the regular taking of vital drugs may be jeopardised by essential prescribing. Every drug prescribed to an elderly patient needs a long hard look.

A major problem of drug compliance trials is assessing the practical clinical importance of the errors found. We included only substantial under- or over-dosage—patients had to be taking all their drugs at roughly under half or over double the prescribed dose to be noted. The large error rates we found may well underestimate the problem. Both old medication and other people's tablets may be outdated and may produce drug interactions or overdosage when taken with the prescribed regimen. Their effects are potentially as serious as under- or over-dosage and have been given equal weight in the analysis. The most frequently prescribed drugs were digoxin, diuretics, potassium supplements, and levodopa preparations. Substantial misuse of any of these drugs can be dangerous, so the high incidence of serious errors found—particularly in the uncounselled patients—is clinically important.

Our main recommendation is that a designated member of staff, preferably the clinical pharmacist, should talk to each

elderly patient for about 15 minutes before discharge to make sure that he understands and remembers his drug regimen. This technique greatly reduces medication errors in even the most confused patients.

We thank the physicians of Sherwood Hospital for permission to study patients under their care, and Mr J Gilby, district pharmaceutical officer, for his encouragement. We also wish to thank Professor M J S Langman for his statistical advice.

References

- ¹ Gibson, I I J M, and O'Hare, M M, *Gerontologia Clinica*, 1968, **10**, 271.
- ² Stewart, R B, and Cluff, L E, *Clinical Pharmacology and Therapeutics*, 1972, **13**, 463.
- ³ Parkin, D M, *et al*, *British Medical Journal*, 1976, **2**, 686.
- ⁴ Law, R, and Chalmers, C, *British Medical Journal*, 1976, **1**, 565.
- ⁵ Wandless, I, and Davie, J W, *British Medical Journal*, 1977, **1**, 359.
- ⁶ Robinson, R A, in *Assessment in Cerebrovascular Insufficiency*, p 89. Stuttgart, Georg Thieme Verlag, 1971.
- ⁷ Shaw, S M, and Opat, L J, *British Medical Journal*, 1976, **1**, 505.

Clinical Topics

Presentation of rheumatoid arthritis and its relation to prognosis*

F DUDLEY HART

British Medical Journal, 1977, **2**, 621-624

Summary

A review of published reports in an attempt to relate the way rheumatoid arthritis presents to its manner of progression and prognosis has provided few positive answers. Certain, but not all, studies indicate that cases with an acute explosive onset do better than those of more insidious onset, but the latter have almost certainly lasted longer by the time they come under medical supervision. Cases of monarthritis and palindromic (remittent) arthritis do better than polyarthritic and persistent cases, but true diagnosis of the former is often uncertain. Undoubtedly persistent high-titre seropositivity and nodule formation are bad prognostic pointers.

A plea is made for a more intensive study of the early case: if any therapeutic agent now or in the future can reverse the inflammatory process this is surely the time it is most likely to do so. This is the curable end of what is now an incurable disease.

*Based on a postgraduate lecture given at the Robert Jones and Agnes Hunt Orthopaedic Hospital in Oswestry on 5 March 1977.

Westminster Hospital, London SW1P 2AP

F DUDLEY HART, MD, FRCP, consulting physician

Introduction

Rheumatoid arthritis is a peculiar disorder; its many modes of presentation and its various patterns of progress make one wonder if it is not several pathological processes with many different starting factors rather than a single entity. This is important when it comes to assessing the value of different therapeutic agents. We put, let us say, a series of 100 patients together, and if drug A does not work in most and fails to ease pain, stiffness, and swelling we consider it a failure. But drug A may work like a charm in 10 or 20% of these cases and fail in the others and so gets lost in the statistical analysis. It would seem logical to look for these differences that may prove highly informative early in the disease.

A study of how the disease starts may possibly clarify not only causes and prognosis but also treatment. It would seem more logical to study early cases than the advanced; in most reported case histories the disease has been present for several years.

Types of onset

Rheumatoid arthritis may start in many ways.

