The Long-Term Effects of Treating Rheumatoid Arthritis

D. L. SCOTT, MD, MRCP(UK)*, *Lecturer, Rheumatism Research Wing, University of Birmingham Medical School*
B. L. COULTON, MB, MRCP, *Hospital Practitioner, Highfield Hospital, Droitwich*
J. H. CHAPMAN, MB, MRCP(UK), *Senior House Officer, Highfield Hospital, Droitwich*
P. A. BACON, MB, FRCP, *Professor of Rheumatology, University of Birmingham*
A. J. POPERT, MD, FRCP, *Consultant Physician and Rheumatologist, Highfield Hospital, Droitwich*

Rheumatoid arthritis is a major chronic disease causing multiple medical and social problems[1]; 63 per cent of cases suffer significant social and economic disadvantages[2]. The Health Service should make a considerable commitment to its treatment. Many changes in treatment have occurred in the last 20 years with the introduction of new drugs and different therapeutic regimens. Most of these drugs produce measurable benefit over one or two years, and leading articles have suggested that therapy successfully modifies the course of the disease[3,4]. We now reconsider the published evidence for such assumptions in the light of results gathered in the past 15 years at the Droitwich Centre for Rheumatic Diseases.

Previous Reviews of the Long-Term Effect of Rheumatic Disease

The major studies are summarised in Table 1. They are all surveys of hospital patients and consider the more severe cases. There are some differences between the studies. For example, Ragan and Farrington[6] reviewed cases with predominantly mild disease when first seen, and Cosh and Rasker[8] described the end results in patients initially seen in the first year of their disease. The other studies review patients admitted to hospital and first seen later in the course of their disease. A number of conclusions can be drawn from these studies. Complete remission is unlikely after the first few years of the disease. By 10 years approximately half the patients will be severely disabled, falling into classes III and IV of the Steinbroker classification for functional capacity[9]. But there is evidence, especially in the series of patients described by Duthie *et al.*[7,10,11] that hospital therapy can improve functional capacity and that this improvement can be maintained.

**Address for correspondence:* Dr D. L. Scott, MRCP (UK), Rheumatism Research Wing, The Medical School, University of Birmingham.

The Current Therapeutic Approach

The general outline of therapy is similar at most centres (Fig. 1)[12-15]. Patients with mild or moderate disease usually receive only symptomatic therapy with analgesics and non-steroidal anti-inflammatory drugs. A large number of these drugs are now available, all of which relieve symptoms such as joint swelling and pain. Patients respond in an individual and often unpredictable manner to different non-steroidal anti-inflammatory drugs[16] and physicians should attempt to find the best one for an individual patient[17]. Patients with severe disease, although in the minority[18], are the most important group since they attend specialist clinics and require intensive therapy. These patients are given 'second-line' drugs, alternatively called 'disease modifying', slow-acting, long-term or 'specific' drugs.

Patients given second-line drugs will usually have disabling joint symptoms, a raised ESR, raised acute phase proteins, and radiological evidence of erosive destructive joint changes. Many will also have significant titres of rheumatoid factor and various extra-articular

Fig. 1. *An outline of the current therapeutic approach. (NSAIDS = non-steroidal anti-inflammatory drugs.)*

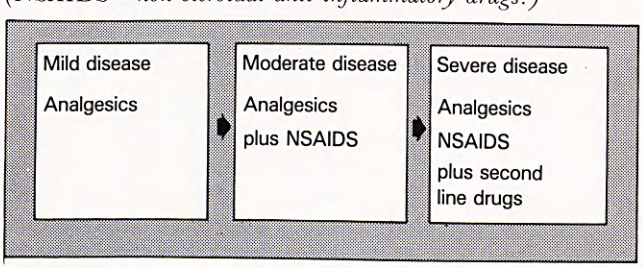

Table 1. The long-term outcome in rheumatoid arthritis: summary of major studies.

