involved, there will be weakness of the gastrocnemius, soleus, tibialis posterior, flexor digitorum longus, flexor hallucis longus, and the intrinsic muscles of the feet. A sensory deficit may be present over the plantar aspect of the foot, including the heel and the posterolateral aspect of the calf.

Peroneal Nerve

Pressure palsy of the common deep, or superficial peroneal nerves is apparently due more to immobility and a pressure vulnerable area rather than a true complication of the rheumatoid process (1)

Posterior Tibial Nerve

The tarsal tunnel syndrome (32) results from compression of the posterior tibial nerve beneath the flexor retinaculum along the medial malleolus in the foot. It is caused by rheumatoid tenosynovitis affecting the tendon sheaths of the tibialis posterior long foot flexor tendons. Clinically there are paresthesias over the first 3 toes and patients may complain of "burning feet" especially at night, and may have difficulty with the intrinsic toe muscles. As with the carpal tunnel syndrome, local corticosteroid injection may be helpful. A partial tarsal tunnel syndrome involving only the medial or lateral plantar nerves may also be seen. Complaints include weakness or burning of the feet.

Peripheral neuropathy is a well recognized complication of rheumatoid arthritis (33,34). A mild distal sensory neuropathy and a severe sensorimotor neuropathy are the two predominant clinical patterns. In each, the major etiologic factor is an occlusive arteriopathy (35,36). According to one study (37), segmental demyelination is the fundamental nerve abnormality in rheumatoid arthritis.

With the distal sensory neuropathy patients may complain of paresthesias, dysesthesias or "burning feet". Examination may reveal decreased touch and pin sensation distally in the toes and feet and decreased vibratory sensation.

With the more severe sensorimotor neuropathy, the patient may have symmetrical distal weakness of the limbs in addition to diminished touch and vibratory sensations.

REFERENCES (Neurologic)

1. Nakano KK: Neurologic complications of RA. Orthopedic Clin N Am 6:862, 1975.

2. Maher JA: Dural nodules in RA. Arch Path Lab Med 58:354-359, 1954.

3. Steiner JW and Gelbloom AJ: Intracranial manifestations in 2 cases of systemic rheumatoid disease. Arth Rheum 2:537-545, 1959.

4. Ouyang R, Mitchell DM, Rozdilsky B: Central nervous system involvement in rheumatoid disease. Report of a case. Neurology 17:1099-1105, 1967.

5. Baggenstoss AH, Bickel WH and Ward LE: Rheumatoid granulomatous nodules as destructive lesions of vertebrae. J Bone Joint Surg 34A: 601-609, 1952.

6. Lorber A, Pearson CM and Rene RM: Osteolytic vertebral lesions as a manifestation of RA and related disorders. Arth Rheum 4:514-532, 1961.

7. Glay A and Rona G: Nodular rheumatoid vertebral lesions versus ankylosing spondylitis. Am J Roentgen 94:631-638, 1965.

8. Bland JH: RA of the cervical spine. Bull Rheum Dis 18:471-476, 1967.

9. Hopkins JS: Lower cervical rheumatoid subluxation with telraplegia. J Bone Joint Surg 49B:46-51, 1967.

10. Boyle JA and Buchanan WW: Clinical Rheumatology, FA Davis Co., Philadelphia, 1971.

11. Williams RC: RA as a systemic disease. IV. in Major Problems in Internal Medicine. WB Saunders. Philadelphia, 1974.

12. Stevens JC, Cartlidge NEF, Saunders M, Appleby A, Hall M and Shaw DA: Subluxation and cervical myelopathy in RA. Quart J Med 40:391-408, 1971.

13. Matthews JA: Atlanto-axial subluxation in RA. Ann Rheum Dis 28:260-266, 1969.

14. Sharp J and Purser DW: Spontaneous atlanto-axial dislocation in ankylosing spondylitis and RA. Ann Rheum Dis 20:47-77, 1961.

15. Martel W: The occipito-atlanto-axial joints in RA and ankylosing spondylitis. Am J Roentgen 86:223-240, 1961.

16. Davis FW Jr, and Markley HE: RA with death from medullary compression. Ann Int Med. 35:451, 1951.

17. Ford FR: Syncope, vertigo and disturbances of vision resulting from intermittent obstruction of the vertebral arteries due to defect in the odontoid process and excessive mobility of the second cervical vertebra. Bull Johns Hopkins Hosp 91:168, 1952.

18. Sharp J and Purser DW: Spontaneous atlanto-axial dislocation in ankylosing spondylitis and RA. Ann Rheum Dis 20:47, 1961.

19. Cregan JCF: Internal fixation of the unstable rheumatoid cervical spine. Ann Rheum Dis 25:242, 1966.

20. Boyle JA, Buchanan WW: Clinical Rheumatology, p. 105, FA Davis Co, Philadelphia, 1971.

21. Maijers KAE, Van Beusekorn GT, Dayfjes F, and Luijendijk W: Treatment of dislocation in the cervical spine in RA and ankylosing spondylitis complicated by signs of cord compression: a followup study. Ann Rheum Dis (Abstr) 32:88-89, 1973.

22. Smith PA, Benn RT and Sharp J: Natural history of rheumatoid cervical luxations. Ann Rheum Dis 31:431-439, 1972.

23. Herbison GJ, Teng C, Martin JH and Ditunno JF: Carpal tunnel syndrome in RA. Am J Phys Med 52:68-74, 1973.

24. Kopell HP, Goodgold J: Clinical and electrodiagnostic features of carpal tunnel syndrome. Arch Phys Med Rehab 49:371-375, 1968.

25. Thomas JE, Lambeck , Czcuz KA: Electrodiagnostic aspects of the carpal tunnel syndrome. Arch Neurol 16:635-641, 1967.

26. Hoffman DE: Carpal tunnel syndrome: Importance of sensory nerve conduction studies in diagnosis. JAMA 233:983-984, 1975.

27. Chamberlain MA, Corbett M: Carpal tunnel syndrome in early RA. Ann Rheum Dis 29:149-152, 1970.

28. Phalen GS: The carpal tunnel syndrome: Sixteen years experience in diagnosis and treatment of 654 hands. J Bone Joint Surg 48A:211-228, 1966.

29. Millender LH, Nalebuff EA and Holdsworth DE: Posterior interosseous nerve syndromes secondary to rheumatoid synovitis. J Bone Joint Surg 55A:753-757, 1973.

30. Marmor L, Lawrence JF and Dubois EL: Posterior interosseous nerve palsy due to RA. J Bone Joint Surg 49A:381-383, 1967.

31. Popelka S and Vainio K: Entrapment of the posterior interosseous branch of the radial nerve in RA. Acta Orthop Scand 45:370-372, 1974.

32. Lloyd K and Agarwal A: Tarsal-tunnel syndrome, a presenting feature of RA. Brit Med J 3:32, 1970.

33. Hart FD and Golding JR: Rheumatoid neuropathy. Brit Med J 1:1594, 1960.

34. Pallis CA and Scott JT. Peripheral neuropathy in RA. Brit Med J 1:1141, 1965.

35. Weller RO, Bruckner FE and Chamberlain MA: Rheumatoid neuropathy: a histological and electrophysiological study. J Neurol Neurosurg Psychiat 33:592, 1970.

36. Haslock DI, Wright V and Harriman DGF: Neuromuscular disorders in RA, a motor-point muscle biopsy study. Quart J Med 39:335, 1970.

37. Beckett JL and Dinn JJ: Segmental demyelination in RA. Quart J Med 16:71-80, 1972.

H. *Muscle Involvement*

In the majority of patients with rheumatoid arthritis, there is some degree of muscle weakness and wasting. This is usually attributed to muscle atrophy which occurs secondary to lack of use of the joints i.e. a disuse atrophy. Thus primary muscle involvement is not a prominent feature of rheumatoid arthritis.

However, muscle biopsies in these patients revealed a vasculitis in 10% of patients (1). Nodular cellular infiltrates of 1 to 2 mm size composed mainly of lymphocytes (lymphorrhages) and plasma cells was believed to be specific for the myositis of rheumatoid arthritis (2). Muscle fiber degeneration was present and most apparent nearest the cellular infiltrate. Nodular myositis was noted in 13 of 16 muscle biopsies from patients with rheumatoid arthritis (3).

The cellular accumulations appear to be quite benign, since muscle necrosis and elevation of muscle enzymes such as creatine phosphokinase and aldolase are not seen in rheumatoid patients (4).

Williams (5) has suggested that the myopathy and wasting of muscles that one sometimes sees in rheumatoid patients over a two to three month period might possibly be due to rapid dissolution of muscle mass brought about by release of a lymphokine-like substance from the lymphocyte clusters. Such a mechanism is probably responsible for the muscle damage which is seen in patients with polymyositis (6).

