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The natural history of rheumatoid arthritis: a fifteen year follow-up study
The prognostic significance of features noted in the first year

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SUMMARY One hundred patients with definite or classical rheumatoid arthritis have been followed since the early months of their disease; after 15 years the 65 surviving patients were reviewed. Their functional capacity had fallen by comparison with reviews made 3 and 11 years after onset, but half were still unimpaired or only moderately so (grade 1 and 2). The number of affected joints had risen to an average of 8 joints in men and 13 in women, but the ESR and the titre of the Rose test were lower than in the first year. Haemoglobin levels had risen in men, but fallen in women. The first-year titre of the Rose test proved to be of great prognostic significance, regarding ARA grading and number of affected joints after 15 years, but it did not correlate with the functional capacity. However, the functional capacity at 3 years correlated significantly with its value at 11 and 15 years. Patients with rheumatoid nodules were significantly worse than the remainder in many respects. A positive Schirmer test, showing diminished tear secretion, did not relate to any of the clinical parameters. The medical and surgical treatment is briefly reviewed.

Key words: Natural History, Rheumatoid Arthritis, Prognostic Features.

INTRODUCTION

In rheumatoid arthritis (RA) the wide variation in the severity and course of the disease in individual patients makes prognosis difficult. The best appreciation of the natural history of RA is derived from a study of a large number of patients followed from the start of the disease.

We present a further review of the group of patients with RA described by Jacoby et al in 1973 (1). They reported on the early features of the disease in 100 patients who had been first seen within a year of onset, and their state 11 years later. By then 17 had died, but the progress of the 83 survivors was in many ways favourable. There was an overall deterioration in their functional capacity over the 11 years, but this was attrib-

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uted mainly to the effect of age. On the whole, the various indices of severity of RA showed an improvement, as did the category of the disease based upon the criteria of the American Rheumatism Association (ARA) (2). The titre of the rheumatoid factor and the functional capacity in the early stages of the disease were seen to be of value in assessing prognosis.

Here we describe the further progress of this group of patients, based on a follow-up at approximately 15 years. By this time there had been 35 deaths. We report the clinical and laboratory findings in the 65 survivors and confirm the prognostic value of features noted in the early years of the disease. We have reported separately on the radiological changes in the cervical spine and hands found in this 15 year follow-up (3). We have also reviewed the causes of death at the time of a later, 18-year, follow up, when 43 patients had died (4).

THE PATIENTS

The original 100 patients formed a consecutive series in that all patients with RA of less than one year's duration, who were referred to JAC were accepted into the series if, by one year from the time of onset, they met the ARA criteria for "definite" or "classical" RA. There were 36 men and 64 women, of ages ranging from 18 to 81 years at onset (mean age 50.6 years). The mean duration of RA when first seen was 3.7 months, and at the end of the first year 48 were categorised as having "definite" and 52 "classical" RA.

Information was available from follow-up reviews made at an average of 3 years and 11 years from onset (1) as well as from many visits to clinics and admissions to hospital.

METHODS

Each of the 65 surviving patients was seen at the Royal National Hospital for Rheumatic Diseases by JJR. A history was taken of the course of the arthritis and its medical and surgical treatment, and a full clinical examination made. A joint score was estimated by counting the number of affected joints; the inter-phalangeal, metacarpo- and metatarso-phalangeal joints in each extremity being regarded as one unit. Functional capacity was assessed in four grades (5): 1 - fit for all activities; 2 - moderately restricted; 3 - markedly restricted; 4 - confined to bed or chair. The severity of the arthritis was categorised according to the eleven ARA criteria (2), the presence of 7 or more criteria being designated as "classical" RA, 5 or 6 criteria as "definite" RA, and less than 5 as "probable" or "possible" RA. Note was made of the presence and site of any rheumatoid nodules. Tear secretion was estimated by a Schirmer test: standardised sterile absorbent paper strips were hooked over the lower lid between the middle and outer thirds and the distance that the tear film spread along the paper in 5 minutes measured. Moistening of less than 5 mm is considered abnormal.

Laboratory investigations included estimations of haemoglobin, ESR (Westergren) and Rose test. The latter was expressed as the number of the serial dilution tube giving a positive result, tube 1 representing a titre of 1 : 4 and tube 10 - 1 : 2048. X-rays were taken of hands, wrists and cervical spine in all patients (3).