Study	Centre	Cases followed for 9 years or more	Years of entry into study	Method of selecting cases	Duration of observation (years)	Results at follow-up
Short *et al.* (1957) [5]	Boston, USA	225	1931–36	Prospective survey of hospital admissions	11–17	Remission 17% Improved 38% Stationary 11% Worse 34%
Ragan and Farrington (1962) [6]	New York, USA	246	Before 1952	Retrospective survey of out-patients	11–15	*Stages I & II 50% *Stages III & IV 50%
Duthie *et al.* (1964) [7]	Edinburgh, UK	200	1948–51	Prospective survey of hospital admissions	9	*Stages I & II 62% *Stages III & IV 38%
Cosh and Raskar (1982) [8]	Bath, UK	54	1957–63	Prospective survey of out-patients with early disease only	20	*Stages I and II 55% *Stages III and IV 45%

*Grading of functional capacity. (After Steinbroker *et al.* [9].)

Table 2. Major controlled trials of second-line drugs against placebo in rheumatoid arthritis.

Drug	Trial	Number of cases	Duration (months)	Withdrawals (% of treated group)	Effect on synovitis	Effect on ESR	Effect on radiological progression
Gold	Empire Rheumatism Council (1960) [25]	200	18	17	Yes	Yes	No
	Co-operating Clinics (1973) [26]	68	6	36	Yes	Yes	Suggestive
	Sigler *et al.* (1974) [27]	27	24	Nil	Yes	Suggestive	Yes
Penicillamine	Multicentre trial Group (1973) [28]	105	19	42	Yes	Yes	No
	Shiokawa *et al.* (1977) [29]	179	6	34	Yes	Yes	No
	Dixon *et al.* (1975) [30]	82	6	57	Yes	Yes	No
Chloroquine and hydroxychloroquine	Freedman and Steinberg (1960) [31]	107	12	21	Yes	Yes	Suggestive
	Popert *et al.* (1961) [32]	122	12–24	15	Yes	Yes	No
	Hamilton and Scott (1962) [33]	41	6	13	Yes	Suggestive	No
Cyclophosphamide	Co-operating Clinics (1970) [34]	64	8	26	Yes	No	Yes

manifestations. Second-line drugs will affect not only local joint inflammation but also laboratory parameters such as ESR and C-reactive protein level[19]. The frequently used second-line drugs are gold, penicillamine and the anti-malarials (chloroquine and hydroxychloroquine), cytotoxic drugs such as cyclophosphamide, azathioprine, and chlorambucil being prescribed less often. The main second-line drugs have all been subject to controlled trials. A number of other drugs such as dapsone[20], levamisole[21] and sulphasalazine[22] have also been shown to have 'second-line' effects. In addition, a few non-steroidal anti-inflammatory drugs may have some of the properties of second-line drugs[23,24].

The important controlled trials of second-line drugs against placebo are shown in Table 2. Second-line drugs consistently show a beneficial effect on local inflammatory

synovitis and on the systemic inflammatory component of the disease as assessed by tests such as the ESR. These effects are also shown in trials of different second-line drugs against each other, for example the trial of gold, azathioprine and cyclophosphamide reported by Currey *et al.*[35]. On the other hand, such treatment has had a variable and inconsistent effect on the progression of radiological changes.

Second-line drugs produce so large a variety of adverse reactions that a high proportion of patients stop therapy. Prospective studies of gold therapy have confirmed the incidence of withdrawal in controlled trials[36,37]. Rothermich *et al.*[38] showed that by five years only 20 of 97 patients given gold were taking the drug; full remission had occurred in only two cases, and the others had been withdrawn due to toxicity or lack of effect. Similar results have been found at other centres (K. Grindulis and B. McConkey, personal communication). Whether gold really is a long-term agent is debatable. A subsequent report by Rothermich *et al.*[39] showed a similar situation with penicillamine; in only 29 per cent of 200 patients could it be used as a long-term agent.

The evidence that second-line drugs significantly affect radiological progression in all cases is questionable. Controlled trials have failed to agree on this point. Luukkainen *et al.*[40,41] suggested that gold therapy reduced the rate of radiological progression, but their study groups were not directly comparable and the differences were small. Other studies have suggested that disease severity, assessed clinically or by the ESR and acute phase protein levels at a point in time, is related to the extent of radiological progression[42-44]. However, these studies fail to show that radiological progression over a period of time is influenced by second-line drugs.