REFERENCES (Muscle)

1. Sokoloff L, Wilens SL and Bunim JJ: Arteritis of striated muscle in RA. Am J Path 27:157, 1951.

2. Steiner G, Freund HA, Leichtentritt B,Maun ME: Lesions of skeletal muscles in RA nodular polymyositis. Am J Path 22:103-145, 1946.

3. DeForest, GK, Bunting H and Kenney WE: RA: diagnostic significance of focal cellular accumulations in skeletal muscles. Am J Med 2: 40-44, 1947.

4. Hendrick F, Kuthan F, Tovarek J and Vitulova V: The enzymatic pattern in the serum of rheumatoid patients related to muscular wasting. Scripta Medica 39:63, 1966.

5. Williams RC: RA as a systemic disease. Chapt. V, p. 88 in Major Problems in Internal Medicine IV. WB Saunders, Philadelphia, 1974.

6. Johnson RL, Fink CW and Ziff M: Lymphotoxin formation by lymphocytes and muscle in polymyositis. J Clin Invest 51:2435-2449, 1972.

I. *Sjögren's Syndrome*

In its simplest form Sjögren's syndrome consists of rheumatoid arthritis and the "sicca syndrome" which usually includes keratoconjunctivitis sicca, or dry eyes, and xerostomia, or dry mouth (Table 21).

Table 21

MAJOR COMPONENTS OF SJÖGREN'S SYNDROME

Rheumatoid Arthritis (or other connective tissue disease)

Keratoconjunctivitis Sicca

Xerostomia

Extensive involvement, however, may produce extreme dryness of the nose, pharynx, tracheobronchial areas, vagina and stomach.

According to Shearn (1), diagnostic categories of definite and probable Sjögren's syndrome can be used as shown in Table 22.

Table 22

Definite Sjögren's syndrome:

The presence of *either*	1) Objective evidence of keratoconjunctivitis sicca
or	2) Characteristic pathologic features in the lacrimal or salivary glands

Probable Sjögren's syndrome:

The presence of *two* of *three* features:	1) Recurrent or chronic "idiopathic" salivary gland swelling
	2) Unexplained xerostomia
	3) Connective tissue disease

from ref. (1), p. 177

The major features of Sjögren's syndrome in 80 patients in whom the diagnosis was established by the criteria shown above (1) are shown in Table 23. Keratoconjunctivitis sicca was the most common, occurring in 87% of patients, xerostomia in 66% and connective tissue disease in 62%. The latter point demonstrates that sicca components may occur alone, without rheumatoid arthritis or other connective tissue disease. Abnormal salivary or lacrimal glands were present in 37% and a positive salivary gland biopsy in 31%.

Table 23

MAJOR FEATURES OF SJÖGREN'S SYNDROME

IN 80 PATIENTS

	Number	Per Cent
Keratoconjunctivitis sicca	69	87
Xerostomia	52	66
Connective tissue disease	49	62
Abnormal salivary or lacrimal gland	29	37
Positive salivary gland biopsy	25	31

Other findings which are commonly seen in patients with Sjögren's syndrome are shown in Table 24.

from ref. (1)

Table 24

OTHER FINDINGS COMMONLY PRESENT IN SJÖGREN'S SYNDROME

Interstitial Nephritis and Renal Tubular Acidosis

Lymphoma or Pseudolymphoma

Pancreatitis

Hepatobiliary Disease

Vasculitis

Thyroid Dysfunction

Hypergammaglobulinemia and Multiple Autoantibodies

Vaginal and Vulvar Dryness

The frequency of eye symptoms in 62 patients seen at the NIH (2) is shown in Table 25. A foreign body sensation, burning, and inability to tear in response to irritants or emotions were the most common symptoms.

Complications included corneal vascularization and ulceration, rarely followed by perforation.

Table 25

FREQUENCY OF EYE SYMPTOMS IN 62 PATIENTS

Symptom	Present	
	No.	Per Cent
Foreign body sensation	46	74
Burning	41	66
Excess of secretions (ropy strands)	39	63
Inability to tear in response to irritants	39	63
Inability to tear in response to emotions	39	63
Tiring, soreness, pain	35	57
Redness	33	53
Photosensitivity	33	53
"Film"	32	52
Itching	30	49
Changes in Visual Acuity	20	32
Difficulty in moving lids	14	23

from ref. (2)

Symptoms of oral and salivary gland involvement in this same study are shown in Table 26. All 62 patients had some type of involvement. All symptoms resulted from decreased or absent saliva, with resulting oral dryness and symptoms secondary to this problem.

Table 26

SYMPTOMS ASSOCIATED WITH XEROSTOMIA

	No.	Per Cent
Number of Patients	62	100
Oral dryness	56	90
Decreased or absent saliva	50	81
Difficulty with mastication (food sticking to mouth)	41	66
Increased fluid intake with meals	39	63
Increased fluid intake in general	26	42
Fissuring or ulceration of mouth or lips	36	58
Oral soreness	29	47
Related dental symptoms (increased dental caries)	37	60

from ref. (2)

As shown in Table 27, in Shearn's 80 patients (1) parotid gland enlargement was much more common than that of the submaxillary or lacrimal glands.

Table 27

SALIVARY AND LACRIMAL GLAND ABNORMALITIES

IN 80 PATIENTS

Abnormality	No. of Patients
Parotid enlargement	26
Submaxillary enlargement	5
Lacrimal enlargement	3
Submaxillary and parotid enlargement	2
Pathologic confirmation	25

from ref. (1)

The major pathologic findings in the salivary glands are listed in Table 28.

Table 28

SALIVARY GLAND PATHOLOGY

Parenchymal and ductal alterations

Decrease or disappearance of acini

Lymphocytic infiltration

Hyperplasia of lining cells of intra-glandular ducts

Formation of "epi-myoepithelial islands"

from ref. (2)

The lymphocytic infiltrate consists primarily of mature lymphocytes (2). Lymph follicles with germinal centers may be present. Plasma cells, neutrophils and foreign body giant cells are occasionally noted and in some glands the interlobular septa show fibrous thickening. There is usually good correlation between the severity of the xerostomia and the extent of the lymphoid infiltration. One recent study demonstrated that the predominant mononuclear cells are T lymphocytes (3). However, in one case of "pseudolymphoma", most of the cells were B lymphocytes.

The symptoms and lesions reported in the respiratory tract are shown in Table 29.

Table 29

RESPIRATORY TRACT INVOLVEMENT

Upper Respiratory Tract

- Nasal dryness
- Crusts in nose
- Chronic sinusitis
- Dryness of the throat, hoarseness and sore throat
- Chronic cough

Lower Respiratory Tract

- Principal Pulmonary Lesions
  - Pleurisy and pleural adhesions
  - Focal and lipoid pneumonia
  - Pulmonary atelectasis and fibrosis
  - Pulmonary nodules

Most of these symptoms and lesions are related to the dryness of the air passageways due to decreased mucous secretions. There is histological evidence of submucous gland atrophy accompanied by infiltration of lymphocytes and plasma cells at all levels of the respiratory tract (2). The pulmonary nodules are composed primarily of lymphocytes, plasma cells, giant cells and a few neutrophils (2). Hyposecretion of mucus, poor bronchial drainage and possibly, secondary infection are probably all related to the development and persistence of most of the pulmonary infiltrates.

Cutaneous manifestations are shown in Table 30 and may be seen in from 15 to 52 per cent of patients (4).

Table 30

CUTANEOUS MANIFESTATIONS

- Dryness
- Purpuric Lesions
- Vasculitis
- Raynaud's Phenomenon

Dryness of the skin is a common finding in Sjögren's patients. Scaling is seen in 25 per cent (1). Biopsy of the skin has shown infiltration of the sweat glands by inflammatory cells (5,6). Sweating is often diminished and hair may be dry and sparse.

Nonthrombocytopenic purpura is seen in a few patients. Cutaneous vasculitis and Raynaud's phenomenon are occasionally seen, as previously discussed for patients with pure rheumatoid arthritis.

Genital dryness in females i.e. dryness of the vulva or vagina is apparently due to hypofunction of the lubricating glands resulting in dry and erythematous vaginal mucosa (2).

Although there are isolated reports of nephrosclerosis, chronic pyelonephritis, necrotizing arteriolitis and thickening of the glomerular capillary basement membranes, the major type of renal involvement seen in patients with Sjögren's syndrome is that of renal tubular acidosis which is usually directly related to an interstitial nephritis. Although interstitial changes may occur without renal tubular acidosis, renal tubular acidosis seldom occurs without interstitial changes (7). Interstitial changes consist primarily of infiltration with lymphocytes and a few plasma cells. Interstitial fibrosis may be present, particularly in long standing disease. Clinical clues to presence of renal disease include slight proteinuria (a trace to 1 gm in 24 hours) and a few formed elements. The incidence of proteinuria in Sjögren's syndrome has been reported to be between 4 and 6% (4,8).

The gastrointestinal lesions which may be related to the Sjögren's process and the pathological or laboratory abnormalities are shown in Table 31.

