MEDICAL PRACTICE

Occasional Survey

Onset, Early Stages, and Prognosis of Rheumatoid Arthritis: A Clinical Study of 100 Patients with 11-year Follow-up

R. K. JACOBY, M. I. V. JAYSON, J. A. COSH

British Medical Journal, 1973, 2, 96–100

"He has the best view who has seen a thing from its start."—ARISTOTLE.

Summary

One hundred patients with "definite" or "classical" rheumatoid arthritis were followed in a hospital clinic from within one year of the onset of the arthritis. The average interval between onset and first attendance was 3·7 months. Onset was commoner in the winter, transient prodromal symptoms being noted in 23, with possible precipitating factors in 14. The serum rheumatoid factor test was positive at some time in 88.

The patients were reassessed between eight and 14 years later. Seventeen died during this period, five possibly as a result of the disease or its treatment.

The remaining patients had improved as a whole in terms of the blood sedimentation rate, haemoglobin, titre of the rheumatoid factor test, and status of the disease, but there was an overall deterioration in functional capacity. Both the rheumatoid factor titre and the functional capacity at an earlier review could be directly correlated with the outcome, but other factors were not found to influence the ultimate prognosis.

Department of Medicine, Bristol Royal Infirmary, Bristol
R. K. JACOBY, M.B., M.R.C.P., Registrar

Royal National Hospital for Rheumatic Diseases, Bath BA1 1RL
M. I. V. JAYSON, M.D., M.R.C.P., Consultant Physician
J. A. COSH, M.D., F.R.C.P., Consultant Physician

Introduction

Although the clinical features of rheumatoid arthritis and its pathology are familiar its cause remains unknown and the course of the individual case is unpredictable.[1] Several reviews of its history and prognosis have been made and its incidence in the population has been assessed by surveys. But these deal mainly with patients with established disease and may consequently present an unfavourable view of rheumatoid arthritis by omitting patients who have suffered the disease only mildly or who have gone into an early remission. A truer picture of the natural history can be obtained by basing an analysis on patients seen initally in the early stages and then followed up. Moreover, in a disease of obscure cause it is worth examining carefully its mode of onset, and this is best done while the details are still fresh in the patient's memory.

The present study was based on 100 patients with rheumatoid arthritis first seen within one year of onset. The follow-up review was made after an average of 11 years, when the importance of features noted in the early stages was assessed in the light of subsequent progress.

PREVIOUS REVIEWS

The Empire Rheumatism Council[2] made a detailed multicentre review of aetiological factors associated with rheumatoid arthritis based on 532 patients and matched controls, and by retrospective inquiry provided much information on prodromal symptoms and on the circumstances of onset. Duthie *et al.*[3] reviewed the effects of hospital treatment on 307 patients in whom the disease had been established for some years when first seen and reported on the subsequent course of these patients.[4,5] Short, *et al.*[6] described in great detail 293

patients with rheumatoid arthritis and matched controls, assessing favourable and unfavourable prognostic features in the light of follow-up reviews at 10 and 14 years. The duration of arthritis on admission to the series ranged up to 10 years or more, but there were 81 patients initially examined within a year of onset. Ragan and Farrington[7] reviewed 500 patients with a six-year follow-up, but the disease had already been established for some years in most of these when they were first seen.

Two surveys have dealt specifically with the onset of the disease. Otten and Westendorp Boerma[8] studied 141 patients, of whom 106 were first seen within three months of the onset, and reported on the relevance of the rheumatoid factor test result to the subsequent course over three years. They found that initially rheumatoid arthritis occurred with practically the same frequency in both sexes, but remissions were commoner in men and the chronic form was commoner in women. Rotes-Querol and Roig-Escofet[9] described in detail the presenting features in 68 patients seen within the first year; women predominated in the proportion of 3:1.

