MEDICAL GRAND ROUNDS

Parkland Memorial Hospital
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CURRENT CONCEPTS OF RHEUMATOID ARTHRITIS

"If rheumatoid arthritis is a parasitic disease, susceptibility must be extremely variable or it must be a relatively rare manifestation of some common disease." --Walter Bauer, 1951.

Case I. [redacted]. This 23 WM [redacted] was referred to the Arthritis Clinic by his private physician for further evaluation of a persistent migratory polyarthritis of 9 months' duration beginning [redacted] 1960. ESR during that time had averaged 25 mm/hr, and ASO titer, latex fixation and LE tests had been negative. He gave a past history of promiscuous premarital sexual activity involving 30 to 40 partners, and of a penicillin-resistant urethritis lasting 2 weeks at age 18. At the onset of arthritis, no urethritis or conjunctivitis were present, but about one year after polyarthritis began, he again experienced two episodes of penicillin-resistant urethritis and associated balanitis. His wife experienced repeated attacks of severe pelvic inflammatory disease resistant to penicillin and eventually required hysterectomy and salpingoophorectomy.

At the time of his initial Arthritis Clinic work-up, his primary complaint was pain in both heels, made worse by weight-bearing, but x-rays showed no spur formation or other abnormalities. Wrists, elbows, shoulders, knees and ankles were painful on motion and showed mild swelling. ESR 18, Latex fixation, sensitized sheep cell agglutination, antinuclear tests were negative, uric acid 2.6 mg% and A/G ratio 4.7/2.1.

He was treated with 3.6 g. of aspirin daily with poor response, and in [redacted], 1961, 300 mg of phenylbutazone daily begun. This had to be withdrawn 6 weeks later because of peptic ulcer-like epigastric pain. Reinstitution 2 weeks later was associated with a prompt recurrence of similar symptoms which were unrelieved by antacids. Because arthritis persisted, he was given a course of gold thiomalate from [redacted] 1961 to [redacted] 1962 with a total dosage of 950 mg. In spite of apparent improvement, gold had to be withdrawn because of the appearance of a skin rash over the abdomen and anterior chest. At this time his diagnosis varied between rheumatoid arthritis and an atypical Reiter's syndrome, and he returned to work, became financially overscaled for the Clinic, and was referred back to his private physician.

However, in [redacted] 1962, he returned having been unemployed for several months because of recurrent arthritis. Painful swelling of both ankles, the right knee and the left elbow were present. Repeat latex fixation showed 1+ positive with a neg. SSCA and ESR 29. Tap of the swollen elbow produced 20 ml. of turbid, yellow, watery synovial fluid containing 15,000 WBC/mm^3, 90% polys. A latex fixation test

on the synovial fluid was 3+ (compared to 1+ for the serum), and a control synovial fluid from a patient with degenerative joint disease gave a negative latex fixation test.

He has been subsequently treated with an increase in aspirin to 4.8 g. daily and intra-articular Depomedral, 40 mg, with dramatic response. His most likely diagnosis would now appear to be mild chronic rheumatoid arthritis.

Case II. [redacted]. This 47 WF was first seen [redacted]-61, with a history of chronic polyarthritis particularly involving her knees and shoulders for 7 years. She gave no family history of arthritis and had been on aspirin and 15 to 20 mg of prednisone for the previous 5 years. She was intermittently confined to a wheelchair because of flareups. On examination, there was "4+ swelling of the left knee with 30° flexion contracture and a painful swollen right ankle; effusions present in both wrists and elbows." ESR 100, A/G ratio 4.2/2.6, uric acid 3.5 mg%, L.E. preps and latex fixation neg., SSCA 1:28. She responded somewhat to intra-articular steroid administered by a Hypospray injector, but benefit was transient. [redacted] 1961, she was begun on daily 200 mg of phenylbutazone, but this had to be withdrawn 3 weeks later due to the appearance of a skin rash.

