COURSE AND PROGNOSIS IN RHEUMATOID ARTHRITIS*

BY

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In a previous communication (Duthie, Thompson, Weir, and Fletcher, 1955), the results of treatment in hospital and the subsequent progress of a group of patients with rheumatoid arthritis were described. At the time of the first report the mean duration of follow-up was 24·4 months. Certain factors which might influence prognosis were considered. It was concluded that improvement following treatment in hospital was reasonably well maintained in the majority of patients if subsequent medical and social supervision were adequate. The most important factors in prognosis proved to be the duration of disease on admission, sex, and type of course run up to the time of admission. Patients admitted within one year of the onset of symptoms fared substantially better than those admitted at a later stage of the disease; the prognosis in males was better than in females; an acute onset followed by a rapidly progressive course in the early stages seemed to indicate a more benign form of the disease. Age at onset, the erythrocyte sedimentation rate (E.S.R.), haemoglobin level, and activity of the disease on admission gave no useful indication regarding the subsequent course of the disease.

The present report is concerned with the further study of this group of patients.

Composition of the Group

The original group consisted of 307 patients admitted to the Rheumatic Unit, Northern General Hospital, Edinburgh, between June, 1948, and July, 1951. At the third and most recent assessment, nearly 6 years (67·4 months) after discharge from hospital, 247 of the original group remained available, 36 had died since discharge, seventeen had left Scotland, and seven had defaulted. The group included all cases of rheumatoid arthritis admitted to the unit in the 3-year period. All had been considered in need of treatment as in-

patients because of active disease, the presence of deformities, or a combination of both. 30 per cent. of males and 18 per cent. of females were admitted within 6 months of the onset. In 32·5 per cent. of males and 44·4 per cent. of females, the duration of the disease on admission was 5 years or over. The composition of the group is shown in Table I.

TABLE I
COMPOSITION OF GROUP

Data	Males	Females	Total
Number of Cases of Rheumatoid Arthritis admitted between June, 1948, and July, 1951			307
Mean Duration of Stay in Hospital (wks)	9·4		
Period between Discharge and First Assessment (mths)	24·4 (range 12 to 50)		
Number of Deaths between Discharge and First Assessment			15
Number no longer Available			10
Number at First Assessment	77	205	282
Period between Discharge and Second Assessment (mths)	52·4 (range 37 to 76)		
Number of Deaths between Discharge and Second Assessment			26
Number no longer Available			23
Number at Second Assessment	69	189	258
Period between Discharge and Third Assessment (mths)	67·4 (range 52 to 92)		
Number of Deaths between Discharge and Third Assessment	14	22	36
Number no longer Available			24
Number at Third Assessment	65	182	247
Mean Age at Onset (yrs)	44·6	43·5	
Mean Age on Admission (yrs)	50·6	50·5	
Mean Age at Third Assessment (yrs)	54·1	55·3	
Mean Duration of Disease on Admission (yrs)	6·0	7·3	
Mean Duration of Disease at Third Assessment	11·3	12·5	

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It must be clearly understood that these patients were selected in the sense that many milder cases were seen during the period who were not considered to be in need of admission to hospital. This must be borne in mind in considering the validity of any conclusions based on the results of the present analysis. Kellgren, Lawrence, and Aitken-Swan (1953), in a survey of rheumatic complaints in an urban population, noted that 38 per cent. of women and 19 per cent. of men with rheumatoid arthritis had not even consulted their family doctors up to the time of the survey. It is likely that in many patients the disease runs a mild course giving rise to little disability.

While in hospital the basic regimen of treatment consisted of rest in bed, the application of plaster splints to affected joints, maximum tolerable doses of aspirin, physiotherapy, and a graduated return to the optimum functional level attainable. Gold, Butazolidin, corticotrophin, and steroids were not used. Throughout the follow-up period patients attended the clinic regularly for review. Adjustments in treatment were made and splints renewed as the need arose. Advice and help were given in the solution of domestic or employment problems.

Deaths.—36 patients (14 males and 22 females) died between discharge from hospital and the time of the third assessment. Six (5 females and 1 male) were under 50 years of age, 21 (12 females and 9 males) were between 50 and 70 years, and the remaining nine (5 females and 4 males) were over 70 years at the time of death. With regard to the duration of the disease, none died within one year of the onset, eleven died between 1 and 5 years, thirteen between 5 and 10 years, and twelve over 10 years from the onset. The causes of death were as follows:

Cause of Death		No.	Percentage
Cardiovascular Disease	Coronary Thrombosis	6	36
	Cerebral Thrombosis	2	
	Congestive Failure	2	
	Hypertension with Renal Failure	3	
Infections	Pneumonia	4	19
	Pulmonary Tuberculosis	2	
	Infective Hepatitis	1	
Renal Disease	Pyelonephritis	3	11
	Amyloid	1	
Malignant Disease		6	17
Gastro-intestinal Disease	Ulcerative Colitis	2	11
	Peptic Ulceration	2	
Pulmonary Embolism		1	6
	Systemic Lupus Erythematosus	1	
Total		36	100

Cobb, Anderson, and Bauer (1953) found that deaths from infections, various forms of nephritis, valvular heart disease, and pulmonary embolism were commoner amongst 583 patients admitted to hospital with rheumatoid arthritis than in the general population of Massachusetts in 1940. Numbers in the present study are too small to justify detailed analysis of this sort, but the causes of death do not appear remarkable.