Comparisons were made with the haemoglobin and ESR at approximately one year and eleven years from onset, but in the case of the Rose test, the one-year figure taken was that of the highest titre found during the course of the first year. Estimates of functional capacity were only available from the time of the 3-year review, and not from the first year.

RESULTS

The 65 survivors were 19 men and 45 women, with a mean age of 61.3 years (s.d.

Table I *Functional Capacity in 65 survivors in the 3 reviews*

Functional Capacity	Year 3			Year 11			Year 15		
Grade	M	F	Total	M	F	Total	M	F	Total
1	13 68 %	30 65 %	43	12 63 %	15 33 %	27	4 21 %	5 11 %	9 14 %
2	5	14	19	4	18	22	9	14	23 36 %
3	1	1	2	3	11	14	4	21	25 38 %
4	0	1	1	0	2	2	2	6	8 12 %
Total	19	46	65	19	46	65	19	46	65

Table II *Mean functional capacity in men and women in the 3 reviews*

	Year 3	Year 11	Year 15
M	1.39	1.53	2.21
F	1.41	2.00	2.61
M + F	1.40	1.86	2.49

The mean is calculated on the basis of scoring 1 for each patient in grade 1; 2 for each patient in grade 2, etc.

13.0). Their mean age at onset was 46.7 years (s.d. 13.2) i.e., less than that of the original 100 at onset (50.6 years). The mean length of follow-up was 14.6 years (s.d. 1.7).

We were not able to confirm the favourable report of the 11-year review. There were a number of indications of deterioration, affecting the women more than the men.

Functional capacity. A significant fall in functional capacity was seen in both sexes, compared with the 3-year and 11-year reviews (Tables I and II). At 3 years the sexes were similar, each having about two-thirds in the highest grade. The 11-years and 15-year reviews showed a progressive deterioration, affecting the women more than the men. Table III shows that between 3 years and 15 years only 18 patients remained in the same grade, and the remainder deteriorated by 1,2 or even 3 grades.

Table III *Functional capacity in the 65 patients compared at 3 and 15 years*

		At the 3-year review			
	Grade	1	2	3	4
	No. of patients	43	19	2	1
At the 15-year review: Grade					
1	9	9	0	0	0
2	23	17	6	0	0
3	25	14	9	2	0
4	8	3	4	0	1
					18

At the time of the 11-year review it appeared that the fall in functional capacity could simply be attributed to age. This explanation is not now tenable, as the functional capacity of patients over 60 years of age at the 15-year review was found to be no worse than of those under 60 years. Details of the patients in the four grades of functional capacity are shown in Table IV.

Table IV *Details of the 65 patients in the 15-year review analysed by functional capacity (s.d. in brackets)*

	FC 1 n = 9		FC 2 n = 23		FC 3 n = 25		FC 4 n = 8	
Mean joint score	1.9	(2.0)	8.0	(4.0)	13.1	(5.0)	16.0	(2.6)
Hb (g/l)	14.2	(0.8)	13.8	(2.0)	12.6	(1.5)	13.2	(3.0)
ESR	18.1	(11.9)	30.6	(26.1)	51.5	(28.4)	43.5	(37.4)
RF titre (tube)	1.0	(1.7)	2.5	(2.6)	3.6	(3.1)	4.6	(3.3)
Nodules	0		4	(17.4 %)	7	(28 %)	5	(62.5 %)
Mean age	59.8	(14.6)	61.1	(12.9)	60.4	(12.1)	66.7	(15.6)

In general, the worse grades are associated with a higher joint score, and higher ESR, a higher titre of rheumatoid factor and a higher proportion with nodules.

ARA category. At the end of the first year, all 65 patients had, by definition, either "definite" or "classical" RA. At 11 years, 18 had improved sufficiently to be recate-

Table V *ARA category in the 65 patients*

	ARA category			
Time of review	Possible	Probable	Definite	Classical
1 year after onset	0	0	35	30
11 years	15	3	18	29
15 years	7	0	27	31

Table VI *Mean ARA category in the 65 patients (s.d. in brackets)*

	1 year		*11 years*		*15 years*	
men	2.4	(1.7)	1.7*	(1.4)	2.2**	(1.1)
women	2.48	(0.5)	2.9	(1.1)	2.3**	(0.9)
total	2.46	(0.5)	1.94**	(2.0)	2.26***	(0.9)

Based on the following scoring system: Possible RA 0: Probable 1: Definite 2: Classical 3.