Because of the persistent pain and swelling of the left knee, a surgical synovectomy was performed on [redacted]-61, and synovial pannus measuring 6x4x2 cm removed. This showed proliferation of the endothelial synovial cells, marked fibrosis, and a large amount of granulation tissue. Post-operatively, the patient had a progressive increase in range of motion of the operated joint, and complete loss of pain. Since that time she has experienced variable remissions and exacerbations of arthritis activity, but the left knee has been essentially free of involvement. Follow-up [redacted]-63 and [redacted]-64 have shown continued full range of motion, and lack of pain in the left knee although other joints have shown active arthritis, and ESR has remained in the 50's.

SYNOVECTOMY IN RHEUMATOID ARTHRITIS

Results on 19 patients, Parkland Memorial Hospital 1961-1964

	Average	Range
Age	47	16-65
Duration of RA (yrs.)	9	1½-25
SSCA titer (dil.)	sl.>112	neg-448
Follow-up period	15 mo.	2-42 mo.
Sex	16 females, 3 males	
Results		
Worse	2	
Unchanged	8	
Much improved	9	

FEATURES OF RHEUMATOID ARTHRITIS

1. Rheumatoid arthritis is a very common disease, twice as frequent in females, which does not shorten the life-span in most cases.

Table 1. Prevalence rates for rheumatoid arthritis Tecumseh, Michigan (Ref. 4)

Diagnostic Category	Males	Females	Both Sexes
	3511	3696	7207
"Definite"	0.20%	0.57%	0.39%
"Probable"	0.26%	1.41%	0.85%
"Possible"	1.71%	2.89%	2.32%
"Questionable"	1.28%	2.54%	1.93%
Total, all categories	3.45%	7.41%	5.48%

2. Although rheumatoid arthritis in isolated instances may show abnormal aggregation in families, recent studies have indicated a random, non-genetic distribution in the general population.

A. Bunim, Burch and O'Brien studied 86% of all Blackfeet and Pima Indians residing on their respective reservations (Ref. 6)

Table 2. Prevalence of rheumatoid factor and rheumatoid arthritis in relatives of probands and in a random sample

	Probands			1° Relatives		
Group	R.F.	R.A.	Number	Number	Pos. R.F.	Rheumatoid Arthritis
A	Pos	Yes	22	71	1(1.4%)	2(2.8%)
B	Pos	No	34	77	4(5.2%)	3(3.9%)
C	Neg	Yes	20	63	4(6.3%)	2(3.2%)
D	Neg	No	55	179	5(2.8%)	5(2.8%)
Matched Controls				211	12(5.6%)	9(4.3%)

B. Moesmann (Ref. 7) and Meyerowitz and Jacox (Ref. 8) have collected monozygotic twins and observed a discordant distribution of rheumatoid arthritis compatible with a non-genetic etiology.

C. Bunim and his coworkers (Ref. 6) have pointed to a statistical selection error known as faulty ascertainment as a possible explanation for the apparent increased incidence of rheumatoid arthritis in families of patients with the disease described by previous investigators. Thus, because each clinic draws from a limited closed population, any family in that population with several arthritic members is more likely to be picked up by a family study than families with only one involved member.

3. Multiple organ systems are involved in severe rheumatoid arthritis with nodule formation, peripheral neuropathy, etc. However, the most characteristic clinical features of the disease result from involvement of the joints.

A. Synovitis in chronic cases shows proliferation of the "A" cells (phagocytic, macrophage-type cells) with thickening of the synovial lining layer. There is a lesser increase in "B" cells (synthesis cells which probably make synovial fluid) and mixed cell types. Lymphocytes and plasma cells heavily infiltrate the connective tissue underlying the synovial cell layer, often with the formation of follicles and aggregates resembling stimulated lymph nodes making antibodies. The synovial cell types in rheumatoid arthritis have been carefully studied by Norton and Ziff (Ref. 9) by electron microscopy.

B. Synovial fluid effusions in acute and chronically active joints are observed in all types of active inflammatory arthritis, and should be examined whenever possible as a valuable aid in differential diagnosis.