The place of corticosteroids is the subject of further debate[45]. They produce rapid symptomatic improvement and reduction in the ESR[46-48]. Patients given steroids have falls in acute phase reactants such as the C-reactive protein similar to those in patients given gold and penicillamine, but with steroids the falls are more rapid and are seen in all patients[49]. There is also some evidence that steroids, compared to aspirin, can slow the rate of radiological progression over a two-year period[50]. Thus, to some extent, steroids have features characteristic of second-line drugs.

The present therapeutic approach in patients with rheumatoid arthritis raises important questions about long-term effects. First, what is the relationship between ESR, functional capacity and radiological changes? Second, is there evidence that treatment is effective in the long term? To examine these questions further we have analysed the results of a long-term study at Droitwich.

The Droitwich Study

Between 1964 and 1976 a prospective survey of the long-term effects of treating rheumatoid arthritis was carried out at the Droitwich Centre for Rheumatic Diseases. Droitwich has a specialised Rheumatology Unit with extensive in-patient and out-patient facilities which is a referral centre for the West Midlands. In the Droitwich survey 112 patients were followed for 10 years; all these cases had intensive therapy, including hospitalisation, physiotherapy, surgery and treatment with analgesics, non-steroidal anti-inflammatory drugs and second-line drugs.

Patients Studied

All the patients had definite or classical disease by the criteria of the American Rheumatism Association[51]. Consecutive patients with severe disease seen by one physician (A.J.P.) between 1966 and 1968 and admitted to hospital at the Droitwich Centre for Rheumatic Diseases for the treatment of their arthritis were included in the study. The patients were assessed when first seen and then at 5 and 10 years. Laboratory data, assessment of functional capacity and radiographic evidence of disease progression were recorded. Laboratory tests included ESR and Rose-Waaler titre. Functional capacity was assessed using a modified Steinbroker grading[9] (I — symptom-free, II — mild incapacity, III — severe incapacity (off work), IV — housebound, V — bedridden). Radiographs of the hands were scored by a modified Steinbroker grading—scoring one point for each proximal interphalangeal (except the thumb), metacarpophalangeal, wrist and radiocarpal joint showing significant cartilage loss, secondary osteoarthritis or subluxation. These are equivalent to Steinbroker grade III changes and give a range of 0–22 points for each pair of hands. The radiographs were read 'blindly' by two independent observers (B.L.C. and J.A.C.) and a reconciled grading was reached.

All second-line drugs given for more than three months and any associated adverse reactions were noted. Surgical procedures undertaken directly for the arthritis were recorded. Deaths (17 patients) were recorded and the causes obtained from death certificates (four based on postmortem examination). Five patients were lost to follow-up during the study and the radiographs of two patients were not available at 10 years.

All patients had similar intensive therapy. Initially they were admitted to hospital in the Droitwich Centre for Rheumatic Diseases and given bed rest for 3–6 weeks with splints and intensive static exercises. When they had shown evidence of a reduction in disease activity they were slowly mobilised over a similar period with intensive physiotherapy and hydrotherapy. They were given analgesics and non-steroidal anti-inflammatory drugs and all received second-line drugs (prednisolone being used as a second-line drug) when first treated. Second-line drugs were given over prolonged periods with the aim of suppressing disease activity as completely as possible. They were only withdrawn because of serious adverse reactions, lack of effect or if patients entered a prolonged remission. If one second-line drug was withdrawn when the patient was not in remission, another was started. In cases failing to respond satisfactorily these drugs were used in combination. Patients were seen regularly, in most cases at intervals of less than six months, and if there was any indication of marked disease activity they were re-admitted to hospital. At the end of the study all the

patients who were alive and could be traced were sent a questionnaire to determine their socio-economic status; 79 (88 per cent) replied.

Results

The patients in the study were a group of mixed sex, age and disease duration (Table 3) and were a typical cross-section of cases secondarily referred to a specialised rheumatology unit. The major changes occurring during the ten-year period of the study are summarised in Tables 4–7. Although not all the patients were seropositive for rheumatoid factor, had a raised ESR and radiological evidence of joint destruction when first seen, only five were initially negative for all these parameters.

Table 3. Patients in Droitwich study.