Onset and Early Stages

The 100 patients in this series were all seen by J.A.C. initially between 1957 and 1963 in clinics in or linked with the Royal National Hospital for Rheumatic Diseases, Bath. They were accepted into the series only if seen within a year of the onset and if by the end of that year they had "definite" or "classical" rheumatoid arthritis according to the criteria of the American Rheumatism Association[10]. The onset was dated by calendar month and classified as "acute" if it could be dated by the patient to a specific day, "subacute" if the onset could be dated only to the nearest week, and "gradual" if only to the nearest month.

In history taking, information was sought on prodromal symptoms—that is, transient pain or stiffness not recognized as due to rheumatoid arthritis at the time and subsiding completely with a clear interval of six months or more before the onset of the disease. The test for rheumatoid factor was performed by the method of Gibson and Ling,[11] in which the patient's serum is tested in serial dilutions against a suspension of human red cells sensitized by sheep antihuman red cell serum. Changes in titre were noted and attention was paid to conversion of the test result from negative to positive and vice versa.

Age and Sex.—The patients' ages at the time of onset are shown in table I. There were 36 men and 64 women, a male to female ratio of 1:1·8. The average age for the whole series was 50·6 years (men 52·2 years, women 49·8 years).

TABLE I—*Age at Onset of Rheumatoid Arthritis and Sex Distribution*

	Age at onset in years							Total
	<19	20–	30–	40–	50–	60–	≥70	
No. of men		3	3	8	9	11	2	36
No. of women ..	1	5	14	8	17	14	5	64
Total..	1	8	17	16	26	25	7	100

Interval between Onset and First Examination.—The calendar months of onset and the first clinic examination were noted and the interval was recorded (average interval 3·7 months). A significant difference in the sex ratios was found between those first seen within three months of onset ("early group") and those first seen between four and 12 months after onset ("later group"). Of the 62 patients in the early group 29 (47%) were men, while of the 38 in the later group only 7 (18%) were men ($P < 0.01$).

Calendar Month of Onset.—This is shown in table II. December was the worst individual month, and in 43 patients onset occurred during December to February.

TABLE II—*Month of Onset*

	J.	F.	M.	A.	M.	J.	J.	A.	S.	O.	N.	D.	Total
No. of cases	10	11	8	8	8	4	8	4	4	8	5	22	100

Prodromal Symptoms.—Twenty-three patients described transient symptoms occurring at least six months, and often a year or more, before the definitive onset of the disease. Generally these took the form of pain and stiffness in a single joint, sometimes of a dramatic nature. In eight one or both *shoulders* were affected. Two of these patients, both men, had been subject for over 10 years to episodes of severe shoulder pain and stiffness for a few days at a time; the others had less well-defined aching and stiffness, often called "fibrositis," also settling completely. When arthritis later developed in these patients it did not necessarily involve the shoulders. Six others had prodromal involvement of a *metacarpophalangeal* or *wrist* joint. One woman, aged 29, had prodromal pain and stiffness in both wrists four months after childbirth. Examination subsequently showed no abnormality; the E.S.R. was normal and the rheumatoid factor was absent. Nineteen months after her prodromal symptoms, however, arthritis developed in the wrists and elsewhere and she became seropositive with erosions; she was in remission when reviewed three years after onset. Four patients had episodes of pain in the first *metatarsophalangeal* joint eight months to four years before the onset of the disease, and in two, both men, it was acute enough to suggest gout and the serum uric acid was normal. Other prodromata were transient hip pain in two and pain and effusion in a knee in one and in an ankle in one. Two patients had had *ganglion* of the wrist treated one year and two years before developing rheumatoid arthritis. *Raynaud's phenomenon* was reported only once, affecting a woman patient's fingers for two years before the onset. The nature of these prodromal symptoms in many cases suggested miniature or "larval" attacks of rheumatoid arthritis in advance of the main onset. Nevertheless, these 23 patients with prodromata did not differ significantly from the remaining patients in the development of a positive result for rheumatoid factor or in the height of the titre achieved as the arthritis proceeded; three of them were consistently seronegative.