Table 31

GASTROINTESTINAL MANIFESTATIONS

Manifestation	Probable Cause or Associated Finding
Dysphagia	Xerostomia or esophageal involvement in association with Raynaud's phenomenon.
Achalasia and Esophageal Stricture	Mucosal atrophy and atrophy and infiltration of submucosal glands by lymphocytes and plasma cells
Achlorhydria	Antibodies to gastric parietal cells Lymphocytosis of pyloric and Brunner's glands
Pancreatitis and Decrease in pancreatic secretion	Lymphocytic infiltration
Chronic Hepatobiliary Disease Chronic Active Hepatitis Primary Biliary Cirrhosis	Lymphocytic infiltration Anti-mitochondrial antibodies

Most of the gastrointestinal lesions shown are probably a result of dysfunction brought about by or associated with lymphocytic infiltration into the target organ, possibly causing direct damage.

Neurologic and cardiac manifestations seen in Sjögren's syndrome, are in general, similar to those seen in pure rheumatoid arthritis.

Various thyroid abnormalities seen in Sjögren's patients are shown in Table 32. Some abnormality was detected in 17 of Shearn's 80 patients.

Table 32

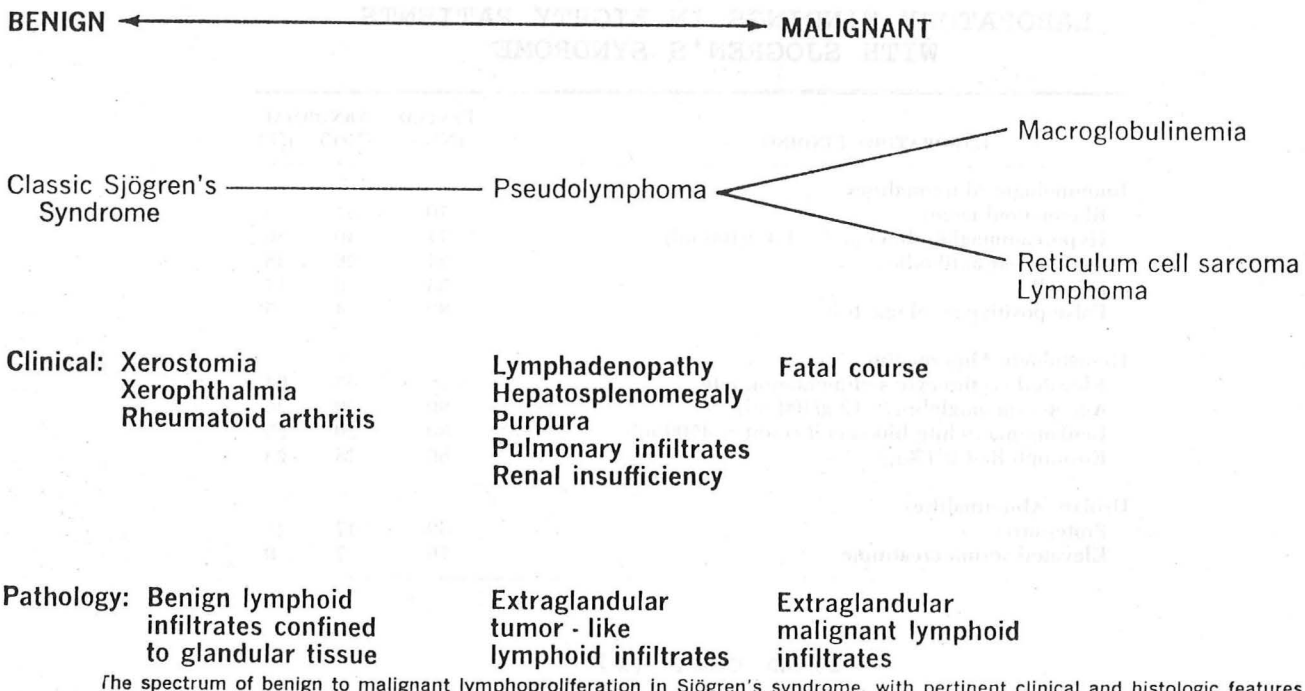
THYROID MANIFESTATIONS IN 17 PATIENTS

	No.
Hyperthyroidism	3
Hypothyroidism	4
Palpable enlargement, 2 with nodules, 3 with Hashimoto's thyroiditis	10

from ref. (1)

Thyroid antibodies were detected in 52 per cent of patients with Sjögren's syndrome in one study (9).

In the great majority of patients, Sjögren's syndrome is a benign disease. However, it has become apparent that some patients are predisposed to the development of lymphoreticular malignancy, such as lymphoma, reticulum cell sarcoma, or Waldenstrom's macroglobulinemia (10-12). A broad spectrum of lymphoproliferation exists in Sjögren's syndrome, ranging from benign to malignant, with the so-called pseudolymphoma occupying the middle portion of the spectrum (see Fig. 13).



The spectrum of benign to malignant lymphoproliferation in Sjögren's syndrome, with pertinent clinical and histologic features noted.

from ref. (10)

Figure 13

The distinction between a benign and malignant lesion may be extremely difficult. Lymphoproliferative diseases which have been reported in Sjögren's patients are shown in Table 33.

Table 33

LYMPHOPROLIFERATIVE DISORDERS SEEN IN SJÖGREN'S SYNDROME

Pseudolymphoma
Stem Cell Lymphoma or
Reticulum Cell Sarcoma
Waldenstrom's macroglobulinemia
Malignant Lymphocytic Lymphoma
Giant Follicular Lymphoma
Lymphosarcoma
Hodgkin's Disease
Lymphoma of Vocal Cords
Thymoma

from ref.(10)

The most characteristic laboratory findings in patients with Sjögren's syndrome are the immunologic abnormalities detected in the serum.

The laboratory findings in 80 patients with Sjögren's syndrome are shown in Table 34.

Table 34

LABORATORY FINDINGS IN EIGHTY PATIENTS WITH SJÖGREN'S SYNDROME

Laboratory Finding	Tested (No.)	Abnormal (No.)	(%)
Immunologic Abnormalities			
Rheumatoid factor	70	51	73
Hypergammaglobulinemia (> 1.4 g/100 ml)	71	40	56
Antinuclear antibodies	54	26	48
LE cell	53	9	17
False positive serologic test	80	4	5
Hematologic Abnormalities			
Elevated erythrocyte sedimentation rate	70	45	64
Anemia (hemoglobin < 12 g/100 ml)	80	29	36
Leukopenia (white blood cell count < 4500/ml)	80	20	25
Eosinophilia (≧ 4%)	80	18	23
Urinary Abnormalities			
Proteinuria	80	17	21
Elevated serum creatinine	76	7	9

from ref. (1)

The patterns of anti-nuclear fluorescence reported include primarily homogeneous and speckled with a few nucleolar patterns (13).

Antibodies to organ constituents which may be found in Sjögren's serum are shown in Table 35. It is apparent that antibodies have been detected against virtually every organ of the body. It is of interest that antibody to salivary duct epithelium was detected in 65 per cent of patients with Sjögren's syndrome and rheumatoid arthritis and in 26 per cent of uncomplicated rheumatoid arthritis patients, suggesting that the Sjögren's process is sub-clinical in many rheumatoid patients (14).

Table 35

ANTIBODIES TO ORGAN CONSTITUENTS

Lacrimal glands
Salivary glands
Thyroid
Kidney
Spleen
Testes
Adrenal gland
Brain
Gastric parietal cells
Liver
Muscle

Serum complement levels are either normal or somewhat elevated (1)

A serum hyperviscosity syndrome has recently been reported in a few patients with Sjögren's syndrome which apparently was due to the presence of intermediate complexes that were formed by interactions between IgG and IgG rheumatoid factor (15,16).

A number of tests and techniques are available for diagnosis of Sjögren's syndrome. In Table 36 are shown the most commonly used ocular diagnostic techniques.

Table 36

OCULAR DIAGNOSTIC TECHNIQUES

Test	Technique and Result
Schirmer Test	Whatman #41 filter paper in inner canthus of the eye - suggestive if less than 5 mm wetting after 5 minutes.
Rose Bengal Staining and Slit Lamp Examination	Dye stains devitalized tissue
Lysozyme in Tears	Concentration is low
Immunoelectrophoresis of Tears	Absent ceruloplasmin Increased IgG
Lacrimal Biopsy	Lymphocytic infiltration

The Schirmer test, while not diagnostic, can serve as a screening method. Perhaps the best technique is use of rose bengal dye to stain devitalized tissue and examination with the slit lamp.

Diagnostic techniques employed in Sjögren's syndrome for salivary gland disorders are shown in Table 37.