Age at start of study (years)	M	F	Total
<30	6	11	17
32–40	4	17	21
41–50	7	23	30
51–60	13	18	31
>60	2	11	13
Disease duration at start of study			
<18 months	10	20	30
18 months–5 years	14	28	42
5–10 years	4	18	22
>10 years	4	14	18

Table 4. Droitwich study: erythrocyte sedimentation rate during 10 years.

	Values (%)		
ESR (mm/h)	Initial (n = 112)	5 years (n = 111)	10 years (n = 90)
0–20	23	47	45
21–49	44	39	43
50 or more	33	14	12

Table 5. Droitwich study: Rose-Waaler titres during 10 years.

	Values (%)		
Rose-Waaler titre (reciprocal)	Initial (n = 112)	5 years (n = 111)	10 years (n = 90)
0	26	26	26
4–32	8	32	23
64 or more	66	42	51

Table 6. Droitwich study: functional capacity during 10 years.

	Values (%)		
Functional capacity	Initial (n = 112)	5 years (n = 111)	10 years (n = 90)
I Symptom free	0	12	30
II Mild incapacity	23	42	37
III Severe incapacity (off work)	63	37	21
IV Housebound	10	7	12
V Bedridden	4	2	0

Table 7. Droitwich study: assessments of hand radiographs. Only the metacarpophalangeal, proximal interphalangeal and wrist joints were assessed, giving a total of 22 joints for both hands.

Radiographical assessment (no. of joints scoring Steinbroker grade III)	Values (%)		
	Initial	5 years (n = 111)	10 years (n = 88*)
0	29	11	8
1– 5	40	32	22
6–10	20	27	26
11–15	5	14	22
16–20	5	9	16
21–22	1	7	6

*Only 88 of the 90 patients followed-up were analysed: in 2 cases hand radiographs were not available.

During the 10 years of the study there was a considerable fall in the number of patients with a greatly elevated ESR; initially 33 per cent had an ESR of over 50mm and by 10 years only 12 per cent had such a high ESR. In contrast, there was relatively little overall change in the number of seropositive patients (Table 5), and there was no marked fall in the mean Rose-Waaler titre.

The functional capacity showed a marked and important improvement during the period of follow-up (Table 6). Initially only 23 per cent of cases were in classes I and II for functional capacity, but by 10 years 67 per cent of cases were in these classes.

However, radiological changes (Table 7) showed a steady progression, and less than one-third of patients did not progress by at least one class. The differences between changes in functional capacity and hand radiographs are illustrated in Fig. 2.

A detailed examination of radiographic progression showed that only 7 patients (8 per cent of cases) did not have significant joint destruction by 10 years: of these, 4 were consistently seronegative for rheumatoid factor and 3 of these never had a raised ESR. In other words, these were an atypical group with mild disease who may not have needed second-line drugs in terms of the severity of their disease. In typical patients it was exceptional not to have radiological changes by 10 years. Comparison of X-ray changes with the initial degree of inflammation indicated by the initial ESR showed that patients who had marked progression (by three or four of the classes given in Table 7) all had an elevated ESR when first seen, although analysis of the relationship between ESR and radiological progression (by chi-squared analysis) did not reach statistical significance ($0.10 > P > 0.05$).

Treatment by surgery and second-line drugs is summarised in Table 8; only second-line drugs given for at least three months are included in this analysis, as a shorter period of administration was considered unlikely to be of clinical value. The object of therapy was to suppress disease activity completely if possible and to

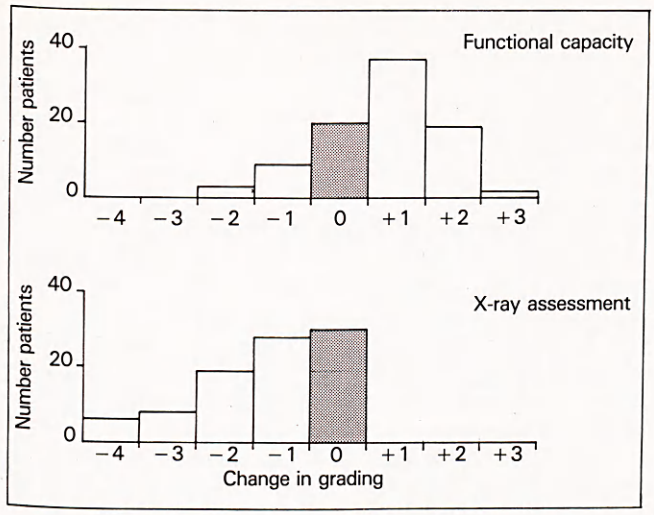

Fig. 2. *The Droitwich survey. A comparison between changes in grading for functional capacity and hand radiographs. Changes in functional capacity are derived fom changes in the modified Steinbroker grading. Changes in X-rays are derived from changes in the number of joints showing damage equivalent to Steinbroker grade III changes; these have been grouped as shown in Table 7. Negative changes represent deterioration and positive ones improvement. The patients showing no change are in the shaded area.*