* Original/ 11 years - significant improvement $p<0.05$
** Original/ 15 years - not significant
11 years/ 15 years - $p<0.05$ deteriorated
} both male and female

*** onset / 11 years t 3.63 $p<0.001$ (improved)
onset / 15 years t 1.85 not significant
11 yrs/ 15 years t 3.21 $p<0.01$ (signififantly worse)
} Total

gorised as having only "probable" or "possible" RA. We now found that much of this improvement had been lost, only 7 patients remaining in these milder categories (Table V).

The mean value for ARA category in both men and women had improved significantly between the first and the 11th year but in both sexes, the 15-years value returned to a figure not significantly different from that of the first year (Table VI).

Joint score. The number of affected joints increased significantly in both men and women by comparison with the 11-year review, now being 8 in men and 13 in women (Table VII). Although at 11 years and 15 years women had more affected joints than men, the differences between the sexes were note statistically significant.

Haemoglobulin. In the men, haemoglobulin levels rose significantly between the 11-year and 15-year reviews, but in women they fell (Table VIII). However, in both sexes values were higher than at 1 year after onset.

Sedimentation rate. In the men, the mean ESR fell between the first and the 11th year, and the lower figure was maintained at the 15th year. In the women, however, the mean ESR, having fallen at the 11th year, rose again at the 15th towards the first year level (Table VIII).

Rose test. The titres of the Rose test, expressed as mean value for men and for women, showed a progressive fall from the first year to the 11th and 15th years. This fall was statistically significant at each stage for each sex (Table IX).

Body weight. No significant change in weight was found in either the men or the women between the 11th and the 15th year.

Nodules. Sixteen of the 65 patients had nodules (29 %) and were significantly worse than those without nodules in respect of functional capacity, ARA category, joint score and Rose titre. They did not differ significantly in respect of haemoglobin, ESR or the Schirmer's test.

Schirmer's test. The 23 patients with a positive test, i.e. reduced tear secretion, did not differ from the rest in respect of functional capacity, ARA category, joint score, haemoglobin, ESR, nodules or Rose titre. However, they had a higher Rose titre than the rest at the 11-year review ($p<0.05$). The antinuclear factor test was positive in six patients with reduced tear secretion, and negative in five others - not a significant difference.

Table VII *Joint score in the 65 patients*

Time of review	Men Mean	(s.d.)	Women Mean	(s.d.)
11 years	5.2	(4.6)	7.8	(4.9)
15 years	7.8	(5.7)	13.2	(16.0)
*Significance	t 3.89	$p<0.01$	t 10.49	$p<0.001$

*Wilcoxon two-sample two-tailed test.
Male/female differences not signifivant (T = 1.44 NS $p\times0.10$). Welch's estimate of pooled variance for the type is also NS d = 2.009; Wilcoxon 2 sample test NS $p\times0.05$.

Table VIII *Haemoglobulin and ESR in 65 patients*

Time of review	Haemoglobulin (g %) Men	(s.d.)	Women	(s.d.)	ESR (mm/hr) Men	(s.d.)	Women	(s.d.)
1 year	13.47	(2.06)	11.54	(1.23)	46.5	(27.2)	47.0	(30.0)
11 years	14.60	(1.57)	13.19	(1.35)	20.5	(17.1)	24.0	(18.1)
15 years	15.05	(1.76)	12.61	(1.36)	25.3	(22.2)	43.3	(30.0)

Table IX *Rose test in the 65 patients. Expressed as the number of the serial dilution tube corresponding to the titre of rheumatoid factor. e.g. 3 signifies 1:16 and 8 1:512.*

Time of test	1st year		11-year review		15-year review	
	Mean	(s.d.)	Mean	(s.d.)	Mean	(s.d.)
Men	7.7	(3.5)	4.9	(3.0)	3.0	(3.1)
Women	7.9	(3.0)	5.0	(2.8)	2.9	(2.9)

Significance:

Men	Year 1/11	T 3.42	$p<0.01$	Women	Year 1/11	T 7.03	$p<0.001$
	Year 1/15	T 5.87	$p<0.001$		Year 1/15	T 10.54	$p<0.001$
	Year 11/15	T 2.98	$p<0.01$		Year 11/15	T 5.85	$p<0.001$

FEATURES WITH PROGNOSTIC SIGNIFICANCE

At the 11-year review of 83 patients, Jacoby et al (1) found that the first-year titre of the *Rose test* correlated significantly with the 11-year figures for the Rose titre, the number of ARA criteria present, and the joint score, but not with the functional capacity.