Precipitating Factors.—In 14 patients the onset occurred shortly after some event which appeared to be a precipitating factor. In six this was *trauma.* Three fell heavily a few days before their polyarthritis began; two injured a knee, which developed a persistent effusion and was followed by the appearance of arthritis elsewhere within one or two months; and one injured a finger and quickly developed joint swellings in the affected finger and then in others. In one *pregnancy* preceded the onset, arthritis beginning four months after normal childbirth. In five the preceding event was *surgery*—three had gynaecological operations four, four, and one month respectively before the onset of rheumatoid arthritis, one had a laparotomy for diverticulitis a month previously, and one had a patellectomy for old trauma to the knee and patella and within a month developed progressive seropositive rheumatoid arthritis. In one the preceding event was *infection*; a man of 65 had influenza leading to bronchopneumonia, and this illness coincided with the onset of seropositive rheumatoid arthritis. In another it was *inoculation* with vaccine; a woman of 40 had poliomyelitis vaccine injected into one deltoid and the following month developed pain in that shoulder, leading to generalized rheumatoid arthritis which was strongly seropositive two months later.

Acuteness of Onset.—Twenty-three patients had an "acute" onset as defined above, 28 were "subacute," and 49 "gradual." There was no difference in the sex ratios within the three groups. The relation to the rheumatoid factor test and prognosis is discussed below.

Site of Onset.—The hands and wrists were the commonest site of onset (53%) followed by ankles and feet (21%), knees (13%), and shoulders (9%). The two sexes were similar in this respect. In four patients the onset took the form of generalized stiffness progressing within a few months to a characteristic pattern of joint involvement. In three patients pain and swelling were confined to a single joint for over a month before other joints were involved.

Joints Affected.—The distribution of affected joints once the disease had become established is shown in table III. Again, no difference in pattern between the sexes was seen. The joints most often involved, in descending order of frequency, were metacarpophalangeals, wrists, proximal interphalangeals, knees, ankles, metatarsophalangeals, and shoulders.

TABLE III—*Joints Ultimately Affected*

	Men		Women		Total
	No.	%	No.	%	
Proximal interphalangeals ..	21	58	42	66	63
Metacarpophalangeals	29	81	58	91	87
Wrists	29	81	53	83	82
Elbows	9	25	12	19	21
Shoulders	15	42	32	50	47
Knees	19	53	37	58	56
Ankles	19	53	34	53	53
Metatarsophalangeals	15	42	33	52	48

Family History.—A history of rheumatoid arthritis in parent or sibling was given by 27 patients. In some this could be verified from hospital records if the affected relative had attended, but in the majority further verification was not attempted. The relation to the rheumatoid factor test and prognosis is discussed below.

Rheumatoid Factor Test.—This gave a positive reading at some time in 88 patients. The interval between the onset of rheumatoid arthritis and the first result is shown in table IV. In the majority the test reading was already positive when first done, so that the time intervals indicated are influenced by the time taken for the patient to reach hospital and be tested. In some patients the initial result was negative and the time of the change to positive could be estimated. *Conversion from negative to positive* was noted in 18 patients; in 9 this was during the first year of the disease, in 4 it was in the second year, and in 5 it was later. In all 18 conversion occurred during exacerbation of the arthritis, the E.S.R. in the first hour being over 50 mm in 5, 20-50 mm in 8, and under 20 mm in 5. In eight patients a *conversion from positive to negative* was noted during remissions; in two this occurred in the first year, in four in the second year, and in two later. Subsequently when reviewed three years after onset 80 patients had a positive test result.

Follow-up Review at 11 Years

The follow-up examinations were carried out by R.K.J. at a mean interval of 11 years from the onset of the disease (range 8 to 14 years). Seventeen patients had then died, and the analysis and comparisons which follow are based on the 83 survivors.