Table 8. Droitwich study: treatment during 10 years. There is a separate analysis for each form of treatment.

	Cases treated (%) (n = 112)	Cases not treated(%) (n = 112)
Long-acting drugs (given for at least 3 months)		
Gold	79	21
Chloroquine	72	28
Steroids	91	9
Penicillamine	18	82
Immunosuppressives (cyclophosphamide, chlorambucil, azathioprine)	16	84
Surgical Procedures		
Hand synovectomy/tendon operations	21	79
Other synovectomies	21	79
Reconstructive surgery	22	78

maintain this suppression once it had been achieved. All the patients had at least one second-line drug for this period of time; the median number of drugs was three; four patients received five different second-line drugs. Combinations of drugs were either given sequentially or concurrently, or occasionally in both ways. Each patient had a somewhat different pattern of drug administration and a complete analysis is outside the scope of this study. Similarly, although lack of effect and adverse reactions were both important causes of changing or withdrawing second-line drug therapy, in many patients they had a composite effect; once again, a meaningful analysis of the reasons for stopping falls outside this study. However, it can be seen that the majority of patients had prolonged and intensive therapy with second-line drugs.

Adverse reactions to second-line drugs were common. There were 225 adverse reactions to steroids, although most were trivial, such as a mildly Cushingoid appearance. The major ones were vertebral collapse (13 cases), infection (11 cases), cataract (6 cases) and myopathy (2 cases). It was difficult to predict the patients who would develop these reactions, which were not simply dose-related. For example, the incidence of vertebral collapse was not related to the dose of steroids. There were 30 adverse reactions to gold, 11 to immunosuppressives and 4 to penicillamine. These were of similar severity with each drug and consisted of: abnormal blood counts (5 cases, 4 with immunosuppressives), rash (20 cases), proteinuria (12 cases) and others such as mouth ulcers, colitis and infection (8 cases). Four patients stopped treatment with chloroquine because of visual reactions, the only adverse effect of the drug. One had a slight corneal opacity but no other lesion. Two had transient blurring of vision with possible macula deposition but, when re-examined after stopping therapy, had recovered normal visual acuity without significant macula deposition. One had slightly reduced visual acuity (6:9 and 6:12 in each eye) associated with some macula chloroquine deposition, but there were other visual problems in this patient (astigmatism and refraction defects) which may also have been significant, and there was no visual deterioration after stopping the drug.

Marked social disadvantage among the patients was apparent at the ten-year survey (Table 9). Only 32 per cent of men and women were undertaking completely normal activities, although a further 9 per cent had retired. The work record broadly corresponds to functional capacity, but some housewives needing help were nevertheless so incapacitated as to fall into category III of the functional capacity assessment. Many patients also required adaptations or various appliances; the relatively small number using kitchen aids (8 per cent) is surprising and probably represents a failure in assessment and supply of these aids. By 10 years 29 per cent of the patients were registered disabled, although some were still working.

There were 17 deaths during the course of the study (Table 10). These patients had a mean age of 61.3 years and they died between 4 and 10 years of follow-up. Four of these deaths were almost certainly related to the rheumatoid disease, including two deaths due to abdominal sepsis (ages 47 and 60) and one due to bronchopneumonia complicated by gastrointestinal haemorrhage (age 29). Another four deaths, including two patients with renal infection as a major or contributory factor, may also have been related to the rheumatoid disease.

Discussion

The Droitwich survey confirms that patients with rheumatoid arthritis referred to a specialised unit and, judged by current criteria, needing second-line drugs, have a severe, progressive and disabling disease. The therapeutic regimen used in this survey reflects both the period

Table 9. Droitwich study: number of patients at work, with home adaptations and aids, or using appliances at the end of 10 years determined by questionnaire. Only 79 of the 90 patients followed-up for 10 years responded (a response rate of 88 per cent).