Table 3. Synovianalysis in Arthritis (modified from Ropes, Ref. 23)

	Appearance	Viscosity	WBC	Hyaluronic acid (Mucin) Clot	γ-Globulin Content	Unusual Features
Normal	Straw, clear	high	60-200 lymphs	good	low	
Degenerative Joint Dis. (Osteoarthr.)	Yellow, clear	high	1000 20% polys	good	low	Cartilage fibrils occ. seen
Rheumatic Fever	Yellow, sl. cloudy	low	10,000 50% polys	good	sl. up	
Systemic Lupus Erythemato.	Straw, sl. cloudy	high	5,000 10% polys	good	sl. up	
Gout	Yellow to milky	low	12,000 60% polys	poor	sl. up	Urate crystals often in polys
Chondrocalcinosis (Pseudogout)	Yellow to milky	low	12,000 60% polys	poor	sl. up	Calcium pyrophosphate crystals
Rheumatoid Arthritis	Yellow to greenish	low	15,000 65-90% polys	poor	high	γ-Globulin inclusions in polys ("glitter bodies")
Tuberculous Arthritis	Yellow, cloudy	low	25,000 50-60% polys	poor	high	Acid fast bacteria
Other Septic Arthritis	Grayish or bloody, turbid	low	80,000 90% polys	poor	high	Bacteria present

4. Often no one therapeutic approach is uniformly successful in controlling active arthritis. Even after aspirin, phenylbutazone, gold and intermittent intra-articular steroids (tried successively and/or concurrently, in that order), joints often persist which remain painful, and retain inflammation producing chronic destructive changes. Recently the application of orthopedic surgical procedures, particularly synovectomy (Ref. 27), have produced encouraging results in selected rheumatoid arthritic patients.

Table 4. Synovectomy in Rheumatoid Arthritis (Paradies & Gregory)

Indications

1. Lack of response to maximum medical therapy with persistent effusions, synovial thickening, and pain.
2. Residue of reasonable range of motion in joint.
3. Adult patient, usually with large joint involvement.

Objectives

1. Prevention of chronic destructive changes in joint.
2. Relief of flare-ups, particularly persistent pain.
3. Permit physical rehabilitation of patient.

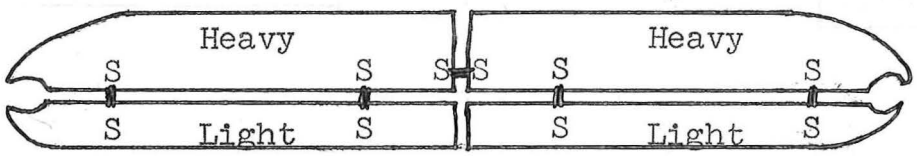
5. Much evidence suggests an immunological etiology for rheumatoid arthritis.

A. Sixty to 95% of patients with the disease have in common with patients with a number of chronic infectious diseases (syphilis, tuberculosis, leprosy, subacute bacterial endocarditis, chronic viral hepatitis) circulating anti γ_2-globulin antibodies of γ_{1M} type known as "rheumatoid factors."

Table 5. Relationships of the immunoglobulins of man

Globulin Type	Molecular Weight	Characteristics
γ_2	160,000	Most viral and bacterial antibodies
γ_{1A}	160,000 plus	Includes allergens
γ_{1M}	1,000,000	Primative antibodies to ? all antigens, isoagglutinins. Rheumatoid factors

All types share common light chains.
Each type has an immunologically different heavy chain.



B. Ten to 44% of patients with rheumatoid arthritis share in common with patients with other "collagen diseases" (SLE, scleroderma, polymyositis, polyarteritis nodosa) a definite incidence of antinuclear factors, including positive L.E. tests, which represent antibodies against nucleic acids or nucleoproteins.