METHOD OF STUDY

Information from the original and follow-up assessments was converted into numerical form and transferred to punch cards and computer tape. Analysis was by standard statistical techniques (Student's *t* test and analysis of regression), the calculations being performed on the University of Bath computer. The following data from the *original assessment* were recorded: (1) sex, (2) history of rheumatoid arthritis in parent or sibling, (3) type of onset (acute, subacute, or gradual, as defined above), (4) site of onset, (5) functional capacity[12] (table V; assessed at a mean of three years after onset), (6) haemoglobin (%) in the first year of disease (100% = 14·8 g/100 ml), (7) maximum E.S.R. (Westergren) in the first hour, (8) maximum rheumatoid factor test titre in the first year (expressed as the number of the tube dilution), and (9) number of diagnostic criteria for rheumatoid arthritis as defined by the American Rheumatism Association.[10]

TABLE IV—*Interval from Disease Onset to Time of First Positive Rheumatoid Factor Test Result in the 100 Patients**

	Positive Result (Time in Months)					Negative Result Throughout
	Within 3	4–6	7–12	After 12	Total	
No. of patients	33	22	21	12	88	12

*Inclusive of month of onset and month of testing.

TABLE V—*Grades of Functional Capacity* (Steinbrocker *et al.*[12])

Grade	Definition	Remarks
1	Fit for all activities	Complete ability to carry on usual duties without handicap
2	Moderate restriction	Adequate for normal activities despite handicap of discomfort or limited motion at one or more joints
3	Marked restriction	Limited only to self-care and little or none of the duties of usual occupation
4	Confined to chair or bed	Incapacitated, largely or wholly bedridden, or confined to wheelchair. Little or no self-care

Data recorded from the *follow-up assessment* were as follows: (1) functional capacity; (2) haemoglobin (%); (3) E.S.R. (Westergren); (4) rheumatoid factor test titre, using the same technique and reagents as in the original assessment; (5) number of American Rheumatism Association diagnostic criteria for rheumatoid arthritis; (6) total clinical joint score—that is, the total number of joints clinically affected—the interphalangeal, metacarpophalangeal, and metatarsophalangeal joints in each extremity being regarded as one unit; and (7) *x*-ray score, assessed separately for large and small joints. The proximal interphalangeal, metacarpophalangeal, and metatarsophalangeal joints were graded by the scale of Steinbrocker *et al.*[12] (table VI) and a mean small joint score was calculated. Involved large joints were *x*-rayed and similarly scored, joints not involved being counted as normal, and the mean large joint score was calculated.

TABLE VI—*Grading of X-ray Changes* (Steinbrocker *et al.*[12])

Grade	
1 ..	No destructive changes. Osteoporosis may be present
2 ..	Osteoporosis with or without subchondral bone destruction. Slight cartilage loss may be present
3 ..	Cartilage and bone destruction, joint deformity
4 ..	Fibrous or bony ankylosis with grade 3 criteria

Results

Seventeen patients had died from the causes listed in table VII. In five patients the disease appeared to have been responsible for death.

Change in Status.—The overall status of the surviving patients at follow-up examination was compared with the original data in order to determine the general course of this

TABLE VII—*Causes of Death*

Case No.	Sex and Age	Cause of Death	Interval from Onset of Rheumatoid Arthritis to Death
1	F. 70	Septicaemia, septic arthritis, steroid treatment*	16 Months
2	M. 61	Carcinoma of lung	19 Months
3	M. 76	Myocardial infarct	2 Years
4	M. 62	Heart block	3 Years
5	M. 35	Vasculitis, neuropathy, malignant hypertension*	5 Years
6	F. 59	Angina. Sudden death	5 Years
7	M. 61	Myocardial infarct	5 Years
8	F. 57	Bronchopneumonia, heart failure, carcinoma breast	5 Years
9	F. 64	Peritonitis, strangulated hernia	6 Years
10	M. 60	Myocardial infarct	6½ Years
11	F. 67	Uraemia, nephrotic syndrome, ?amyloid*	7 Years
12	F. 60	Constrictive rheumatoid pericarditis: postoperative death*	7 Years
13	F. 69	Rheumatoid heart disease, pulmonary emboli*	8 Years
14	F. 68	Cerebral thrombosis	8 Years
15	F. 67	Uraemia, congestive heart failure	8 Years
16	M. 72	Myocardial infarct	9 Years
17	F. 78	Myocardial infarct	12 Years