ACUTE MONARTHRITIS

In 1973 Rasmussen *et al*¹ in Copenhagen reported on 65 patients with monarthritis of over three months duration, who had been observed on average for three years. Only four developed rheumatoid arthritis. The largest group (46 cases) were labelled "benign arthritis";

the essential differences in the biopsy results were less proliferation in the lining cells with minimal fibrinoid necrosis and rare fibrin deposits, whereas fibrin deposits in the patients with rheumatoid disease were almost constant and pronounced.

Over the whole series the prognosis was good, 76% having no symptoms after three years. Eight of the 46 cases of benign arthritis had persistent symptoms over this period. Rasmussen found an inflammatory reaction in both rheumatoid monoarthritis and benign monoarthritis, and, while both might be manifestations of rheumatoid arthritis of different intensity, the absence of fibrin deposits in the benign group was interesting, suggesting that these patients could dispose of their inflammatory fibrin deposits and recover normal function. Proliferation of synovium and lymphoid cells were similar in both groups, but greater in the rheumatoid patients. Although such cases of monoarticular rheumatoid arthritis do occur, in most clinicians' experience they are rare, and, though they usually have a better prognosis than other groups, they sometimes can and do progress relentlessly. Rasmussen's benign monoarthropathies probably included many rheumatoids that resolved completely and never progressed to diagnosable rheumatoid arthritis.

SUDDEN ONSET ACUTE POLYARTHRITIS

Duthie in Edinburgh studied the natural history of rheumatoid arthritis extensively, and in 1955² he reported the progress of 282 inpatients followed up for two years. He noted three types of course of the disease: (1) slowly progressive, (2) exacerbations and remissions, and (3) rapidly progressive. Eighty-four cases were admitted within one year of onset of the disease, 46 in group 3, and 38 in groups 1 and 2. Of these, the rapidly progressive group 1 did best, 87% improving greatly or moderately compared with 81.6% in the rest, but the difference is not significant. When progress was measured by improvement by grades of functional capacity 82.6% of the rapidly progressive group were found to have advanced by one or more grades compared with 71% of the other groups admitted within a year. At a nine-year assessment^{3,4} 52.9% of these patients were without residual disability as compared with 13.9% of cases starting more insidiously and 20% of other cases admitted within a year of onset. Those cases running an acute progressive course and admitted early to hospital for conservative inpatient treatment ran a more benign course than the others.

Short⁵ also found that patients with acute explosive onset did better than the others. Jacoby *et al*⁶ in a study of 100 cases of definite or classic rheumatoid arthritis seen within one year of onset (average duration three to nine months) noted that 23 had an acute, 28 sub-acute, and 49 gradual onset. Eight to 14 years later (mean interval 11 years) no appreciable differences were seen in the three groups. Unlike the patients in Duthie's series early admission to hospital did not appear to affect progress as assessed 11 years later. Corrigan *et al*⁷ in a study of 110 patients with rheumatoid arthritis starting after the age of 60 noted that 29 (15 men and 14 women aged 60 to 86) starting with abrupt acute explosive disease settled down within 18 months and fared better than the rest.

Kinsella⁸ and Porsmann⁹ had described a clinical subgroup of elderly rheumatoid patients with an acute stormy onset and a good prognosis with remission usually in a year. Hence the type of rheumatoid arthritis with acute rapid onset has probably generally a rather better prognosis than average, possibly because it tends to bring the patient under medical care sooner than the more insidious type, but Jacoby *et al*⁶ failed to confirm this.

LOW-GRADE DISEASE OF INSIDIOUS ONSET

In most studies patients with low-grade disease of insidious onset, including those of Duthie,² did less well than those with acute onset but the hard fact is that by the time they came under observation and were diagnosed their disease was of longer duration and was more advanced. Short *et al*¹⁰ in their classical study of the natural history of rheumatoid disease divided patients at onset of the disease into two types—acute (21.8%) and gradual (78.2%). In an attempt to obtain factors of prognostic importance those patients admitted first to hospital between 1930 and 1936 were reassessed in 1937, 1947, and 1954. In 250 patients in the 1947 study the rate of improvement (53.2%) was much the same as in the 1937 assessment; the factors associated with improvement were male sex, aged under 40, duration arthritis under one year on admission, and mild disease severity on admission. By 1954, with an average follow-up of 14 years, the percentage thought to have improved had fallen to 35%.

