
SERONEGATIVE POLYARTHRITIS

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Contents

<i>Acknowledgements</i>	vii
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Chapter 1. The Meaning of Seronegativity and Seropositivity

1.1. Historical background	1
1.2. Rheumatoid factors	2
1.2.1. Physiochemical features of rheumatoid factors	2
1.2.2. Basis for tests to demonstrate rheumatoid factors	3
1.2.3. Nature of interaction between rheumatoid factor and sensitised particle	3
1.2.4. Routine tests for demonstrating rheumatoid factors	4
1.2.4.1. Sheep cell agglutination test (SCAT)	4
1.2.4.2. Latex flocculation test (LFT)	5
1.2.5. "Rheumaton" — A new screening test for rheumatoid factor ...	5
1.2.6. Comparability between sheep cell and latex tests	6
1.2.7. Rheumatoid rosette test	7
1.3. Results of tests for rheumatoid factors in rheumatoid arthritis and non-rheumatic disorders	8
1.3.1. Prevalence of seropositivity in rheumatoid arthritis	8
1.3.2. Prevalence of seropositivity in conditions other than rheumatoid arthritis	10
1.3.2.1. Rheumatoid factor in other "collagen disorders"	10
1.3.2.2. Rheumatoid factor in non-rheumatic diseases	11
1.3.3. Prevalence of seropositivity in the general population	12
1.4. Seronegative arthritis	13
1.5. Conclusions	17
1.6. Summary	18
1.7. References	19
Appendix 1.1. The Rheumaton test — Directions and technical information ..	24
Appendix 1.2. ARA criteria for rheumatoid arthritis	25

Chapter 2. The "Seronegative Spondarthritides" — A New Concept

2.1. Introduction	29
2.2. Concept of interrelationships between "variants of rheumatoid arthritis": the seronegative spondarthritides	31
2.3. Clinical and radiological features of the seronegative spondarthritides ...	32
2.3.1. Negative tests for rheumatoid factors	33
2.3.2. Absence of subcutaneous nodules	34
2.3.3. Inflammatory polyarthritis	35
2.3.4. Sacro-iliitis and ankylosing spondylitis	36
2.4. Clinical interrelationships	41
2.4.1. General comment	41
2.4.2. Evidence from personal study	42
2.4.2.1. Study of individual patients	42
2.4.2.2. Epidemiological evidence	44
2.4.3. Summary of evidence for clinical interrelationships	46
2.5. Familial aggregation and familial interrelationships among the seronega- tive spondarthritides	48
2.5.1. Evidence for familial aggregation	49
2.5.1.1. Evidence from previous workers	49
(1) General comment — (2) Ankylosing spondylitis — (3) Uncomplicated psoriasis — (4) Psoriatic arthritis — (5) Reiter's disease — (6) Behçet's syndrome — (7) Ulcerative colitis — (8) Crohn's disease — (9) Whipple's disease	
2.5.1.2. Evidence from personal study	61
2.5.2. Evidence for familial associations	63
2.5.2.1. Evidence from previous workers	63
2.5.2.2. Evidence from personal study	65
2.5.3. Evidence from HLA antigen studies	67
2.5.4. Summary of evidence for familial aggregation and association ...	67
2.6. Concluding remarks	69
2.7. Practical importance of the concept	70
2.8. Summary	71
2.9. References	72
Appendix 2.1. Pedigrees illustrating intrafamilial associations	79