*Patient died as a result of rheumatoid arthritis.

group of 83 patients (table VIII). There was a significant deterioration in functional capacity but a significant improvement in the E.S.R., haemoglobin, rheumatoid factor titre, and stage of the disease (derived from the American Rheumatism Association's criteria).

TABLE VIII—*Change in Status of Surviving 83 Patients comparing Initial and Follow-up Observations at 11 years*

Observation	Time of Observation	Mean Value of Observation ± S.D.	t Value	P
Rheumatoid factor titre (tubes dilution)	First year	7·9 ± 3·1	5·65	<0·001
	11-year follow-up	5·2 ± 2·9		
Functional capacity	3-year follow-up	1·4 ± 0·7	4·58	<0·001
	11-year follow-up	2·1 ± 1·0		
American Rheumatism Association stage*	First year	0·5 ± 0·5	3·69	<0·001
	11-year follow-up	1·0 ± 1·0		
E.S.R. (Westergren)	First year	46·5 ± 29·4	5·57	<0·001
	11-year follow-up	25·1 ± 19·0		
Haemoglobin (%)	First year	83·2 ± 10·9	4·76	<0·001
	11-year follow-up	91·3 ± 10·8		

*Expressed as 0 = classical, 1 = definite, 2 = probable, 3 = possible rehumatoid arthritis.

Prognostic Markers.—In the knowledge of the subsequent course of surviving patients certain factors noted at the original examination were assessed as prognostic markers.

Rheumatoid Factor Titre.—A significant direct correlation was found between the original and final rheumatoid factor titres. The original titre could also be directly correlated with the final number of American Rheumatism Association criteria and the total clinical joint score, but not with the functional capacity or the small joint *x*-ray (table IX). Although the relation with the mean large joint score was statistically significant the coefficient was low, indicating that the large joint score was only slightly influenced by the original titre.

TABLE IX—*Correlation between Maximum Rheumatoid Factor Titre in First Year and Follow-up Observations*

Follow-up Observations Correlation with Initial Rheumatoid Factor Titre	Regression Equation	P
Rheumatoid factor titre	1·46 + 0·48 T	<0·05
Functional capacity	1·74 + 0·04 T	>0·05
Number of criteria	2·77 + 0·34 T	<0·05
Mean *x*-ray score: small joints	1·31 + 0·04 T	>0·05
Mean *x*-ray score: large joints	1·63 + 0·07 T	<0·05
Total clinical joint score	3·78 + 0·46 T	<0·05

T = Original rheumatoid factor titre as tubes dilution.

Sex.—At follow-up there were no significant differences in any of the assessments between male and female patients.

Type of Onset.—Comparisons were drawn between patients with acute, subacute, and gradual patterns of onset of rheumatoid arthritis but no significant differences were found at final follow-up.

Family History.—No differences emerged between patients with and without family histories of rheumatoid arthritis.

Site of Onset.—The final data were examined to determine whether onset of the disease at any particular site influenced the final prognosis. No such influence could be determined.

Haemoglobin.—A significant correlation was found between the final haemoglobin (Hb_2) and that at the initial presentation (Hb_1). ($Hb_2 = 55{\cdot}64 + 0{\cdot}43\ Hb_1$.)

Functional Capacity.—Of the 83 survivors 31 were in grade 1, 25 in grade 2, 18 in grade 3, and 9 in grade 4. A significant positive correlation was found between the final functional capacity (FC_2) and that at the three-year review (FC_1). ($FC_2 = 1{\cdot}34 + 0{\cdot}47\ FC_1$.)