Table 37

DIAGNOSTIC TECHNIQUES FOR SALIVARY GLAND DISORDERS

Test	Technique or Result
Salivary Flow Measurements	Normal 1.26 ml/15 min Sjögren's .03-.46 ml/15 min
Salivary $Beta_2$ Microglobulin	Increased in Sjogren's
Sialography	Injection of dye through catheter in the parotid or submandibular duct
Radioisotopic Studies	^{99m}Tc scintiscan of salivary glands
Lip Biopsy	Lymphocytic infiltration in minor salivary glands

The changes seen in sialograms during the filling phase have been divided into four stages (17). These are shown in Table 38.

Table 38

SIALOGRAM PATTERNS

1. Punctate

   Diffuse punctate dilatation of the peripheral ducts, with narrowing of the interlobular ducts. This is the earliest stage.

2. Globular

   Globules of contrast material increase in diameter but are uniform in distribution. Appearance is termed a "mulberry pattern" or appears as a branchless, fruit-laden tree. Seen in moderately advanced disease.

3. Cavitary

   Coalescence of globules, which are irregular, distorted, and decreased in number, with areas of cystic dilatation.

4. Destructive

   The pattern of the end stage is bizarre, with puddling and pooling.

from ref. (17)

Probably the best single diagnostic technique is the lip biopsy, since the minor salivary glands are commonly involved. In addition, this site is easily accessible, the biopsy is simple, bleeding is easily controlled, there is relatively little pain, and there is no noticeable scar.

REFERENCES (Sjögren's)

1. Shearn MA: Sjögren's Syndrome - Major Problems in Internal Medicine II. WB Saunders, Philadelphia, 1971.

2. Block KJ, Buchanan WW, Wohl MJ, Bunim JJ: Sjögren's Syndrome. Med 44:187-231, 1965.

3. Tannenbaum H, Pinkus GS, Anderson LG and Schur PH: Immunologic characterization of the mononuclear cell infiltrates in rheumatoid synovia, in rheumatoid nodules and in lip biopsies from patients with Sjögren's Syndrome. Arth Rheum 18:305-314, 1975.

4. Block KJ, Bunim JJ: Sjögren's syndrome and its relation to connective tissue disease. J Chron Dis 16:915-927, 1963.

5. Ellman P, Weber FP, Goodier TEW: A contribution to the pathology of Sjögren's disease. Quart J Med 20:33-42, 1951.

6. Szanto L, Farkas K, Gyulai E: On Sjögren's Disease. Rheumat 13:60-63, 1957.

7. Shioji R, Furuyama T, Onodera S, Soito H, Ito S and Sasaki Y: Sjögren's syndrome and renal tubular acidosis. Am J Med 48:456-463,1970.

8. Vanselow NA, Dodson VN, Angell DC, Duff IF: A clinical study of Sjögren's syndrome. Ann Int Med 58:124, 1963.

9. Heaton, A.M. Sjogren's Syndrome. Proc Roy Soc Med. 55:479-480, 1962

10. Cummings NA, Schall GL, Asofsky R, Anderson LG and Talal N: Sjögren's syndrome - newer aspects of research diagnoses and therapy. Ann Int Med 75:937-950, 1971.

11. Steinberg AD, Talal N: The coexistence of Sjögren's Syndrome and systemic lupus erythematosus. Ann Int Med 74:55-61, 1971.

12. Erlich JC, Greenberg G: Sicca Syndrome. Arch Int Med 93:731-741, 1954.

13. Beck JS, Anderson JR, Block KJ, Buchanan WW and Bunim JJ: Antinuclear and precipitating autoantibodies in Sjögren's Syndrome. Ann Rheum Dis 24:16-22, 1965.

14. Macsween RNM, Goudie RB, Anderson JR, Armstrong E, Murray MA, Mason DK, Jasani MK, Boyle JA, Buchanan WW and Williamson J: Occurence of antibody in salivary duct epithelium in Sjögren's disease, RA and other arthritides. A clinical and laboratory study. Ann Rheum Dis 26:402-411, 1967.

15. Alarcon-Segovia D, Fishbein E, Abruzzo JL and Heimer R: Serum hyperviscosity in Sjögren's syndrome. Interaction between serum IgG and IgG rheumatoid factor. Ann Int Med 80:35-43, 1974.

16. Blaylock WM, Waller M and Normansell DE: Sjögren's syndrome: Hyperviscosity and intermediate complexes. Ann Int Med 80:27-34, 1974.

17. Rubin P, Holt JF; Secretory sialography in diseases of the major salivary glands. Am J Roentgen 77:575-598, 1957.

J. *Skin*

Skin involvement in rheumatoid arthritis is nonspecific. Involvement can be categorized into three major entities: vasculitis, subcutaneous nodules and Raynaud's phenomenon (Table 39).

Table 39

SKIN INVOLVEMENT IN RHEUMATOID ARTHRITIS

A. Vasculitis	Vessels Involved
1. Digital infarcts	Small muscular arteries
2. Peripheral gangrene	Small muscular arteries
3. Hemorrhagic bullae and purpuric papules	Post capillary venules
4. Subcutaneous nodules and ulcers and livedo reticularis	Small and medium muscular arteries or veins
B. Subcutaneous rheumatoid nodules	
C. Raynaud's phenomenon	

from ref. (1)

Vasculitis may involve small muscular arteries, arterioles, venules, and capillaries (2). The lesions typically involve isolated segments of arterioles and small muscular arteries. Reactive changes range from proliferative to necrotizing and include intramural deposition of fibrinoid material and a mixed cellular infiltrate consisting primarily of lymphocytes.

In the more fulminant forms of rheumatoid disease large numbers of neutrophils or eosinophils, massive necrosis, thrombosis or aneurysm formation may be present but these findings are uncommon (2). When these changes are present, ischemia or hemorrhage may occur, producing myalgias, peripheral neuropathy, localized purpura and cutaneous ulceration. However, such changes may also be due to venular-capillary derangement (2).

The histological features of venulitis and capillaritis are similar to those seen in the arteries. It has been suggested that the initial histological defect in rheumatoid disease is rapid plasma leakage from dilated terminal venules and capillaries (2). The resulting interstitial accumulation of protein-rich exudate correlates with proliferation of connective tissue with resultant connective tissue necrosis.

According to Gilliam (1), Table 39, digital infarcts and peripheral gangrene are probably due to vasculitis of small muscular arteries, hemorrhagic bullae and purpuric papules are produced by damage to postcapillary venules and subcutaneous nodules, ulcers and livedo reticularis are due to involvement of small and medium muscular arteries and veins. Unusual plaques and papules resembling granuloma annulare (3) and lesions resembling pyoderma gangrenosum have also been described (4). Biopsy of the lesions in these cases showed necrotizing vasculitis or rheumatoid granulomas. Williams (5) has recently reported the occurrence of nodules on the palmar surfaces of the hands and fingers immediately following the development of 1 to 2 mm, slightly raised areas of cutaneous vasculitis. Initially, these areas are the size of a pencil point. They persist for two to three weeks and are then followed by the development of a 2 to 3 mm painful subcutaneous nodule. In some patients with extensive vasculitis, crops of as many as 10 to 20 such lesions may be seen within a 7- or 10-day period.

The incidence of clinical digital arteritis in rheumatoid arthritis has been reported as 34 to 36.5% in males (6,7) and 18 to 32.4% in females (6,7). Both studies showed that the incidence of arteritis varies in proportion to the number of times the patients are examined. The incidence rose from 4.2% at the first examination to 33.9% at the fourth examination.

These studies (7) also pointed out that a distinction should be made between nail fold lesions and splinter hemorrhages since splinter hemorrhages occur in other diseases and in the normal population (8,9). Nail fold lesions, however, occur only in adult rheumatoid arthritis patients (7). The incidence of nail fold lesions was 14.6% in males and 4.6% in females with an overall incidence of 7.9%.

Rheumatoid vasculitis tends to occur in patients with high titers of IgM rheumatoid factor (10-12). In fact, it seldom occurs in seronegative rheumatoid arthritis (11). It is associated with a decreased complement level in the blood (11). More recently it has been shown that IgG rheumatoid factor and low molecular weight IgM (7S IgM)are present in the blood in a large number of patients (13,14). For example, IgG rheumatoid factor was found in 67% of patients with vasculitis and in only 9% of patients without vasculitis. 7S IgM was found in 80% of patients with rheumatoid vasculitis and only 18% of patients without vasculitis (13).

Although they are probably of no clinical significance, dermo-epidermal immunoglobulin deposits staining primarily for IgM, C3 and fibrinogen have been noted in patients with rheumatoid arthritis (15,16). The presence of the deposits correlated with presence of serum cryoglobulins.