We repeated tests of correlation on the 65 patients surviving at 15 years, and confirmed these relationships with the same degree of significance (Table X).

We also found a correlation between the *haemoglobin* level at one year and its levels at the 11th and 15th years, and between the *functional capacity* at 3 years and its value at 11 and 15 years (Table X).

The *sedimentation rate* at one year did not

Table X *Prognostic markers: their later significance in 65 patients*

Correlation with:			
Feature		at 11 years	at 15 years
Rose titre in	Rose titre	$p<0.001$	$p<0.001$
	ARA category	$p<0.001$	$p<0.001$
	Joint score	$p<0.05$	$p<0.05$
	Functional Capacity	NS	NS
Hb at 1 year	Hb	$p<0.001$	$p<0.001$
ESR at 1 year	ESR	NS	$p<0.05$
Functional Capacity at 3 years	Functional Capacity	$p<0.001$	$p<0.001$
Weight at 1 year	Weight	NS	NS

correlate with its value at 11 years, though there was some correlation with its value at 15 years.

Treatment

Space only permits reference to certain aspects of treatment here.

Hospital admission. Fifty of the 65 patients had a period of in-patient treatment. Twenty were admitted once only but the remaining 30 had a total of 132 hospital admissions among them. At the time of the 3-year review patients who had had in-patient treatment had a worse functional capacity and a worse disease category than the rest. This was no longer the case at the 11-year and 15-year reviews.

Drug treatment. Virtually all patients had taken paracetamol and aspirin in various forms, althought only eight of the 65 were taking aspirin at the time of review.

Phenylbutazone had been given to 35 patients, though only six were still taking it. New prescriptions for phenylbutazone were infrequently issued after 1967. By then indomethacin was more often prescribed for 30 patients in all and eight were still taking it. We cannot attempt to analyse the many other non-steroidal anti-inflammatory drugs coming into use after 1970.

Second line drugs

Hydroxy-chloroquine was given to 55 patients, mostly as a course of 200 mg two or three times daily for 3 to 12 months, continuing longer if beneficial. Eye checks were made 6 monthly (later annually) while the drug was being taken. No cases of retinal damage were found.

Myocrysin was given to 35 patients, 21 having a single course and the remainder 2 - 4 courses. Initially, all courses were of 50 mg weekly up to a total of 1000 mg, but in the later years under review dosage became more flexible, often continuing beyond the 1000 mg total as 20 mg (fortnightly or 50 mg monthly. Most patients reported benefit, but in 12 patients the drug was stopped because of a skin reaction, in one with diarrhoea, in another with proteinuria and in two because of the lack of response.

D-Penicillamine was introduced in 1972, and was given to eight patients in all. The daily dose was built up gradually to 500 or 750 mg but the drug was continued beyond six months only in four patients.

Cytotoxic drugs. Azathioprin was given to five patients, and methotrexate to one, who also had psoriasis. Corticosteroids were being given to 29 patients at the time of review, usually as prednisone 2.5 to 7.5 mg daily. These patients were significantly worse than the rest in functional capacity ($p<0.001$), joint score, ESR, presence of nodules, and had a higher platelet count ($p<0.05$). They did not differ in ARA category, haemoglobin or Rose titre.

Orthopaedic surgery. As a result of their arthritis twenty nine of the 65 patients had had operations. There was a total of 65 operations i.e. an average of over two per patient. The commonest operation was knee synovectomy (17 times); other common sites for surgery were the hands, wrists and feet. Most operations were performed from the 8th year onwards; the few done in the first four years included carpal tunnel release and repair of ruptured extensor pollicis tendon.