Jacoby *et al*⁶ noted at their final assessment eight to 14 years after onset that although the 83 surviving patients had improved as a whole in terms of sedimentation rate, haemoglobin, titre of rheumatoid factor, and state of disease, there was an overall deterioration in functional capacity, only the rheumatoid factor titre and functional capacity of the earlier review correlating with the ultimate outcome.

PALINDROMIC TYPE

The so-called palindromic rheumatism described by Hench and Rosenberg in 1944¹¹ contains probably several different disorders but it is most clinicians' impression that many of these patients have rheumatoid arthritis of relapsing-remitting type. Ward and Okihiro¹² followed up 140 of these patients seen at the Mayo Clinic for at least five years. Of these, 73 continued to suffer attacks, 11 experienced complete remission, while 50 had become rheumatoid arthritics.

Mattingly¹³ studied 20 such patients over 10 years and concluded that they were probably all rheumatoid arthritics in episodic form. Eleven had rheumatoid factor in the serum, and 10 had radiological evidence of arthritis, largely confined to the small joints of hands and feet. He considered that the disorder was a mild variant of rheumatoid arthritis with a good prognosis. Williams *et al*¹⁴ reviewed 35 patients, diagnosed initially as having palindromic rheumatism, some 7.4 years after symptoms started. Nineteen had persistent arthropathy, and most had rheumatoid factor in the serum. Three had developed rheumatoid nodules.

CARPAL TUNNEL MEDIAN NERVE COMPRESSION

Carpal tunnel median nerve compression may be an early, and occasionally the first, sign of rheumatoid arthritis.¹⁵ Brewerton¹⁶ considered it to be common in the early stages of the disease, becoming less frequent later. Barnes and Currey⁷ in a study of 45 classic cases of rheumatoid arthritis found abnormal electrodiagnostic test results in 49%, of whom 33% had also clinical evidence of median nerve compression, and a further 20% with symptoms and signs of the condition, a total of 69%.

Chamberlain and Corbett¹⁸ in a study of 72 patients with early rheumatoid arthritis found 17 (23%) with clinical evidence of the condition, but only four of 36 tested had positive electrodiagnostic findings. Polley and Lipscomb¹⁹ reported that 100 of a series of 1215 patients with the carpal tunnel syndrome had co-existent rheumatoid disease; in 38 the signs and symptoms of both conditions came on simultaneously. So far as I know, no follow-up of these patients has been reported yet, but neither Jacoby *et al*⁶ nor Otten and Westendorp Boerma²⁰ noticed any prognostic significance in the wrists or fingers being affected early.

EARLY NODULE FORMATION

Extensive nodule formation is usually associated with a high titre of rheumatoid factor and a bad prognosis. Wawrynska-Pagowska *et al*²¹ in a study of 202 patients with early rheumatoid arthritis found that 81 of 83 with positive rheumatoid factor had progressive disease, and among other bad prognostic features associated with persisting disease were subcutaneous nodules, atrophy of hand muscles, lymphadenopathy, anaemia, and the presence of C-reactive protein. They regarded an insidious onset with minimal involvement of hands and feet as bad prognostic pointers.

EARLY SEROPOSITIVITY

Like early nodule formation, an early high titre of rheumatoid factor in the serum would appear to be a bad prognostic pointer. Otten and Westendorp Boerma²⁰ in Holland studied 141 early cases of rheumatoid arthritis, 106 in the first three months of their disease (group A) and 35 with disease duration of four to six months (group B). Of the 106 early cases, 48 were men and 58 women. Over a three-year follow-up the patients whose disease persisted were mostly women, those who remitted mostly men. In group A 71% of seronegative patients recovered, but only 30% of seropositive: in group B half the seronegative but none of the seropositive patients recovered. They observed, however, that whether seropositive or seronegative, if the joints were still affected one year after onset recovery was rare.

Kellgren and O'Brien²² in a 10-year follow-up of 60 unselected rheumatoid patients (20 seronegative and 40 seropositive when first seen with severe active disease) reported 14 deaths—three in seronegative and 11 in seropositive patients. Of the survivors, 12 of 17 seronegative and 11 of 29 seropositive patients had partial or complete remission. Ligamentous instability and severe erosive disease progressing to arthritis mutilans occurred almost entirely in the seropositive group. Only two of 20 seronegative patients developed visceral lesions, but 16 of 32 seropositive sufferers developed serious vascular or visceral lesions or both, six proving fatal.