Chapter 3. Ankylosing Spondylitis

3.1. Synonyms	81
3.2. Historical outline	81
3.3. Prevalence	84

3.4. Aetiology and pathogenesis	87
3.4.1. Genetic factors	87
3.4.2. Other factors	89
3.5. Clinical features	91
3.5.1. Symptoms	92
3.5.2. Physical signs	94
3.5.2.1. Chest and spinal rigidity	94
3.5.2.2. Extra-articular bony tenderness	99
3.5.2.3. Peripheral joint involvement	99
3.5.2.4. Posture	100
3.6. Complications	102
3.6.1. Iritis	102
3.6.2. Heart disease	102
3.6.3. Central nervous system complications	103
3.6.4. Amyloidosis	104
3.6.5. Pulmonary complications	104
3.6.6. Complications of treatment	105
3.7. Radiological features	106
3.7.1. Sacro-iliitis	106
3.7.2. Spinal changes	111
3.7.2.1. Paravertebral ossification	111
3.7.2.2. Anterior spondylitis ("Romanus lesions") and vertebral squaring	114
3.7.2.3. Osteoporosis	115
3.7.2.4. Changes in the intervertebral disc ("spondylodiscitis")	116
3.7.2.5. Apophyseal joint involvement	117
3.7.2.6. Peripheral arthritis	118
3.7.2.7. Other bone and joint changes	118
3.8. Pathology	120
3.9. Laboratory findings	123
3.10. Course and prognosis	124
3.11. Diagnosis and diagnostic criteria	125
3.12. Differential diagnosis	130
3.13. Management and treatment	136
3.14. Summary	136
3.15. References	140
Appendix 3.1. <i>Sur la Spondylose Rhizomélique</i> , by Pierre Marie 1898	148
Appendix 3.2. Schober's modified method to measure anterior spinal flexion, and the normal range of this movement	151
Appendix 3.3. An objective method to measure lateral spinal flexion, and the normal range of this movement	152

Appendix 3.4. An objective method to measure spinal extension, and the normal range of this movement	157
Appendix 3.5. Measurement of chest expansion, and the normal range of this movement	160
Appendix 3.6. Case history of a patient with idiopathic ankylosing spondylitis complicated by polyarteritis nodosa	164

Chapter 4. Psoriatic Arthritis

4.1. General comment	169
4.2. Synonyms	169
4.3. Historical outline	169
4.4. Epidemiological background and prevalence	171
4.4.1. Prevalence of psoriasis in inflammatory "rheumatoid" polyarthriti-	
tis	172
4.4.2. Prevalence of psoriasis in the general population	172
4.4.3. Prevalence of polyarthriti in psoriatic subjects	174
4.4.4. Prevalence of rheumatoid arthritis in the general population	175
4.4.5. Prevalence of psoriasis in seronegative and seropositive polyarthri-	
tis	176
4.4.6. Prevalence of psoriatic arthritis in the general population	176
4.5. Aetiology and pathogenesis	177
4.5.1. Genetic and familial aspects	177
4.5.1.1. Uncomplicated psoriasis	177
4.5.1.2. Psoriatic arthritis	178
4.5.2. Other aetiological factors and pathogenesis	180
4.6. Clinical features	184
4.6.1. Sex ratio	184
4.6.2. Age of onset	185
4.6.3. Nature of onset	185
4.6.4. Patterns of psoriatic arthritis	187
4.6.5. Ankylosing spondylitis	190
4.6.6. Nature of rash	192
4.6.7. Nail changes	195
4.7. Other features	199
4.8. Radiological features	200
4.9. Pathology	209
4.10. Laboratory findings	210
4.11. Course and prognosis	211
4.12. Definition and diagnostic criteria	213

4.12.1. Definition	213
4.12.2. Diagnostic criteria	213
4.13. Diagnostic problems and differential diagnosis	214
4.14. Management and treatment	216
4.15. Summary	216
4.16. References	218
Appendix 4.1. Clinical, radiological and serological data on pedigrees 13, 25, 30, 43, 46, 56, 67, 94, 107 and 111	226
Appendix 4.2. Criteria for the diagnosis of borderline psoriasis	234
Appendix 4.3. Criteria for the inflammatory peripheral arthritis of psoriatic ar- thritis	234

Chapter 5. Reiter's Disease

5.1. Historical outline	237
5.2. Aetiology	240
5.2.1. Prevalence	240
5.2.2. Incidence	242
5.2.3. Sex ratio	243
5.2.4. Epidemiological studies	243
5.2.5. Family studies	243
5.2.6. Other theories	244
5.3. Clinical features	246
5.3.1. Arthritis	246
5.3.2. Uro-genital lesions	249
5.3.3. Ocular lesions	252
5.3.4. Integumentary lesions	252
5.3.5. Oral lesions	255
5.3.6. Other lesions	255
5.4. Radiological features	256
5.5. Laboratory findings	257
5.5.1. Pathology	257
5.5.1.1. Histology 257	
5.5.1.2. Synovial fluid 258	
5.5.2. Blood tests	258
5.6. Differential diagnosis	260
5.7. Management and treatment	261
5.8. Summary	261
5.9. References	263