DISCUSSION

We consider that our observations on the natural history of RA represent the true state of affairs in that our original 100 patients were selected only on the basis of being first seen in the clinic within a year at most from onset, and meeting the criteria for "definite" or "classical" RA at the end of a year. All were followed for 15 years. Other reported series (6,7,8,9) are less representative, being based on patients already admitted to hospital, sometimes with long-established RA. It is possible in those series that patients with mild or remitting arthritis might escape notice through not being admitted to hospital. There also is a certain

from of selection in our series, as 35 of the original 100 patients had died in the meantime. The cause of and age at death are discussed elsewhere (4). We found appreciable evidence of joint damage after 15 years. Only 9 of the 65 surviving patients were classed as fit for all activities. Women were affected more than men as judged by functional capacity, joint score and ESR. The improvement in ARA category at 11 years had been partly lost at 15 years. The majority still required drug therapy and nearly half had undergone orthopaedic surgery. There is evidence that men with RA tend to die earlier, but that those who survive have a less severe disease (4). These findings are in accordance with those of Short (8).

We have confirmed the prognostic value of the Rose test, using the highest titre found during the first year of the disease. It is a good indicator of the titre found at 11 years and 15 years, although there is a tendency for the titre to fall with the passage of the years. The first year titre is also a guide to the number of ARA criteria found in later years and to the joint score, a higher titre carrying a worse prognosis. It is also known that a higher titre is more often associated with vasculitis and we have reported elsewhere (4) that vasculitis was a contributory cause of death in four patients in our series. Others have found an association of rheumatoid factor with disease activity (10) and with X-ray changes (1, 11). Surprisingly, we found no correlation between the Rose titre in the first year and the functional capacity at 11 yars or 15 years. Here we differed from other authors (7). However, we did find that the functional capacity after 3 years was an indicator of the functional capacity at 11 and 15 years; the same relationship was found for haemoglobin. Thus once the disease is established we can find some basis, at one year and at 3 years after onset, for assessing its later course. Knowledge of the natural history of a disease is important for prognosis. From our results we may not make conclusions for the prognosis of an individual patient where other factors may play a role. We found some variables with prognostic significance so that when disease is established, after one or three years, we are able to tell something about the further course of the disease. The implication of our findings may be that in the case of a patient with a bad prognosis, we may in an earlier stage decide to use medication with more side effects like D-Penicillamine or Imuran.

It is of some interest to compare our figures for functional capacity at 11 and 15 years with those of Duthie (7) (Table XI). Duthie states that the deterioration of functional capacity could be ascribed to age, but we consider that the rather worse figures for functional capacity in our patients at 15 years are the results of the disease and are not merely due to age. Duthie's 200 patients were selected in a way different from our own, but among them were 84 comparable with those in our series in that their disease was of less than a year's duration at the time of admission to hospital. After 9 years 37 % of these 84 patients remained in functional capacity grade 1, exactly the same as Jacoby et al. found in our series at 11 years.

We did not find that sex or body weight had a statistically significant bearing on prognosis although our figures for functional capacity and joint score were worse for women than for men at 15 years. Patients with nodules were generally worse than those without. Also patients treated with corticosteroids were worse than the rest, their need for corticosteroids resulting from their more serious disease.

Thus, 15 years after the onset of definite or classical RA, 35 % of patients have died, the mortality from all causes being greater in those with classical than in those with definite RA (4). Of the survivors, half remain able to lead normal (14 %) or only moderately restricted (36 %) lives, but the other half are markedly (38 %) or totally (12 %) restricted. These figures of functional capacity are even biased by the fact that many patients had

Table XI *Functional capacity compared with other reviews*

Functional Capacity	*Duthie (N=200)* 9 years	Bath *Jacoby (N=83)* + *Cosh* 11 years	*Rasker (N=65)* + *Cosh* 15 years
	%	%	%
I all activities	20.5	37.3	13.8
II moderate restriction	41	30.1	35.4
III marked restriction	27	21.7	38.5
IV confined to bed or chair	11.5	10.8	12.3

died who had been in grade 3 or 4 after 3 years (4). We feel that our therapeutic efforts have gone some way in reducing symptoms and making disability more bearable. But we suspect that the only measures that may have made any real impact on the natural history of the disease have been the specific anti-inflammatory drugs such as gold, penicillamine, azathioprine and perhaps antimalarials. From our study we cannot conclude that the prognosis of RA patients had improved as result of all the new medical treatments we gave; nor does it confirm that what we do today produces a better end result than our fumblings of yester year. Our review shows that to some extent the outcome of the disease can be usefully gauged by a knowledge of the effects it has had in the first 1-3 years.

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