Methods of Assessment

The methods used for assessing disease activity and functional capacity were described in the first report, but for convenience the details are reproduced in Table II and Table III (opposite). An overall assessment of clinical progress was also made, but did not provide any additional information and so has been omitted from the present analysis.

TABLE II
GRADES OF FUNCTIONAL CAPACITY

Grade	Definition	Remarks
I	Fit for All Normal Activities	Full employment in usual work Full house duties
II	Moderate Restriction	Usual employment with modifications Light or part-time work All housework save the heaviest No dependency on others
III	Marked Restriction	Only very light work or light housework Some degree of dependency on others
IV	Confined to Chair or Bed	Not capable of any work Completely dependent on others

Results

Functional Capacity.—The proportion of patients in each grade of functional capacity on admission, discharge, first assessment, and third assessment is shown in Table IV. As there were no significant changes in the distribution of patients over the four grades between the second assessment (52.4 mths after discharge) and the third assessment (67.4 mths after discharge) the figures for the second assessment have been omitted from the Table. In the last two columns the proportion of cases in the upper two grades is contrasted with that in the lower two grades. Between admission and discharge the percentage of cases in the upper two grades rose from 35.4 to 75.5, but only 11.3 were considered to have no significant disability (Grade I).

TABLE IV
FUNCTIONAL CAPACITY ON ADMISSION, DISCHARGE, FIRST ASSESSMENT, AND THIRD ASSESSMENT

Time of Estimation	No. of Cases	Functional Grades (per cent. of total)					
		I	II	III	IV	I+II	III+IV
Admission	282	—	35.4	42.6	22.0	35.4	64.6
Discharge	282	11.3	64.2	24.1	0.4	75.5	24.5
First Assessment	282	28.4	44.0	25.1	2.5	72.4	27.6
Third Assessment	247	23.5	40.5	26.7	9.3	64.0	36.0

TABLE III
DEGREES OF DISEASE ACTIVITY

Degree of Activity	Erythrocyte Sedimentation Rate (mm./hr)	Haemoglobin (per cent.)	Joint Involvement	Systemic Disturbance
Inactive	20 or Under	85 or Over	No symptoms due to inflammation in the joints	None
Moderately Active	20-60	65-85	Signs of activity in several joints	Moderate, weight steady
Very Active	Over 60	65 or Under	Signs of acute inflammation in many joints	Marked, with loss of weight

TABLE V
CHANGES IN FUNCTIONAL CAPACITY BETWEEN ASSESSMENTS

Grade	Increase or Decrease in Each Grade as a Percentage of Total				
	Admission to Discharge	Discharge to First Assessment	First Assessment to Second Assessment	Second Assessment to Third Assessment	Admission to Third Assessment
I	+11.3	+17.1	-0.5	-4.4	+23.5
II	+28.8	-20.2	-1.8	-1.7	+5.1
III	-18.5	+1.0	-1.5	+3.1	-15.9
IV	-21.6	+2.1	+3.7	+3.1	-12.7
No. of Cases	282	282	258	247	247

At the first assessment 28.4 per cent. were placed in Grade I, indicating continued improvement since discharge. Between the first and third assessments remarkably little change had taken place. As might have been anticipated, if only on account of increasing age and duration of the disease, the proportion in the lower grades had increased, but only 9.3 per cent. had become so severely disabled as to be dependent on others. 23.5 per cent. were considered to have no significant disability; 40.5 per cent. suffered only moderate impairment of function. In Table V this information is presented in a more dynamic fashion. Changes in the proportion of patients in each grade are shown as percentages of the total. It is of interest to note that between discharge and the first assessment the proportion in Grade II diminished by 20.2 per cent., 17.1 per cent. moving to Grade I and 3.1 per cent. to the lower two grades. Between the first and second and the second and third assessments a small percentage were relegated to the lower grades. Between admission and the third assessment there was an overall increase of 28.6 per cent. in the two upper grades.

Disease Activity.—Table VI shows the distribution of patients in the three degrees of disease activity. The percentage rated as moderately active showed little variation during the period of observation, but there was a significant diminution in the very active group, with a corresponding increase in those considered to be inactive at the time of assessment.