REFERENCES (Skin)

1. Gilliam JN: Personal communication.

2. Kulka JP: Vascular derangement in RA. Mod Trends in Rheumatology, Chapt. 4, Butteworths, 1966.

3. Baker RJ, Johnson WC and Burgoon CF: Unusual skin lesions of RA. Dermatologica 143:300-314, 1971.

4. Stalman LP, Rosenthal D, Yaworsky R and Horan F: Pyoderma Gangrenosum and RA. Arch Derm 111:1020-1023, 1975.

5. Williams RC: RA as a Systemic Disease. IV in Major Problems in Internal Medicine, WB Saunders, Philadelphia, 1974.

6. Golding JR, Hamilton MG and Gill RS: Arteritis of RA. Brit J Derm 77:207, 1965.

7. Dequeker J and Rosberg G: Digital capillaritis in RA. Acta Rheum Scand 13:299-307, 1967.

8. Dowling RH: Sub-ungual splinter haemorrhage. Postgrade Med J 40: 595, 1964.

9. Kilpatrick ZM, Greenberg PA and Sanford JP: Splinter hemorrhages - their clinical significance. Arch Int Med 115:730, 1965.

10. Schmid FR, Cooper NS, Ziff M and McEwen C: Arteritis in RA. Am J Med 30:56-83, 1961.

11. Mongan ES, Cass RM, Jacox RF, Vaughn JH: A study of the relation of seronegative and seropositive RA to each other and to necrotizing vasculitis. Am J Med 47:23-34, 1969.

12. Epstein WV, Engleman EP: The relation of the rheumatoid factor content of serum to clinical neurovascular manifestations of RA. Arth Rheum 2:250-258, 1959.

13. Thiofilopoulos AN, Burtonboy G, LoSpalluto JJ and Ziff M: IgG rheumatoid factor and low molecular weight IgM, an association with vasculitis. Arth Rheum 17:272-284, 1974.

14. Stage DE, Mannik M: γ M-globulin in RA. Evaluation of its clinical significance. Arth Rheum 14:440-450, 1971.

15. Donde R: Orthopaedic Review IV (12) p. 50, 1975 presented at 8th European Rheumatology Congress, Helsinki, Finland, 1975.

16. Baldassare A, Wiess T, Tsai C, Auclair R and Zuckner J: Immune complexes in the skin of patients with RA. Abs. 101, p. 74. Presented at 40th annual meeting Arth Fdn., June 9-11, 1976, Chicago.

K. *Circulating Immune Complexes and Serum Hyperviscosity Syndrome*

The presence of immune complexes during the course of rheumatoid arthritis has been demonstrated by studies of synovial tissue, synovial fluid and serum samples (1-11). These have been discussed in some detail in the section on Felty's syndrome.

The complexes of intermediate size (11S to 15S) are presumably produced by the combination of IgG with IgG rheumatoid factor (RF). This complex will fix complement as shown in Fig. 14.

Figure 14

$$IgG + IgG_{RF} + C'$$

$$\downarrow$$

$$IgG - IgG_{RF} - C'$$

from ref. (12)

These complexes then apparently can react with IgM RF to form IgG-IgM-C' complexes (see Fig. 15).

Figure 15

$$IgG - IgG_{RF} - C' + IgM_{RF}$$

$$\downarrow$$

$$IgG - IgG_{RF} - IgM_{RF}$$

$$|$$

$$C'$$

from ref. (12)

These complexes presumably are of 22S size by ultracentrifugation.

Jasin, LoSpalluto and Ziff (13) reported two patients with large quantities of intermediate IgG complexes and high titers of IgM rheumatoid factor present in the serum. The isolated intermediate complexes produced serum hyperviscosity when interacted with IgM rheumatoid factor *in vitro*. The rheumatoid hyperviscosity syndrome is uncommon and has been reported infrequently (14,15) although high serum viscosity has been reported in rheumatoid patients (16-18).

Clinical features seen in patients with the rheumatoid hyperviscosity syndrome are shown in Table 40.

Table 40

RHEUMATOID HYPERVISCOSITY SYNDROME

Nodular rheumatoid arthritis
Bleeding diathesis
Dyspnea and weakness
Palmar erythema
High titer of rheumatoid factor
Serum hyperviscosity

from ref. (13)

Cryoglobulinemia may also result from the precipitation of these rheumatoid factor - IgG complexes (19,20).

Very recent studies (21) have described the use of a very sensitive test for determination of both circulating and intra-articular immune complexes. This test involves a measure of immune complexes which bind to ^{125}I-Clq. Results demonstrated that the serum Clq binding activity (Clq-BA) in patients with rheumatoid arthritis and extra-articular disease manifestations (40±34% in those with IgM rheumatoid factor, 32±29% in those which were factor negative) was significantly increased as compared to the serum Clq-BA in patients with joint disease alone (24±30% in those with rheumatoid factor, 10±13% in those without).

The presence of circulating immune complexes correlates with many extra-articular manifestations of rheumatoid arthritis (see sections on vasculitis and Felty's syndrome).

REFERENCES (Circulating Immune Complexes)

1. Munthe E and Natvig JB: Characterization of IgG complexes in eluates from rheumatoid tissue. Clin Exp Immunol 8:249-262, 1971.

2. Kinsella TD, Baum J and Ziff M: Immunofluorescent demonstration of an IgG-B_1c complex in synovial lining of rheumatoid synovial membrane. Clin Exp Immunol 4:265-271, 1969.

3. Hannestad K: Presence of aggregated gamma globulin in certain rheumatoid synovial effusions. Clin Exp Immunol 2:511-529, 1967.

4. Winchester RJ, Agnello V and Kunkel HG: Gamma-globulin complexes in synovial fluids of patients with RA. Partial characterization and relationship to lowered complement levels. Clin Exp Immunol 6:689-706, 1970.

5. Winchester R,Kunkel HG and Agnello V: Occurrence of gamma globulin complexes in serum and joint fluid of RA patients: use of monoclonal rheumatoid factors as reagents for their demonstration. J Exp Med 134:286S-295S, 1971.

6. Franklin EC, Holman HR, Müller-Eberhard HJ and Kunkel HG: An unusual protein component of high molecular weight in the serum of certain patients with RA. J Exp Med 105:425-438, 1957.

7. Kunkel HG, Müller-Eberhard HJ, Fudenberg HH and Tomasi TB: Gamma-globulin complexes in RA and certain other conditions. J Clin Invest 40:117-129, 1961.

8. Chodirker WB and Tomasi TB: Low molecular weight rheumatoid factor J Clin Invest 42:876-884, 1963.

9. Schrokenloker RE: Characterization of the gamma globulin complexes present in certain sera having high titers of anti-gamma-globulin activity. J Clin Invest 45:501-512, 1966.

10. Hannestad K: Rheumatoid factors reacting with native gamma G-globulin and joint fluid gamma G-aggregates. Clin Exp Immunol 3:671-690, 1968.

11. Pope RM, Mannik M, Gilliland BC and Teller DC: The hyperviscosity syndrome in rheumatoid arthritis due to intermediate complexes formed by self-association of IgG-rheumatoid factors. Arth Rheum 18:97-106, 1975.

12. Ziff M: The nature of rheumatoid inflammation. International Colloquium on The Nature and Future of Rheumatic Disease, Nov., 1970 at Louvain.

13. Jasin HE, LoSpalluto J and Ziff M: Rheumatoid hyperviscosity syndrome. Am J Med 49:484-493, 1970.

14. Cowan IC, Harkness J: Plasma viscosity in rheumatic disease. Brit Med J 2:686, 1947.

15. Houston J, Whittington RB, Cowan IC, Harkness J: The plasma viscosity in pulmonary tuberculosis and rheumatic diseases. J.C.I. 21:752,1949.

16. Shearn MA, Epstein WV, Engleman EP: Serum viscosity in rheumatic diseases and macroglobulinemia. Arch Int Med 112:98, 1963.

17. Meltzer M, Franklin EC, Elias K, McCluskey RT, Cooper N: Cryoglobulinemia - a clinical and laboratory study. II. Cryoglobulins with rheumatoid factor activity. Am J Med 40:837, 1966.

18. Hollingsworth JW: Local and systemic complications of RA. WB Saunders Co., p. 97, Philadelophia, 1968.

19. Grey JD and Kunkel HG: Amino acid sequence similarities in 2 human anti-gamma-globulin antibodies. Proc Nat Acad Sci 67:87-92, 1970.

20. Meltzer M and Franklin EC: Cryoglobulinemia: a study of 29 patients. Am J Med 40:828-836, 1966.

21. Zubler RH, Nydegger U, Perrin LH, Fehr K, McCormick J, Lambert PH and Miescher PA: Circulating and intra-articular immune complexes in patients with RA. Correlation of ^{125}I-Clq binding activity with clinical and biological features of the disease. J Clin Invest 57:1308, 1976.

L. *Bones*

There are no specific bone lesions associated with rheumatoid arthritis. However, the features listed in Table 41 have been described in these patients.

Table 41

BONE INVOLVEMENT IN RHEUMATOID ARTHRITIS

Osteoporosis

Rib Erosions

Granulomatous Lesions

Geodes

Osteoporosis in rheumatoid patients is by far the most common type of bone involvement. It occurs in patients who have never received corticosteroids as well as in, of course, those patients who do (1). The causes are probably multiple, with contributions from generalized malnutrition, immobilization due to the disease, loss of anabolic effects of androgens and estrogens in patients of older age groups, and possibly, excessive generalized protein catabolism brought about by the disease process (2,3).