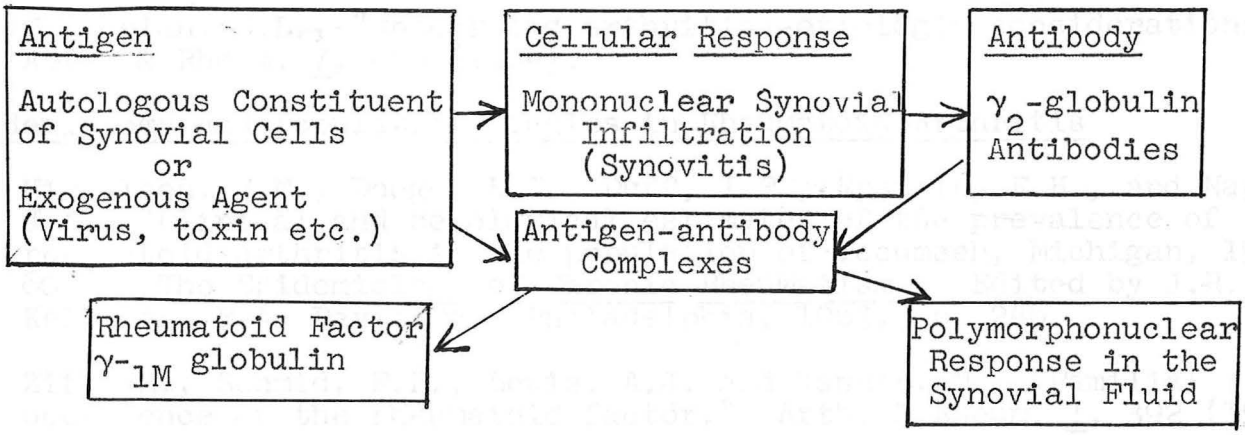
C. Both rheumatoid factor and antinuclear-like factors have recently been produced experimentally by Arbuzzo and Christian (Ref. 30 & 34) in rabbits in response to chronic immunization with E. coli, and confirmed by other workers (Ref. 32) using different antigens.

D. A 10 to 15% incidence of secondary amyloidosis is found in autopsied patients with rheumatoid arthritis, again in keeping with similar findings in chronic infectious states and experimental prolonged hyperimmunization studies.

E. Hollander and his coworker (Ref. 38) and Bollet (Ref. 39), using fluorescent-staining techniques, have observed γ_2-globulin rheumatoid factor-containing inclusion bodies to be present within polymorphonuclear cells of synovial fluid removed from nearly all patients who have acute exacerbations of rheumatoid arthritis. These inclusions have been seen in occasional patients with Reiter's disease, but not in other types of arthritis studied. Hollander has also injected experimentally produced complexes of γ_2-globulin:rheumatoid factor into the knee joint of a patient with rheumatoid arthritis in remission, and produced an acute attack of arthritis in that joint.

F. Arthritis resembling rheumatoid arthritis, including nodule formation, is seen in one-third of patients with agammaglobulinemia (Ref. 35) with a significant increase in both rheumatoid arthritis and rheumatoid factor in the families of these patients. This raises the possibility that their altered immunologic response has enhanced their chances of having clinically severe rheumatoid arthritis.

6. A general theory embodying the above observations can be presented to explain the pathogenesis of rheumatoid arthritis.



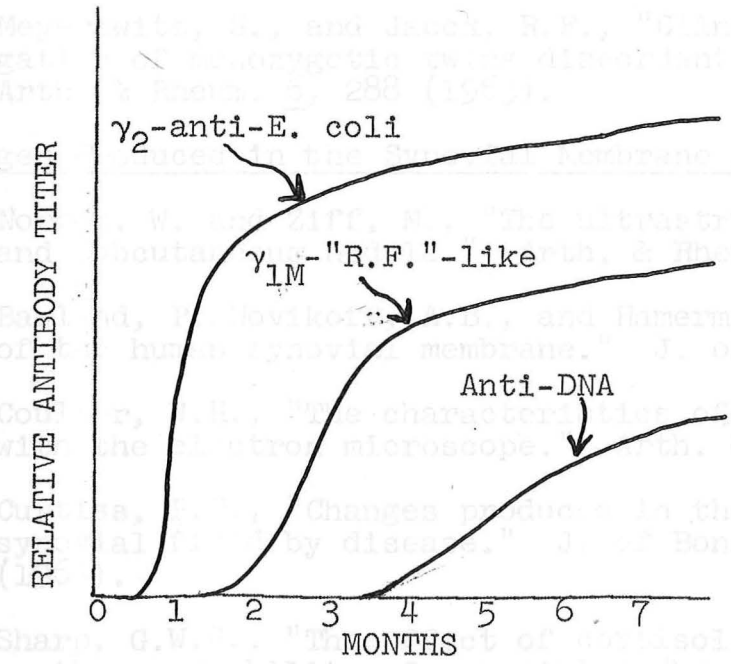


Figure 1. Formation of rheumatoid and Antinuclear-like factors following chronic immunization with E. coli in rabbits (Ref. 34)

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