Chapter 6. The Arthritis of Ulcerative Colitis

6.1. Historical outline	271
6.2. Aetiology	273
6.2.1. Prevalence	273
6.2.2. Sex ratio	276
6.2.3. Family studies	277
6.2.4. Other theories	279
6.3. Clinical features	280
6.3.1. Colitis	280
6.3.2. Peripheral arthritis	282
6.3.3. Ankylosing spondylitis	284
6.4. Prognosis	285
6.5. Radiological features	285
6.6. Laboratory findings	285
6.6.1. Pathology	285
6.6.2. Blood tests	286
6.7. Differential diagnosis	287
6.8. Management and treatment	288
6.9. Summary	288
6.10. References	291

Chapter 7. The Arthritis of Crohn's Disease

7.1. Historical outline	295
7.2. Aetiology	299
7.2.1. Prevalence	299
7.2.2. Sex ratio	300
7.2.3. Family studies	301
7.2.4. Other theories	302
7.3. Clinical features	305
7.3.1. General features	305
7.3.2. Gastro-intestinal manifestations	306
7.3.3. Extra-intestinal lesions	308
7.3.4. Peripheral arthritis	308
7.3.5. Ankylosing spondylitis	310
7.3.6. Clubbing	311
7.3.7. Contrast with joint involvement in ulcerative colitis	312
7.4. Radiological features	315

7.5. Laboratory findings	315
7.5.1. Pathology	315
7.5.2. Blood tests	318
7.6. Differential diagnosis	318
7.7. Management and treatment	319
7.8. Summary	320
7.9. References	323

Chapter 8. Whipple's Disease

8.1. Historical outline	329
8.2. Aetiology	331
8.2.1. Prevalence	331
8.2.2. Age of onset	332
8.2.3. Sex ratio	332
8.2.4. Family studies	333
8.2.5. Role of infection	334
8.2.6. Host factors	335
8.2.7. Concluding remarks	336
8.3. Clinical features	336
8.3.1. Extra-articular features	336
8.3.2. Peripheral arthritis	337
8.3.3. Ankylosing spondylitis	339
8.3.4. Course of disease	340
8.4. Radiological features	340
8.5. Laboratory findings	340
8.5.1. Blood tests	340
8.5.2. Pathology	341
8.6. Differential diagnosis	343
8.7. Management and treatment	344
8.8. Summary	344
8.9. References	347

Chapter 9. Behcet's Syndrome

9.1. Historical outline	353
9.2. Aetiology	355
9.2.1. Prevalence	355

9.2.2.	Age of onset	355
9.2.3.	Sex ratio	356
9.2.4.	Family studies	356
9.2.5.	Other theories on aetiology	357
9.3.	Clinical features	358
9.3.1.	Oral ulcers	358
9.3.2.	Genital ulceration and inflammation	359
9.3.3.	Eye lesions	359
9.3.4.	Skin lesions	360
9.3.5.	Gastro-intestinal lesions	361
9.3.6.	Thrombophlebitis	361
9.3.7.	Central nervous system involvement	361
9.3.8.	Peripheral arthritis	361
9.3.9.	Ankylosing spondylitis	362
9.4.	Radiological features	362
9.5.	Pathology	363
9.6.	Laboratory findings	363
9.7.	Differential diagnosis	364
9.8.	Management and treatment	365
9.9.	Summary	365
9.10.	References	367

Chapter 10. Still's Disease

10.1.	Historical outline	371
10.2.	Aetiology	373
10.2.1.	Prevalence	373
10.2.2.	Incidence	373
10.2.3.	Family studies	374
10.2.4.	Other theories on aetiology	375
10.3.	Clinical features	375
10.3.1.	Mode of onset	375
10.3.2.	Clinical course	376
10.3.2.1.	Peripheral arthritis	376
10.3.2.2.	Ankylosing spondylitis	380
10.3.2.3.	Other features	384
10.3.3.	Prognosis	386
10.4.	Radiological features	387
10.5.	Pathology	388
10.6.	Laboratory findings	388
10.7.	Differential diagnosis	390