Gordon *et al*²³ in a study of 127 rheumatoid patients found that the development of extra-articular features related to rheumatoid factor titre, IgM levels, and the presence of soluble immune complexes, but not definitely to IgG levels. Those patients with extra-articular features had worse x-ray findings and more evidence of clinical damage: at the five-year follow-up mortality was twice as high in those patients with extra-articular features as in the others. There is little doubt, on existing evidence, that a high titre of rheumatoid factor in the serum concentration is a bad prognostic pointer. Although seropositive cases may revert to seronegativity, Jacoby *et al*⁶ found that subsequently 80% became positive again within three years; Dixon²¹ noted that seronegative disease could be serious and occasionally fatal.

PRODROMAL SYMPTOMS

Other types of onset have been observed: a diffuse stiffness syndrome, intermittent hydrarthrosis, tender painful feet (metatarsal head involvement), shoulder girdle syndromes, and others. The so-called prodromal signs and symptoms would appear to be either completely unrelated or probably in most cases the first sign of remitting-relapsing rheumatoid disease. The Empire Rheumatism Council's Survey²⁵ showed that in 302 rheumatoid patients and 302 control cases, the rheumatoid sufferers experienced considerably more undue fatigue, loss of weight, transient pains in muscles and joints, sweating, paraesthesia, and migrant swelling before the characteristic features of the disease developed.

Jacoby *et al*⁶ also observed that 23 of 100 patients described transient symptoms six to 12 months before the definitive onset of the disease; pains, stiffness or "fibrositis" in the shoulder in eight cases, transient involvement of wrist or metacarpophalangeal joint in six, pain in the first metatarsophalangeal joint in four, transient hip pain in two, pain and effusion in a knee in one, Raynaud's phenomenon in one, and wrist ganglia in two. They observed that these prodromal syndromes suggested miniature or "larval" attacks of rheumatoid arthritis, but found such cases did not differ from the others in their progression in the follow-up study.

Relationship of radiological changes to clinical outcome

The extent and rapidity of the development of bony erosions in the early stages of rheumatoid arthritis may give some indication of the prognosis, and erosive disease developing early and progressing rapidly in the first 18 months of the course of the disease is usually considered to be a bad prognostic pointer. Brook *et al*²⁶ recently reported a follow-up of 94 rheumatoid patients seen within one year of onset of the disease. These patients had annual radiography and were followed for a mean of 63.1 months. An erosive arthropathy occurred in 72, and the severity of the erosive changes showed a significant correlation with the eventual clinical outcome. These authors consider that it is possible to predict a favourable outcome in those patients whose erosive changes become static at an early stage in the course of the disease.

Discussion

It does not appear from published reports that the mode of onset is important in deciding the prognosis of a given patient. On the whole, patients with acute onset appear to do better than those of insidious onset but in the latter the disease has almost certainly lasted longer when first seen. The rheumatoid factor titre and the functional capacity early in the disease appear to correlate with the outcome, but sex, family history, prodromal factors, initial haemoglobin, and erythrocyte sedimentation rate and other factors do not. Early and extensive nodule formation is usually associated with a high titre of

rheumatoid factor in the serum concentration and may be generally regarded as of bad prognostic significance,³ though the evidence is sometimes conflicting.¹⁰

The effect of treatment on prognosis is difficult to evaluate, Duthie's¹ figures suggesting that early diagnosis and the institution of a management programme early in the disease course does help. While many treatments undoubtedly improve the quality of life led by the patient there is little evidence so far that any has any real effect on the eventual outcome. Certain treatments carry a definite risk to life, whether by gastrointestinal haemorrhage or perforation, aplastic anaemia or blood dyscrasia. As Jacoby *et al*⁶ say, a true picture of the natural disease can best be obtained by continued observation from early in the disease: in most series reported the disease has already been present for several years. The effect of any form of anti-inflammatory treatment can only be truly assessed early in the disease and before much irreversible destructive change has occurred; long-term assessment is much more difficult as many other factors operate.