E.S.R.—No correlation could be found between the initial and follow-up E.S.R. values or with the other follow-up assessments.

Initial "Early Group."—When the patients were reviewed at three years from onset it was found that the 62 patients who had initially presented to the clinic within three months of onset were progressing significantly better than the remaining 38. In the 11-year survey this distinction had been lost and the survivors of the groups were similar in functional capacity.

Patients Admitted to Hospital.—When reviewed at three years the 62 patients who had been admitted to hospital for treatment had a significantly worse functional capacity than the remaining 48. In the 11-year survey this distinction too had been lost and the survivors of the two groups were similar in functional capacity.

Discussion

This series of patients were similar in respect of age and sex to those reported on by Short *et al.*[6] but were some six years older than those in the series of Duthie *et al.*[3-5] and there were fewer women. The predominance of onset of rheumatoid arthritis in winter months was also noted by Duthie *et al.*,[3] Short, *et al.*,[6] and Loxton,[13] although the frequency of onset in December in this series was not seen in the others.

The occurrence of prodromal symptoms was well documented in the Empire Rheumatism Council report[2] and was not found in matched controls. Such symptoms appear to have no bearing on the prognosis but are of interest as a pointer to the early diagnosis. Their nature suggests that they are forerunners of the disease itself rather than due to an infection which subsequently sets up an autoimmune inflammation. They may be likened to the temporary appearance of diabetes under conditions of stress in a prediabetic patient.

The role of precipitating factors was also reviewed in the Empire Rheumatism Council report and no significant difference in the incidence of these factors in patients and controls was found. Short *et al.*,[6] however, considered that trauma may occasionally precipitate or localize rheumatoid arthritis. Kelly[14] and Williams and Scott[15] also reported examples of injury to a single joint being followed by generalized polyarthritis.

The difference in sex ratio and in prognosis of the "early group" of 42 patients seen within three months of onset when compared with the remainder is of considerable interest. The near-equal numbers of the sexes in the early group and their better prognosis at three years resembled the findings of Otten and Westendorp Boerma.[8] They concluded that rheumatoid arthritis was a disease which initially attacked both sexes equally but remitted more readily in men, leaving a prepon-

derance of women in the more chronic stages. Alternatately it might be argued that men forced to be absent from their work by rheumatoid arthritis may report to their practitioners and thence to the hospital clinic more readily than women. This was also noted by Duthie *et al.*, who found that 30% of men reported within six months of onset compared with 18% of women. If a proportion of early cases remit this will appear to give a better prognosis for the largely male group who report early to the clinic; perhaps a similar proportion of women patients remit but do so undetected, as they tend not to reach the clinic in the early months. Nevertheless, the figures do not rule out the conclusion reached by Otten and Westendorp Boerma—namely, that rheumatoid arthritis initially attacks both sexes equally but remits more often in men.

When patients in this series were reviewed three years after the onset those who had been admitted to hospital for treatment were significantly worse than those not admitted. Although this difference had been lost by the time of the 11-year review this observation illustrates how a misleading concept of rheumatoid arthritis may be derived from surveys based only on hospital inpatients. Clinical judgements on the pronosis of disease are often grossly biased because of the selection of patients seen in hospital. Rheumatoid arthritis has been estimated as affecting 2·1% of males and 5·2% of females.[16] Not all these patients, however, would be referred to a rheumatology clinic, and the milder cases which perhaps remit completely may never be seen by a physician. In hospital practice patients with severe disease return to the clinic over many years, wheras those with transient inflammatory arthritis may attend on only one or two occasions. It is therefore very easy to become convinced that the prognosis of rheumatoid arthritis is considerably worse than is actually the case.

Over the 11 years the overall numbers of diagnostic criteria for rheumatoid arthritis and the laboratory indices of activity of the disease improved. This suggests that on the whole in patients with early arthritis the activity of the disease is transient and will tend to remit. Relatively few patients will deteriorate considerably but it is these that can lead to the impression that rheumatoid arthritis has a poor prognosis. There was, however, some deterioration in the functional capacity. This could well reflect the increase in age of the patients over the intervening period.