10.8. Management and treatment	391
10.9. Summary	391
10.10. References	393

Chapter 11. Uncomplicated Seronegative Polyarthriti

11.1. General comment	397
11.2. Epidemiological studies	397
11.3. Family studies	399
11.4. Clinico-pathological features	400
11.5. Radiological studies	401
11.6. Follow-up studies	405
11.7. Diagnostic studies	406
11.8. Summary and conclusions	408
11.9. References	408

Chapter 12. Management and Treatment

12.1. General comment	411
12.2. Ankylosing spondylitis	411
12.2.1. Physical measures and appliances	411
12.2.2. Medication	415
12.2.3. Irradiation	417
12.2.4. Surgery	417
12.3. Psoriatic arthritis	418
12.3.1. Medication in psoriatic arthritis	418
12.3.2. Physical measures in psoriatic arthritis	421
12.3.3. Treatment of psoriasis	421
12.3.3.1. General measures	421
12.3.3.2. Oral and parenteral drugs	421
12.3.3.3. Local therapeutic regimes	421
12.3.4. Surgical implications in the treatment of psoriatic arthritis	422
12.4. Ulcerative colitis and Crohn's disease	423
12.4.1. Treatment of the arthritis of ulcerative colitis and Crohn's disease	423
12.4.2. Treatment of the bowel disease in ulcerative colitis	424
12.4.3. Treatment of the bowel disease in Crohn's disease	426
12.5. Whipple's disease	428

12.6.	Behçet's syndrome	428
12.7.	Reiter's disease	429
12.7.1.	Arthritis	429
12.7.2.	Urogenital system	431
12.7.3.	Eyes	433
12.7.4.	Skin and mucosal lesions	433
12.7.5.	Other manifestations	434
12.8.	Still's disease (juvenile chronic polyarthritis)	434
12.8.1.	General supportive measures	434
12.8.2.	Drug therapy	435
12.8.3.	Surgery	437
12.9.	Summary	438
12.10.	References	439

Chapter 13. Seronegative Spondarthritides and Histocompatibility Antigens

13.1.	Introduction	449
13.2.	Present concepts of the HLA system	450
13.3.	Antigens of the HLA system	451
13.4.	Chemical nature of HLA antigens	454
13.5.	HLA antigens and disease	454
13.5.1.	General comment	454
13.5.2.	Histocompatibility antigens and their relation to rheumatic diseases	456
13.5.2.1.	General comment	456
13.5.2.2.	Ankylosing spondylitis	458
13.5.2.3.	Ulcerative colitis and Crohn's diseases	463
13.5.2.4.	Psoriasis and psoriatic arthritis	466
13.5.2.5.	Reiter's disease	466
13.5.2.6.	Reactive arthritis (Post-dysenteric Reiter's disease — Yersinia arthritis — Salmonella arthritis)	468
13.5.2.7.	Behçet's syndrome	469
13.5.2.8.	Acute anterior uveitis	470
13.5.2.9.	Juvenile chronic polyarthritis	472
13.5.2.10.	Uncomplicated seronegative polyarthritis	472
13.5.2.11.	Infective sacro-iliitis	472
13.5.3.	Negative associations	473

13.6. Genetic implications of HLA and disease associations	473
13.7. Concluding remarks	474
13.8. Summary of present situation	475
13.9. References	478
Appendix 13.1. Complete list of recognised HLA specificities showing new no- menclature	482
<i>Subject Index</i>	483

The Meaning of Seronegativity and Seropositivity

1.1 Historical background

Until recently medical writers were barely able to distinguish different types of chronic arthritis and observers up till the turn of the century considered them all to be variants of gout.

It is probable, however, that both Hippocrates and Soranus of Ephesus (second century A.D.) were aware of the difference between "chronic rheumatoid arthritis" and "chronic podagra". In more modern times, H. W. Fuller in 1854 (cited by Copeman 1964) provided a good description of rheumatoid arthritis, calling it "rheumatoid gout".