Although probably some long-term treatments, such as gold and penicillamine, may alter the disease course and reduce or prevent radiological changes, much longer and larger follow-up series need to be done before this can be considered proved. The final therapeutic answer to this baffling disease will probably come from a greater study of the early cases when inflammatory features dominate the disease picture; it is in just these cases that gold and penicillamine appear on present evidence to have their best therapeutic effect. It is only in these early reversible cases that cures would be possible, even given a curative agent.

The value of long follow-up periods is very apparent from these studies. Often statements are made at one time, only to be contradicted later. Duthie²⁷ observed that after six years men did better than women, but after nine years both fared equally. Jacoby *et al*⁶ at a three-year follow-up found that 62 patients who had initially presented to the clinic within three months of onset were progressing better than the remaining 38, and 62 patients who had been admitted to hospital for treatment had a significantly worse functional capacity than the remainder: both these differences had disappeared in the 11-year survey.

It is appropriate to conclude with the nine-year follow-up findings of Duthie *et al* in Edinburgh.³ Of his original 307 patients, 75 had died and 32 could not be traced. Of the 200 survivors, 20.5% were without appreciable disability, 41% were moderately incapacitated, 27% were more severely crippled, and 11.5% had become completely dependent on others. For the first two years after discharge from hospital there was an overall improvement, thereafter a gradual and progressive deterioration in the functional state, due, in part, at least to advancing age and degenerative changes in damaged joints. Those whose disease was rated as inactive on at least one occasion fared distinctly better than those whose disease remained active throughout.

References

- 1 Rasmussen, E, Reimann, I, and Andersen, R B, *Scandinavian Journal of Rheumatology*, 1973, 2, 65.
- 2 Duthie, J J R, *et al*, *Annals of the Rheumatic Diseases*, 1955, 14, 133.
- 3 Duthie, J J R, *et al*, *Annals of the Rheumatic Diseases*, 1964, 23, 193.
- 4 Duthie, J J R, in *Textbook of the Rheumatic Diseases*, ed W S C Copeman, 4th edn, p 287. Edinburgh, Livingstone, 1969.
- 5 Short, C L, *Medicine*, 1964, 43, 401.
- 6 Jacoby, R K, Jayson, M I V, and Cosh, J A, *British Medical Journal*, 1973, 2, 96.
- 7 Corrigan, A B, *et al*, *British Medical Journal*, 1974, 1, 444.
- 8 Kinsella, R A, *Proceedings of the Interstate Post-Graduate Medical Assembly of North America 1942*, 1943, p 13.
- 9 Porsmann, V A, in *Proceedings 2nd European Congress of Rheumatology*, vol 2, p 479. Barcelona, editorial Scientia, 1951.
- 10 Short, C L, Bauer, W, and Reynolds, W E, *Rheumatoid Arthritis*, Cambridge, Massachusetts, Harvard University Press, 1957.
- 11 Hench, P S, and Rosenberg, E F, *Archives of Internal Medicine*, 1944, 73, 293.
- 12 Ward, L E, and Okishiro, M M, *Archives of Interamerican Rheumatology*, 1959, 2, 208.

- ¹³ Mattingly, S, *Annals of the Rheumatic Diseases*, 1966, **25**, 307.
- ¹⁴ Williams, M H, *et al*, *Annals of the Rheumatic Diseases*, 1971, **50**, 375.
- ¹⁵ Copeman, W S C, *Annals of the Royal College of Surgeons of England*, 1968, **43**, 274.
- ¹⁶ Brewerton, D A, in *Progress in Clinical Rheumatology*, ed A St J Dixon, p 56. London, Churchill, 1965.
- ¹⁷ Barnes, C G, and Currey, H L F, *Annals of the Rheumatic Diseases*, 1967, **26**, 226.
- ¹⁸ Chamberlain, M A, and Corbett, M, *Annals of the Rheumatic Diseases*, 1970, **29**, 149.
- ¹⁹ Polley, H F, and Lipscomb, P R, *Médecine et Hygiène* (Genève), 1966, **24**, 408.
- ²⁰ Otten, H A, and Westerndorp Boerma, F, *Annals of the Rheumatic Diseases*, 1959, **18**, 24.