	Number of patients
Work	
Normal work	9
Normal housewives	16
Light work only	5
Housewives needing some help	34
Not working	3
Housewives needing total help	5
Retired	7
Total	79
Home adaptations and aids	
Lift	2
Kitchen aids	6
Bathroom aids	28
Toilet aids	18
Stair adaptations	6
Ramps	5
Total	65
Appliances supplied in previous 12 months	
Splints	21
Surgical shoes	8
Surgical corset	6
Cervical collar	6
Walking stick	9
Crutches/walking frame	7
Total	57

during which it was undertaken, with drugs such as penicillamine used only towards the end of the study, and the personal preference of the physicians involved, as shown by the frequent use of chloroquine. The mortality in the survey was similar to that previously reported[52–55], with an apparent excess of deaths due to infection.

The changes measured in the outcome indices showed an improvement in functional capacity and a reduction in ESR, but a radiological progression of disease in many patients. In other words, there is a divergence between radiological changes and function. The possible reasons for this are many. We believe that, once a joint is significantly damaged, the damage will get worse, despite treatment, because of simple mechanical derangement. This view concurs with the results of this study. Similarly, there is no direct relationship between function and radiological evidence of joint damage. Muscle power, pain and local inflammation, as well as personality, may influence function. Our results do not show whether the rate of joint destruction is reduced by adequate treatment with second-line drugs; we consider this to be an important question and we are at present undertaking further studies to answer it.

The Droitwich survey also establishes that adequate treatment may influence disease progression. This is proved by the number of cases showing improved functional capacity and by the number of people engaged in useful work at the end of the ten-year period. The ability of treatment to affect the disease is also shown by the reduction in the number of patients with an elevated ESR.

Duthie *et al.*[7,10,11] clearly established the benefit of hospitalisation, and subsequent reports have described the advantages of bed rest[56] and physiotherapy[57]. In the Edinburgh series of Duthie *et al.*, only minimal therapy with second-line drugs was used, although patients had intensive physical treatment, splinting, bed rest and aspirin, and it is relevant to compare this with the Droitwich survey. The number of patients in Functional Classes I and II at initial assessment was 35 per cent of the Edinburgh series and 25 per cent of the Droitwich series; at 9-10 years these classes contained 62 per cent of the Edinburgh series and 67 per cent of those at Droitwich. Despite all the changes in therapy between 1950 and 1965, and the intensive second-line drug therapy used at Droitwich, the improvement in functional capacity (in the long term) was almost identical in both surveys. This confirms the significant contribution made by hospital admission.

Table 10. Droitwich study: deaths during 10 years.

Cause of death	Number	Further details
Cardiovascular	6	Myocardial infarction (2 cases) Cardiac failure—hypertensive (1 case) Cardiac failure—ischaemic (1 case) Arrhythmia (1 case) Ruptured aortic aneurysm (1 case)
Infective	6	Lobar pneumonia (1 case) Bronchopneumonia (3 cases) Peritoneal/retroperitoneal abscesses (2 cases)
Renal	2	Pyelonephritis (1 case) Chronic renal failure (1 case)
Carcinoma	1	Prostatic carcinoma
Pneumothorax	1	Complication of chronic obstructive airways disease
Rheumatoid arthritis	1	—

Should we use second-line drugs? The current answer appears to be yes. The main objective in treating rheumatoid arthritis should be to improve the quality of life. Whatever their long-term effects, second-line drugs give considerable symptomatic benefit and we consider that this is their major advantage. However, therapy with second-line drugs is only one aspect of the treatment of rheumatoid arthritis. The importance of admission to specialised rheumatic units in hospitals, which provide a wide range of supportive and physical treatments, cannot be over-emphasised. These units should be provided by the Health Service. Even if rheumatoid arthritis is not cured by treatment, its management requires long-term commitment.