The major clinical manifestation of osteoporosis is fracture, either occurring spontaneously or in association with minimal trauma. Most of these fractures involve the collapse of the dorsal or lumbar vertebrae. Other less common sites are the ribs, hips, femurs, tibia and humeri (3). The pain of such fractures may simulate a flare-up of the rheumatoid arthritis or an acute gouty attack (2).

A very interesting and unusual manifestation of rheumatoid arthritis is that of rib erosions. They consist of a localized notch or a more diffuse erosion involving the outer aspects of the second to the sixth ribs, at or just beyond the angle of the rib (4,5). The erosions were more easily seen on x-rays of the shoulder than by routine chest film. Clinically, the patients are quite disabled, with stiff shoulders and a dorsal kyphosis. It is believed that the erosions result from pressure from the fixed scapulae and frequently were associated with an overlying acquired bursa.

Subchondral granulomatous lesions that appear as cystic or lytic areas on roentgenograms are frequent findings in rheumatoid patients (6,7). In one case report (8) a lytic lesion developed in the right femoral neck and head. Because of the location and size of the lesion and the rapid development of pain in the absence of typical symptoms of rheumatoid arthritis in that joint, a malignant tumor was suspected. However, histological examination showed it to be a rheumatoid granulomatous lesion.

The geologists' term geode has been used to describe the radiological appearance of cavities in the bone ends in patients with various forms of arthritis. They have been reported in patients with rheumatoid arthritis (7). Jayson and coworkers (9,10) have shown that use of a swollen joint produces a high intra-articular pressure which, in patients whose articular surfaces have been eroded and weakened by disease, could lead to extrusion of the joint contents into the bone ends. At some subsequent time the communication between the knee and geode then closed and was obliterated by the dense fibrous tissue. Occasionally, as the geode contents become static, calcium aggregates within its center, producing a large central radio-opaque mass. In this particular case calcified geodes were present in the upper end of the left tibia and in the right lateral femoral condyle.

REFERENCES (Bone)

1. Bjelle AO and Nilsson BE: Osteoporosis in RA. Calc Tiss Res 5:327-332, 1970.

2. Hart DF: Complicated rheumatoid disease. Brit Med J 16 July, p. 131-135, 1966.

3. Hollingsworth JW: Local and systemic complications of RA. Chapt. 16, p. 74, WB Saunders Co., Philadelphia, 1968.

4. Park W, Ward D, Ball J and Bane A: Rheumatoid disease and rib defects. Ann Rheum Dis 30:466-475, 1971.

5. Anderson IF, Corrigan AB, Champion GD: Rib erosions in RA. Ann Rheum Dis 31:16-21, 1972.

6. Baggenstoss AH, Bickel WH and Ward LE: Rheumatoid granulomatous nodules as a destructive lesion of vertebrae. J Bone & Joint Surg 34A:601-609, 1952.

7. Cruickshank B, Macleod JG and Shearer WS: Subarticular pseudocysts in RA. J Fac Radiologists 5:218-226, 1954.

8. Hunder GG, Ward LE and Ivins JC: Rheumatoid granulomatous lesinn simulating malignancy in the head and neck of the femur. Mayo Clin Proc 40:766-70, 1965.

9. Jayson MIV, Dixon A.St.J and Yeoman P: Unusual geodes ('bone cysts') in RA. Ann Rheum Dis 31:174-178, 1972.

10. Jayson MIV, Rubenstein D and Dixon A.St.J: Intra-articular pressure and rheumatoid geodes ('bone cysts'). Ann Rheum Dis 29:496, 1970.

M. *Hematologic*

The most common hematologic abnormalities seen in patients with rheumatoid arthritis are shown in Table 42.

Table 42

HEMATOLOGIC ABNORMALITIES IN

RHEUMATOID ARTHRITIS

Anemia

Eosinophilia

Felty's Syndrome

Anemia is very common in patients with rheumatoid arthritis. The types of anemia which may be seen are shown in Table 43.

Table 43

TYPES OF ANEMIA IN

RHEUMATOID ARTHRITIS

Normocytic hypochromic

Megaloblastic

Sideroblastic

By far the most important type of anemia is the normocytic hypochromic form. Approximately 65% of women and 45% of men with rheumatoid arthritis have this type of anemia (1). The hemoglobin concentration correlates well with activity of the disease and the erythrocyte sedimentation rate (ESR) although there is no correlation with duration of the arthritis (2). The plasma iron level is low and there is no increase in plasma iron binding capacity (3). In one series the mean hemoglobin concentration was 11.7 gm per 100 ml in patients as compared with 14.9 gm per 100 ml in controls. The mean hematocrit level was 38.2 per cent for patients and 43.1 per cent for controls (4).

The mechanisms involved in the pathogenesis of this type of anemia have been quite extensively studied. Some of the demonstrated abnormalities are shown in Table 44.

Table 44

PATHOGENESIS OF NORMOCYTIC ANEMIA

IN RHEUMATOID ARTHRITIS

Iron absorption normal or slightly decreased

Bone marrow iron deposits variable but mostly normal

Synovial iron deposits markedly increased

Small increase in plasma volume and hemodilution (primarily in Felty's syndrome)

Blood loss from salicylates and other anti-inflammatory agents

Failure of bone marrow to increase erythrocyte production

Results of one study of the bone marrow iron content of rheumatoid patients are shown in Table 45.

Table 45

IRON CONTENT OF BONE MARROW IN IRON-DEFICIENCY ANEMIA, RHEUMATOID ARTHRITIS, AND NORMAL SUBJECTS

Diagnosis	Iron Content (μg/100 mg protein±ISD)
Normal	86±34 (16)
Rheumatoid arthritis	55±30 (53)
Iron-deficiency anemia	12±5 (6)

Number of observations in parentheses from ref. (5)

In a histological study of 100 synovial membranes by Muirden (6), iron deposits were seen in 96. Some were quite extensive. Electron microscopic examination revealed ferritin within synovial cell cytoplasm and concentrated into lysosomes in 16 of 20 biopsies. He suggested that the iron deposits arose from continued oozing of blood from the vascular granulation tissue into the synovial cavity. In fact, the sequence from erythrophagocytosis to ferritin formation could be followed with the electron microscope. He also showed data suggesting that iron given as parenteral therapy found its way into synovial macrophages. A highly significant relationship was found between the presence of anemia due to rheumatoid arthritis and the extent of iron deposits in the synovium. He also

found a relationship between the duration of disease in the joint, the grade of x-ray change and the iron deposits.

He concluded that the synovial membrane is an important source of iron sequestration and that a delay in release of iron from this and the reticuloendothelial storage sites could explain many of the features of the anemia of rheumatoid arthritis.

A small increase in plasma volume with hemodilution occurs in a small number of patients, particularly in those with Felty's syndrome with a large spleen (7,8). The average spleen in rheumatoid patients has been found to be increased twofold in size and weight (9).

Daily blood loss of up to 4 ml per day may occur in patients taking salicylates (10). However, this is only enough blood loss to produce anemia in menstruating women with marginal iron stores (1). There is no evidence to suggest that continued salicylate therapy enhances the degree of anemia in patients with rheumatoid arthritis (11).