Further strength was added to the distinction between true gout and other forms of arthritis by Sir Alfred Garrod's discovery of an excess of uric acid in the blood of gouty subjects. Garrod in 1859 was the first to give rheumatoid arthritis its present name.

In 1857, osteoarthritis (or osteoarthrosis as it is now called) became separated from rheumatoid arthritis by Robert Adams in his *Treatise on the Rheumatic Gout*. Ankylosing spondylitis also became widely known as a separate entity at about this time, not only due to the classical reports by Bechterev and Strümpell from Germany and Marie from France, but also in the United Kingdom from the work of C. Hilton Fagge in 1877. For further historical details the reader is referred to the excellent monograph by Copeman (1964).

The next significant advance in rheumatological classification was made by Waaler in 1940, and again by Rose et al. in 1948, when rheumatoid factor, a gamma-M immunoglobulin, was discovered. This finding made possible a division of inflammatory arthritis into two main groups, i.e. those in which rheumatoid factor was present (seropositive and usually typical rheumatoid arthritis), and those in which the factor was consistently absent throughout the natural history of the disease (seronegative arthritis). It is with this second group, the seronegative arthritides, that we have been particularly concerned, and in order to study this subject in further detail it is clearly important to examine in some depth the immunological background to rheumatoid factor.

1.2 Rheumatoid factors

1.2.1 Physicochemical features of rheumatoid factors

Rheumatoid factors are antibodies mainly of the IgM class with a molecular weight of about 1,000,000 and an ultracentrifugal sedimentation coefficient of 19S (Franklin et al. 1957). These macro-gamma globulins constitute a class of proteins which contain, in addition to rheumatoid factors, many other types of antibody such as cold agglutinins, the Wassermann and heterophil antibodies, and typhoid "O" agglutinin.

The evidence for the antibody nature of rheumatoid factors has been summarised by Anderson and Buchanan (1966):

(1) Rheumatoid factors are immunoglobulins (usually IgM, sometimes IgG) which react only with IgG and with no other protein or tissue antigen.

(2) Rheumatoid factors demonstrate, with few exceptions, primary specificity for human IgG and cross-reactivity with other mammalian IgG (Butler and Vaughan 1964), which is consistent with the behaviour of classical antibody.

(3) Rheumatoid factors frequently demonstrate specific reactivity with certain genetically determined groupings (Gm Groups) (Grubb 1961; Fudenberg and Kunkel 1961) which suggests the specificity characteristic of antibodies.

(4) Rheumatoid factors have been shown by immunofluorescent techniques to be located in, and hence presumably produced by, cells capable of producing antibodies. These cells include plasma cells and germinal centre cells of lymph nodes, and also plasma cells in affected synovia and around subcutaneous nodules (Mellors et al. 1959; Mellors et al. 1961; McCormick 1963).

(5) Rheumatoid factor-like serum factors, albeit of IgG class, have been produced in animals by immunization with autologous denatured IgG incorporated in Freund's adjuvant (Milgrom and Witebsky 1960; McCluskey et al. 1962).

Although it is now reasonably clear that rheumatoid factors are antibodies to IgG, it is still not fully understood whether they are antibodies to native IgG or IgG denatured by immune complex formation or by physical aggregation. There is equally good evidence to support both the "native" (Grubb 1961; Fudenberg and Kunkel 1961) and "denatured" (Christian 1958; Edelman et al. 1958) hypotheses.

There is also controversy as to whether rheumatoid factors should be regarded as auto-antibodies or iso-antibodies (Milgrom and Witebsky 1960). However, as McCormick (1963) has pointed out, rheumatoid factors probably represent a heterogeneous collection of immunoglobulins, some behaving as auto-antibodies, some as iso-antibodies, and some as hetero-antibodies to IgG. It is also apparent that the reactant (IgG antigen) of normal human serum and other mammalian sera is complex in its antigenicity, and it is likely that different rheumatoid factors react with different parts of the IgG reactant molecules.