References

1. Bennett, P. H. and Wood. P. H. N. (1968) *Population studies on the Rheumatic Diseases.* Amsterdam: Excerpta Medica.
2. Meenan, R. F., Yelin, E. H., Nevitt, M. and Epstein, W. V. (1981) *Arthritis and Rheumatism,* **24,** 544.
3. Wright, V. and Amos, R. (1980) *British Medical Journal,* **280,** 964.
4. Leading article (1981) *Lancet,* **1,** 193.
5. Short, C. L., Bauer, W. and Reynolds, W. E. (1957) *Rheumatoid Arthritis.* Cambridge, Mass.: Harvard University Press.
6. Ragan, C. and Farrington, E. (1962) *Journal of the American Medical Association,* **181,** 663.
7. Duthie, J. J. R., Brown, P. E., Truelove, L. H., Baragar, F. H. and Lawrie, A. J. (1964) *Annals of the Rheumatic Diseases,* **23,** 193.
8. Cosh, J. A. and Rasker, J. J. (1982) *Annals of the Rheumatic Diseases,* **41,** 317.
9. Steinbroker, O., Traeger, C. H. and Batterman, R. C. (1949) *Journal of the American Medical Association,* **140,** 659.
10. Duthie, J. J. R., Thompson, M., Weir, M. M. and Fletcher, W. B. (1955) *Annals of the Rheumatic Diseases,* **14,** 133.
11. Duthie, J. J. R., Brown, P. E., Knox, J. D. E. and Thompson, M. (1957) *Annals of the Rheumatic Diseases,* **16,** 411.
12. Hart, F. D. (1978) *Drug Treatment of the Rheumatic Diseases.* Lancaster: MTP Press.
13. Huskisson, E. C. (1979) *Clinics in Rheumatic Diseases,* **5,** Part 2.
14. Huskisson, E. C. (1980) *Clinics in Rheumatic Diseases,* **6,** Part 3.
15. Bunch, T. W. and O'Duffy, J. D. (1980) *Mayo Clinic Proceedings,* **55,** 161.
16. Huskisson, E. C., Woolf, D. L., Balme, H. W., Scott, P. J. and Franklyn, S. (1976) *British Medical Journal,* **2,** 1048.
17. Scott, D. L., Roden, S., Low-Beer, T. S. and Takavashara, L. (1982) *Postgraduate Medical Journal,* **58,** 146.
18. O'Sullivan, J. B. and Cathcart, E. S. (1972) *Annals of Internal Medicine,* **76,** 573.
19. McConkey, B., Crockson, R. A., Crockson, A. P. and Wilkinson, A. R. (1973) *Quarterly Journal of Medicine,* **42,** 785.
20. McConkey, B., Davies, P., Crockson, R. A., Crockson, A. P., Butler, M. and Constable, T. J. (1976) *Rheumatology and Rehabilitation,* **15,** 230.
21. Runge, L. A., Pinals, R. S., Lourie, S. H. and Tomar, R. H. (1977) *Arthritis and Rheumatism,* **20,** 1445.
22. McConkey, B., Amos, R. S., Durham, S., Forster, P. J. G., Hubball, S. and Walsh, L. (1980) *British Medical Journal,* **280,** 442.
23. Berry, H., Fernandes, L., Ford-Hutchinson, A. W., Evans, S. J. W. and Hamilton, E. B. D. (1978) *Annals of the Rheumatic Diseases,* **37,** 93.
24. Meacock, S. C. R., Kitchen, E. A. and Dawson, W. (1979) *European Journal of Rheumatology and Inflammation,* **3,** 23.
25. Research Subcommittee of the Empire Rheumatism Council (1960) *Annals of the Rheumatic Diseases,* **19,** 95.
26. The Co-operating Clinics Committee of the American Rheumatism Association (1973) *Arthritis and Rheumatism,* **16,** 353.
27. Sigler, J. W., Bluhm, G. B., Duncan, H., Sharp, J. T., Ensign, D. C. and McCrum, W. R. (1974) *Annals of Internal Medicine,* **80,** 21.
28. Multicentre Trial Group (1973) *Lancet,* **1,** 275.
29. Shiokawa, Y., Horiuchi, Y., Honma, M., Kageyama, T., Okada, T. and Azuma, T. (1977) *Arthritis and Rheumatism,* **20,** 1464.