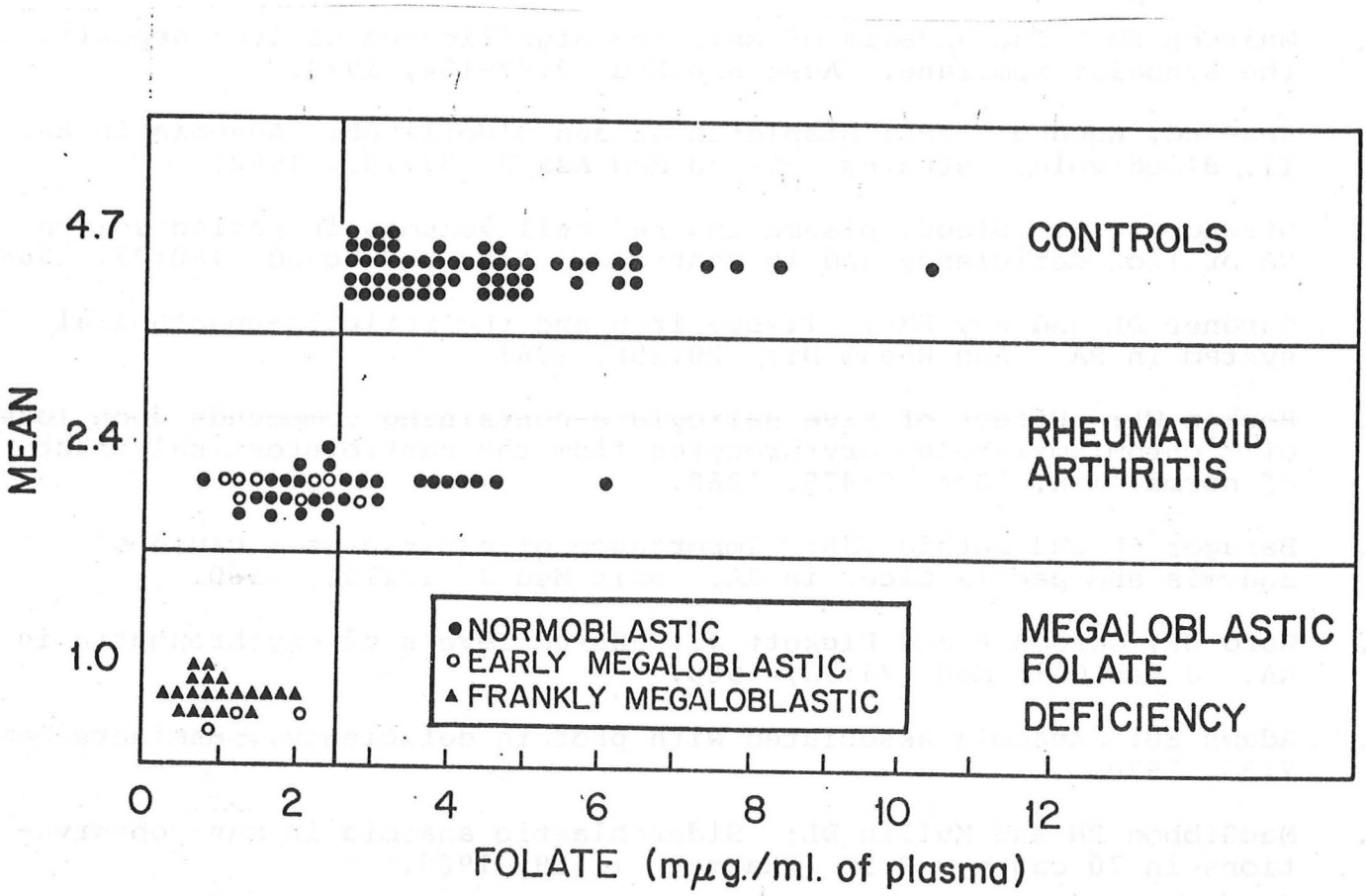
Only slightly increased levels of erythropoietin have been found in rheumatoid patients (12). Why erythropoietin production is not more strikingly increased is not known. Another possible mechanism is that rheumatoid patients commonly have low serum albumin levels. A low serum albumin contributes to a diminished production of erythrocytes and prevents correction of anemia even in the presence of adequate iron (13).

Megaloblastic anemia has been reported in rheumatoid patients but the incidence may be increased only with folate deficiency and not with vitamin B_{12} deficiency (1). The low folate levels seen in patients with rheumatoid arthritis are shown in Fig. 16.

Secondary sideroblastic anemia occurs rarely in patients with rheumatoid arthritis and has been due to pyridoxine or folate deficiency (14).

Eosinophilia ranging from 20% to 89% has been reported in patients with severe deforming articular disease and a high prevalence of rheumatoid vasculitis, pleuritis and subcutaneous nodules (15-17). The cause of the eosinophilia is unknown.

Felty's syndrome has been discussed in detail under a separation section.



from ref. (1)

Figure 16

REFERENCES (Hematologic)

1. Mowat AC: Hematologic abnormalities in RA. Sem in Arth Rheum 1:195-219, 1971.

2. Engstedt L and Strandberg O: Haematological data and clinical activity of the rheumatoid disease. Acta Med Scand 180:13, 1966.

3. Roy LMH, Alexander WRM and Duthie JJR: Nature of anaemia in RA. I. Metabolism of iron. Ann Rheum Dis 14:63, 1955.

4. Freireich EJ, Ross JF, Bayles TB, Emerson P and Finch SC: Radioactive iron metabolism and erythrocyte survival studies of the mechanisms of the anemia associated with RA. J Clin Invest 36:1043, 1957.

5. Kerr LMH: A method for the determination of non-haem iron in bone marrow. Biochem J 67:627, 1957.

6. Muirden KD: The anaemia of RA: The significance of iron deposits in the synovial membrane. Aust Ann Med 2:97-104, 1970.

7. Read HC, Woodbury JPL, Stapleton JE and O'Neill AB: Anaemia in RA. II. Blood volume studies. Canad Med Ass J 87:781, 1962.

8. Strandberg O: Blood, plasma and red cell volumes in patients with RA or iron deficiency and in controls. Acta Med Scand 180:73, 1966.

9. Gardner DL and Roy LMH: Tissue iron and the reticulo-endothelial system in RA. Ann Rheum Dis 20:258, 1961.

10. Becken WL: Effect of five salicylate-containing compounds upon loss of ^{5}'chromium-labeled erythrocytes from the gastrointestinal tract of normal man. Gut 9:475, 1968.

11. Barager FD and Duthie JJR: Importance of aspirin as a cause of anaemia and peptic ulcer in RA. Brit Med J 1:1106, 1960.

12. Ward HP, Gordon B and Pickett JC: Serum levels of erythropoetin in RA. J Lab Clin Med 74:93, 1960.

13. Adams EB: Anaemia associated with protein deficiency. Seminars Hemat 7:55, 1970.

14. MacGibbon BH and Mullin DL: Sideroblastic anaemia in man; observations in 70 cases. Brit J Haemat 11:59, 1965.

15. Panush RS, Franco AE and Schur PH: RA associated with eosinophilia. Ann Int Med 75:199-205, 1971.

16. Portner MM and Gracie WA: Rheumatoid lung disease with cavitary nodules, pneumothorax and eosinophilia. New Eng J Med 275:697-700, 1966.

17. Sylvester RA, Pinals RS: Eosinophilia in RA. Ann Allerg 28:565-568, 1970.

N. *Gastrointestinal and Liver*

No specific gastrointestinal lesions associated with the rheumatoid process have been described except possibly arteritis of the bowel and of other intra-abdominal structures. Involvement of small arteries can cause multiple ischemic ulcers of the intestine, which usually cause severe hemorrhage and may perforate (1). Involvement of larger arteries may cause segmental or extensive bowel gangrene or intraperitoneal hemorrhage (2). Acute arteritis may occur in hepatic, cystic, pancreatic, renal arteries and in vessels of the peritoneum (1). Perisplenitis and splenic infarcts may cause left hypochondrial pain in theumatoid patients (3). Thus in a rheumatoid patient, necrotizing arteritis should be considered in any patient with an acute abdomen.

In a few reports, malabsorption syndrome has been documented (4,5).

In these cases there was very little histologic evidence of villous atrophy of the small bowel.

In some patients, primary amyloid involvement within the gastrointestinal tract has resulted in infarction and perforation (6).

Most gastrointestinal disease in patients with rheumatoid arthritis is related to the various anti-inflammatory or immunosuppressive agents which are used as treatment.

In one instance (7), chronic ulceration of the ascending colon occurred in a 57 year old woman treated with steroids for her rheumatoid arthritis. It was suggested that both the steroids and vasculitis-induced ischemia may have been etiologically important.

Liver involvement is almost never seen in patients with pure rheumatoid arthritis. Most liver involvement is associated with either Felty's or Sjögren's syndrome or some type of overlap syndrome and includes a few isolated cases of primary biliary cirrhosis or chronic aggressive hepatitis (8).

REFERENCES (Gastro & Liver)

1. Lindsay MK, Tavadia HB, Whyte AS, Lee P and Webb J: Acute abdomen in RA due to necrotizing arteritis. Brit Med J 2:592-593, 1973.

2. Adler RH, Norcross BM and Lockie M: Arthritis and infarction of the intestine in RA. JAMA 180:922, 1962.

3. Sinclair RJG and Cruickshank B: A clinical and pathological study of 16 cases of RA with extensive visceral involvement ('Rheumatoid Disease'). Quart J Med 25:313, 1956.

4. Pettersson T, Wegelins D and Shrifvars B: Gastrointestinal disturbances in patients with severe RA. Acta Med Scand 188:139-144, 1970.

5. Dyer NH, Kendall MJ and Hawkins CF: Malabsorption in rheumatoid disease. Ann Rheum Dis 30:626-630, 1971.

6. Akbarian M and Fenton J: Perforation of a small bowel in amyloidosis. Arch Int Med 114:815-821, 1964.

7. McMahon MJ and Harse J: Ulceration of the colon associated with RA and steroid treatment: report of a case. Dis Col and Rect 27:94-97, 1974.