- ²¹ Wawrynska-Pagowska, J, *et al*, *Acta Rheumatologica Scandinavica*, 1970, **16**, 99.
- ²² Kellgren, J H, and O'Brien, W M, *Arthritis and Rheumatism*, 1962, **5**, 115.
- ²³ Gordon, D A, Stein, J L, and Broder, I, *American Journal of Medicine*, 1973, **54**, 445.
- ²⁴ Dixon, A St J, *Annals of the Rheumatic Diseases*, 1960, **19**, 209.
- ²⁵ Empire Rheumatism Council, *Annals of the Rheumatic Diseases*, 1950, **suppl 9**, 53.
- ²⁶ Brook, A, Fleming, A, and Corbett, M, *Annals of the Rheumatic Diseases*, 1977, **36**, 274.
- ²⁷ Duthie, J J R, *et al*, *Atti del X Congresso della Lega Internazionale contro il Rheumatismo*, 1961, **1**, 213.

(Accepted 3 June 1977)

Today's Treatment

Diseases of the urinary system

High blood pressure and renal disease

GRAHAM A MACGREGOR

British Medical Journal, 1977, **2**, 624-626

High blood pressure is almost invariably found at some stage in patients with renal disease. This is unsurprising for not only does the kidney control sodium and water balance but it also secretes renin, which through angiotensin II is the most powerful arteriolar and venous constrictor known. Damage to the kidney, particularly that predominantly affecting the cortex, disturbs this finely balanced system and leads to an inability to control sodium and water excretion. On a normal salt intake there is retention of sodium and water so that sodium balance can be maintained. At the same time accompanying damage to the small arterioles leading to and from the glomeruli or directly to the juxtaglomerular cells themselves, leads to inappropriately high renin secretion for the state of sodium balance. These two factors—an increase in sodium and water or volume and inappropriately high renin—are the most important underlying mechanisms for the high blood pressure seen in renal disease. It must be remembered, however, that some patients with renal disease predominantly affecting the medulla—for instance, phenacetin nephropathy—may be unable to conserve sodium on a normal salt intake. These patients have a low or normal blood pressure, which in advanced renal disease is often the first sign of progressive sodium depletion.

While a rise in blood pressure may therefore be seen as an appropriate response, high blood pressure can of itself further damage the kidney and compound the underlying disease. Reduction of the high blood pressure slows down or halts the progressive development of renal failure. An interruption of this vicious circle of renal disease leading to high blood pressure, which further damages the kidney, leading to a higher blood pressure, is one of the few therapeutic moves that prevents or delays the need for long-term dialysis.

Risks of high blood pressure

Patients with a raised blood pressure in renal disease are as likely to develop a stroke or heart attack as hypertensive patients without renal disease. Moderately or mildly raised blood pressure leads to thickening of the arteriolar wall, which does not seriously impair renal function in a previously normal kidney but will do so if there is underlying renal disease. Severely raised blood pressure may cause damage to small arterioles causing fibrinoid necrosis and proliferation of arterioles. This leads to glomerular ischaemia and malignant hypertension. Malignant hypertension, whether caused by an underlying renal disease or causing the destruction of the kidney itself invariably leads, if *not* treated immediately and adequately, to progressive renal failure, and therefore to a lifetime of dialysis or transplantation.

An interruption of this vicious circle by reducing blood pressure is known to halt or even improve the renal failure. Despite this knowledge many patients with malignant hypertension are inadequately treated. They are referred to renal units with terminal renal failure when it is too late to reverse the process. The importance of early and effective reduction of blood pressure in malignant hypertension cannot be over-emphasised.

Mechanism

Recent advances in the more accurate measurement of the renin angiotensin system and the use of inhibitors have shown that raised blood pressure can be caused by excessive renin secretion. Measurements of body composition have shown that at the opposite extreme raised blood pressure can be due to excess sodium and water or volume. These two extremes are best illustrated by some patients on maintenance haemodialysis.

There are a few patients whose raised blood pressure does not fall with progressive weight reduction or sodium and water removal. These patients have high levels of plasma renin activity and angiotensin II. Infusion of saralasin, a competitive inhibitor of angiotensin II, reduces the raised blood pressure to normal,

Department of Medicine, Charing Cross Hospital Medical School, Fulham Palace Road, London W6 8RF

GRAHAM A MACGREGOR, MA, MRCP, senior registrar