30. Dixon, A. St. J., Davis, J., Dormandy, T. L., Hamilton, E. B. D., Holt, P. J. L., Mason, R. M., Thompson, M., Weber, J. C. P. and Zutshi, D. W. (1975) *Annals of the Rheumatic Diseases,* **34,** 416.
31. Freedman, A. and Steinberg, V. L. (1960) *Annals of the Rheumatic Diseases,* **19,** 243.
32. Popert, A. J., Meijers, K. A. E., Sharp, J. and Bier, F. (1961) *Annals of the Rheumatic Diseases,* **20,** 18.
33. Hamilton, E. B. D. and Scott, J. T. (1962) *Arthritis and Rheumatism,* **5,** 502.
34. Co-operating Clinics Committee of the American Rheumatism Association (1970) *New England Journal of Medicine,* **283,** 883.
35. Currey, H. L. F., Harris, J., Mason, R. M., Woodland, J., Beveridge, T., Roberts, C. J., Vere, D. W., Dixon, A. St. J., Davies, J. and Owen-Smith, B. (1974) *British Medical Journal,* **3,** 763.
36. Kean, W. F. and Anastassiades, T. P. (1979) *Arthritis and Rheumatism,* **22,** 495.
37. Rothermich, N. O., Phillips, V. K., Bergen, W. and Thomas, M. H. (1976) *Arthritis and Rheumatism,* **19,** 1321.
38. Rothermich, N. O., Phillips, V. K., Bergen, W. and Thomas, M. H. (1979) *Arthritis and Rheumatism,* **22,** 423.
39. Rothermich, N. O., Thomas, M. H., Phillips, V. K. and Bergen, W. (1981) *Arthritis and Rheumatism,* **24,** 1473.
40. Luukkainen, R., Kajander, A. and Isomaki, H. (1977) *Scandinavian Journal of Rheumatology,* **6,** 189.
41. Luukkainen, R., Isomaki, H. and Kajander, A. (1977) *Scandinavian Journal of Rheumatology,* **6,** 123.
42. Brook, A., Fleming, A. and Corbett, M. (1977) *Annals of the Rheumatic Diseases,* **36,** 274.
43. Young, A., Corbett, M. and Brook, A. (1980) *Rheumatology and Rehabilitation,* **19,** 14.
44. Amos, R. S., Constable, T. J., Crockson, R. A., Crockson, A. P. and McConkey, B. (1977) *British Medical Journal,* **1,** 195.
45. Gerber, E. K., Fan, P. T. and Bluestone, R. (1981) *Seminars in Arthritis and Rheumatism,* **11,** 231.
46. Joint Committee of the Medical Research Council and Nuffield Foundation (1954) *British Medical Journal,* **1,** 1223.
47. Joint Committee of the Medical Research Council and Nuffield Foundation (1955) *British Medical Journal,* **2,** 695.
48. Joint Committee of the Medical Research Council and Nuffield Foundation (1957) *British Medical Journal,* **1,** 847.
49. McConkey, B., Davies, P., Crockson, R. A., Crockson, A. P., Butler, M., Constable, T. J. and Amos, R. S. (1979) *Annals of the Rheumatic Diseases,* **38,** 141.
50. Joint Committee of the Medical Research Council and the Nuffield Foundation (1959) *Annals of the Rheumatic Diseases,* **18,** 173.
51. Ropes, M. W., Bennett, E. A., Lobb, S., Jacox, R. and Jessar, R. (1958) *Bulletin of the Rheumatic Diseases,* **9,** 175.
52. Uddin, J., Kraus, A. S. and Kelly, H. G. (1970) *Arthritis and Rheumatism,* **13,** 125.
53. Koota, K., Isomaki, H. and Mutru, O. (1977) *Scandinavian Journal of Rheumatology,* **6,** 241.
54. Constable, T. J., McConkey, B. and Paton, A. (1978) *Annals of the Rheumatic Diseases,* **37,** 569.
55. Rasker, J. J. and Cosh, J. A. (1981) *Annals of the Rheumatic Diseases,* **40,** 115.
56. Smith, R. D. and Pulley, H. F. (1978) *Mayo Clinic Proceedings,* **53,** 141.
57. Glass, J. (1978) *Australian and New Zealand Journal of Medicine,* **8,** (suppl. 1), 168.