8. Ellman MH, Weis MJ and Spellberg MA: Liver disease in RA. Am J Gastro 62:46-53, 1974.

O. *Miscellaneous*

1) Psychiatric Manifestations

According to Wolff (1) the four major questions concerning psychiatric traits in patients with rheumatoid arthritis are (1) whether the majority of rheumatoid patients evidence some common and typical personality and

psychosocial characteristics, (2) whether such characteristics are specific for rheumatoid arthritis, (3) whether these characteristics are secondary to the physical disease and (4) what the mechanism is whereby these behavioral factors precipitate or influence the physical disease.

In answering these questions on the basis of many studies Wolff (1) has concluded with respect to the above questions that (1) many, but not all, rheumatoid patients demonstrate some common personality characteristics, such as neurotic response patterns, especially depression, over concern with bodily functions, rigidity, dependency, emotional instability, low ego-strength and feelings of guilt. Thus the answer to the first question is in the affirmative. (2) These personality characteristics are not, however, specific for rheumatoid arthritis since they are observed in other disease groups. The answer, therefore, to the second question is negative. (3) These characteristics are associated with the physical condition and symptoms and are thus most likely secondary to the disease processes. Thus the concept of a "rheumatoid personality" appears to be unwarranted. (4) Pain, disability and generalized malaise are the triggering mechanisms for the behavioral changes.

Not all studies agree with the above ideas, however. In a recent study (2), when 50 patients with rheumatoid arthritis were compared with 32 patients with other chronic painful non-inflammatory skeletal diseases (osteoarthritis, chronic backache and/or sciatica), it was found that there was a significant excess of mood disturbance and depressive reactions among the patients with rheumatoid arthritis. No correlation with age, sex, duration of disease, disability grading, disease severity or steroid therapy was seen. Hospitalization had a beneficial effect on the depressed patients with rheumatoid arthritis.

Two other studies (3,4) support the conclusions made by Wolff (1). These studies revealed tendencies in rheumatoid patients to low ego strength, anxiety and dependency and that they differed significantly in personality from normal and neurotic people. However, they found that the differences were accentuated with chronicity in the rheumatoid process, and concluded that the differences develop as a result of the arthritis.

A significant relationship was also found between the patients' personalities and the dependency upon oral corticosteroid drugs. In comparison with those who had never received oral corticosteroids, those who had received such drugs were found to be less persevering, more depressed, complaintive and demanding, more dependent and easily upset (3). These authors concluded that the use of oral corticosteroids might be contingent upon the psychologic rather than the specific rheumatological needs of the rheumatoid patient.

REFERENCES (Psychiatric)

1. Wolff BB: Current psychosocial concepts in RA. Bull Rheum Dis 22: 656-660, 1971-1972 series.

2. Zaphiropoulos G and Burry HC: Depression in rheumatoid disease. Ann Rheum Dis 33:132-135, 1974.

3. Moldofsky H and Rothman AI: Personality, disease parameters and medication in RA. J Chron Dis 24:363-372, 1971.

4. Ward DJ: Rheumatoid arthritis and personality: a controlled study. Brit Med J 2:297-299, 1971.

2) Amyloidosis

The disease underlying most cases of secondary amyloidosis is now rheumatoid arthritis (1). The incidence of amyloid in rheumatoid patients varies considerably in various studies as shown in Table 46.

Table 46

INCIDENCE OF AMYLOIDOSIS IN

RHEUMATOID ARTHRITIS

No. RA Patients	% with Amyloid	Ref.
181*	14	(2)
28	61	(3)
289	29	(4)
115**	5	(5)

* Postmortem series
** Diagnosis made by rectal biopsy

Although there is much individual variation, clinical evidence of amyloidosis usually appears several years after the onset of rheumatoid arthritis and the diagnosis is seldom made during the first 2 years of the disease (6). In one study it occurred at a mean of 16 years (one to 41 years) after the onset of arthritis (7).

Many organs can be involved. Renal involvement causes the most common as well as the most serious symptoms. One of the most frequent clinical findings is proteinuria which may be severe enough to cause the nephrotic syndrome. Gastrointestinal amyloidosis may cause bleeding or malabsorption (7-9). Enlargement of the liver or spleen may also occur. Other sites which may contain amyloid include the gingiva, rectum, lymph nodes, bone marrow, skin, endometrium, adrenals, thyroid, parathyroids, pituitary, heart, lungs and urinary bladder (10). The survival time after diagnosis of amyloid in rheumatoid patients was up to 8 years in one study (11).

The diagnosis is best made by biopsy. Sites which are well recognized as suitable for the biopsy diagnosis include the gingiva, liver, kidney and rectum. Of these, the rectum is probably the best site. In known cases of amyloidosis, from 70-75% of rectal biopsies were positive in one study (12). It is a simple procedure causing little discomfort to the patient and almost devoid of danger (10).

Since generalized amyloidosis almost always kills by renal involvement, biopsy of the kidney is also of much value (10). In a study by Blum and Sohar (12), 21 of 24 renal biopsies (87.5%) in proven cases of amyloidosis contained amyloid. In contrast, in the same studies only 13 of 27 (48%) liver biopsies and 6 of 32 (19%) gingival biopsies were positive for amyloid. One possible reason for the decreased yield by liver biopsy is that the amyloid deposits in the liver are commonly restricted to the periportal vessels and these regions may not be represented in small needle biopsy specimens (10).

The pathologic diagnosis is made by use of the methods of Congo Red staining or methyl violet metachromasia. In addition, amyloid fluoresces when stained with Thioflavine T. By examination of Congo Red stained sections with the polarizing microscope, one can see green bifringent material. Finally, amyloid fibrils are quite characteristic by electron microscopy.

REFERENCES (Amyloidosis)

1. Husby G: Amyloidosis in rheumatoid arthritis. Ann Clin Res 7:154-167, 1975.

2. Missen GAK and Tailor JD: Amyloidases in RA. J Path Bact 71:179, 1956.

3. Teilum G, Lindahl A: Frequency and significance of amyloid changes in rheumatoid arthritis. Acta Med Scand 49:540, 1954.

4. Laine V, Vainio K, Ritamaa VV: Occurrence of amyloid in rheumatoid arthritis. Acta Rheum Scand 1:43, 1955.

5. Arapakis G, Tribe CR: Amyloidosis in rheumatoid arthritis investigated by means of rectal biopsy. Ann Rheum Dis 22:256, 1963.

6. Calkins E, Cohen AS: Amyloidosis: Arthritis and Allied Conditions. p. 1283, ed. JL Hollander and DJ McCarthy, Lea & Febiger, Philadelphia, 1972.

7. Cohen AS: Amyloidosis associated with rheumatoid arthritis. Med Clin N Am 52:643, 1968.

8. Petterson T, Wegelius O: Biopsy diagnosis of amyloidosis in RA. Gastroenterology 62:22, 1972.

9. Lobe B and Andrews G: Rheumatoid arthritis with secondary amyloidosis and malabsorption syndrome. Effect of D-Penicillamine. Am J Med 44:105-116, 1968.

10. Tribe CR: Amyloidosis in RA. p. 121-138, Mod. trends in Rheumatology, Butterworths, 1966.

11. Brandt K, Cathcart ES, Cohen AS: A clinical analysis of the course and prognosis of 42 patients with amyloidosis. Am J Med 44:955, 1968.

12. Blum A and Sohar E: The diagnosis of amyloidosis - ancillary procedures. Lancet 1:721, 1962.

3) Laryngeal

Crico-arytenoid joint disease due to the rheumatoid process may cause pain or difficulty with swallowing, hoarseness, dyspnea and a feeling of fullness in the throat. Stridor may also be present. If the joints become immobilized the vocal cords may be adducted to the midline, producing a marked impairment in airway diameter. Superimposed respiratory infection can cause life-threatening airway obstruction due to laryngeal and cord edema (1).

The possible presence of compromised cricoarytenoid motion should be borne in mind when intubation is needed in a patient with rheumatoid arthritis (1). Arytenoidectomy may rarely be necessary for treatment of this condition.

REFERENCES (Laryngeal)

1. Decker J: in Arthritis and Allied Conditions. Hollander JL and McCarty DJ Jr, Eds., Lea and Febiger, Philadelphia, 8th ed., p. 347.

III. SUMMARY

It is readily apparent that rheumatoid arthritis is not confined to the joint. There is an extraordinary range of systemic manifestations associated with this disease. Most of these manifestations can be attributed to a few basic disease processes e.g. joint involvement in an unusual location such as involvement of the odontoid process or crico-arytenoid joints; rheumatoid nodules in unusual locations such as the eye, lungs, heart etc; and production of immune complexes with resultant vasculitis in many different sites. In Sjögren's syndrome there is an intensive lymphocytic infiltration of all tissues. Amyloidosis is presumably related to the deposition of immunoglobulin molecules. Thus the manifestations are many and varied.

It should be borne in mind that while death due solely to rheumatoid arthritis is rare, it may occur in patients with extra-articular manifestations. Thus, extra-articular features merit greater attention than they are generally given when considering patients with rheumatoid disease, since they appear to have an important bearing on mortality.