A significant correlation was found between the rheumatoid factor titre within the first year of onset of arthritis and several of the parameters reflecting the outcome of the disease. Other workers have also found a positive relation between the presence of rheumatoid factor and functional capacity, disease activity,[17 18] and *x*-ray changes.[19] The rheumatoid factor titre therefore appears to be of some value in predicting the long-term course of the disease.

The sex of the patient did not influence the final prognosis. In contrast, Duthie *et al.*[3] found that patients admitted to hospital because of arthritis fared better if they were males. The final outcome could not be correlated with the presence or absence of a family history of rheumatoid arthritis. This is of considerable practical importance; patients frequently have such a family history, and if a member of the family has been crippled they will usually anticipate a similar outcome in their own disease. This study should enable the doctor to adopt a far more optimistic outlook.

Neither the type nor the site of onset of the arthritis appeared to influence the ultimate prognosis. In particular, the small joint *x*-ray score showed that early involvement of the wrists and hands did not imply that small joint damage is inevitable. A direct correlation was found between the three-year and 11-year functional capacities, so that the degree of involvement by the disease by the time the patient is referred to hospital is a good guide to the degree of disability to be expected in the future.

We wish to thank Mrs. Elizabeth Collins and Mr. Gordon Turner for their help with the statistical analysis of the results. M.I.V.J. is in receipt of a grant from the Medical Research Council.

Requests for reprints should be addressed to M.I.V.J. at the Royal National Hospital for Rheumatic Diseases, Bath.

References

1. *British Medical Journal*, 1962, 2, 391.
2. Empire Rheumatism Council, *Annals of the Rheumatic Diseases*, 1950, 9, Supplement.
3. Duthie, J. J. R., Thompson, M., Weir, M. M., and Fletcher, W. B., *Annals of the Rheumatic Diseases*, 1955, 14, 133.
4. Duthie, J. J. R., Brown, P. E., Knox, J. D. E., and Thompson, M., *Annals of the Rheumatic Diseases*, 1957, 16, 411.
5. Duthie, J. J. R., Brown, P. E., Truelove, L. H., Baragar, F. D., and Lawrie, A. J., *Annals of the Rheumatic Diseases*, 1964, 23, 193.
6. Short, C. L., Bauer, W., and Reynolds, W. E., *Rheumatoid Arthritis*. Cambridge, Mass., Harvard University Press, 1957.
7. Ragan, C., and Farrington, E., *Journal of the American Medical Association*, 1962, 181, 663.
8. Otten, H. A., and Westendorp Boerma, F., *Annals of the Rheumatic Diseases*, 1959, 18, 24.
9. Rotes-Querol, J., and Roig-Escofet, D., *Revue du Rhumatisme*, 1968, 35, 21.
10. Ropes, M. W., *Annals of the Rheumatic Diseases*, 1959, 18, 49.
11. Gibson, H. J., and Ling, N. R., *Annals of the Rheumatic Diseases*, 1956, 15, 246.
12. Steinbrocker, O., Traeger, C. H., and Batterman, R. C., *Journal of the American Medical Association*, 1949, 140, 659.
13. Loxton, G. E., *British Medical Journal*, 1959, 2, 1094.
14. Kelly, M., *Annals of the Rheumatic Diseases*, 1951, 10, 307.
15. Williams, K. A., and Scott, J. T., *Annals of the Rheumatic Diseases*, 1967, 26, 532.
16. Lawrence, J. S., *Annals of the Rheumatic Diseases*, 1961, 20, 11.
17. Cats, A., and Hazevoet, H. M., *Annals of the Rheumatic Diseases*, 1970, 29, 254.
18. Kellgren, J. H., *British Medical Journal*, 1957, 1, 850.
19. Ball, J., *Annals of the Rheumatic Diseases*, 1952, 11, 97.