TABLE VI
DISEASE ACTIVITY ON ADMISSION, DISCHARGE, FIRST ASSESSMENT, AND THIRD ASSESSMENT

Time of Estimation	No. of Cases	Disease Activity (per cent.)		
		Very Active	Moderately Active	Inactive
Admission ..	282	26.2	63.5	10.3
Discharge ..	282	5.0	59.2	35.8
First Assessment ..	282	3.5	65.6	30.9
Third Assessment ..	247	1.2	69.6	29.2

Capacity for Work.—Arbitrary methods of assessment may have little meaning. The results of treatment must be related to the capability of patients to resume their daily activities on discharge from hospital. Only 76 patients had been gainfully employed within one year of admission. Their employment status on admission, first assessment, and third assessment is shown in Table VII.

TABLE VII
EMPLOYMENT STATUS ON ADMISSION, FIRST ASSESSMENT, AND THIRD ASSESSMENT

Time of Estimation	No. of Cases	Employment Status (per cent.)			
		Normal Employment	Light Work	No Work	Fit but Unemployed
Admission ..	76	5.3	18.4	76.3	—
First Assessment ..	76	38.2	43.4	11.8	6.6
Third Assessment ..	66	39.4	37.9	18.2	4.5

Only 5.3 per cent. were capable of their normal work on admission. At the first assessment 38.2 per cent. were engaged in their previous occupation and 43.4 per cent. had obtained suitable light work. At the third assessment, when 66 of the original group were still available, the proportion engaged in normal employment had altered little. There had been a moderate increase (11.8 to 18.2 per cent.) in those unfit for any type of employment.

In view of the large number of housewives in the group, an assessment of their capacity for household duties was made. The results are shown in Table VIII. The pattern of continued improvement between discharge and the first assessment is again evident. Little change took place between the first and third assessments, when 19.4 per cent. reported themselves fit for all household duties and 41.0 per cent. fit for all but the heaviest tasks.

TABLE VIII
HOUSEWIVES CAPACITY FOR WORK ON ADMISSION,
DISCHARGE, FIRST ASSESSMENT, AND THIRD
ASSESSMENT

Time of Estimation	No. of Cases	Housewives Capacity for Work (per cent.)			
		All Work	All Duties Save Heaviest	Light Housework	No Work
Admission ..	171	—	8.8	50.9	40.3
Discharge ..	171	2.9	41.5	48.6	7.0
First Assessment ..	171	15.8	45.6	27.5	11.1
Third Assessment ..	134	19.4	41.0	22.4	17.2

Social and Economic Factors

Social and economic factors were dealt with in some detail in the first report. The value of skilled assistance in the solution of domestic and employment problems was emphasized. There was a close correlation between improvement in the medical sense and betterment in social circumstances. At the third assessment this relationship was preserved. In 96.6 per cent. of 58 cases in Grade I of functional capacity, improvement in social circumstances was reported by the patient or almoner. 82.7 per cent. of 98 cases in Grade II and 55.7 per cent. of 88 cases in Grades III and IV reported improvement. Only among the cases in Grades III and IV had deterioration occurred in a significant number (26.1 per cent.).

Employment.—At the third assessment, 90.9 per cent. of 33 cases in Grade I of functional capacity and 63.9 per cent. of 36 cases in Grade II, who were considered eligible for work on discharge from hospital, were employed in remunerative occupations. All 27 cases in Grades III or IV at the third assessment were unemployed.

Of 151 housewives, 96.1 per cent. of 26 in Grade I, 81.2 per cent. of 64 in Grade II, and 18 per cent. of 61 in Grades III and IV at the third assessment were performing all, or all but the heaviest, of their household duties. Thus the day-to-day activities of these patients showed reasonably good correlation with the four gradings of functional capacity used in making the assessments.

Type of Occupation.—In the first report it appeared at the first assessment that members of the professional and clerical classes had fared less well than manual workers. At the third assessment this difference was no longer significant.

Prognosis

This general analysis of results provides no guidance as to the course the disease is likely to run in the individual patient. An analysis has been made of various factors which might be of help in this connexion. The most important have proved to be the duration of the disease before admission to hospital, the sex of the patient, the type of course run before admission, and the response to treatment. The results of the sensitized sheep cell test suggest that this may also be of prognostic significance.

Duration of Disease.—The most important single factor was found to be the duration of the disease at the time of the patient's admission to hospital. The relationship between this factor and functional capacity is shown in Table IX (opposite).

At the first assessment the percentage of cases in Grade I of functional capacity was greatest (42.9) in those admitted within one year of the onset, and least (16.3) in those admitted more than 5 years after the onset. The differences between the four groups were highly significant ($P < 0.01$).^{*} The differences between the proportions in Grades I and II in the four groups are also highly significant ($P < 0.01$). At the second and third assessments these differences were equally marked. Cases admitted more than one year after the onset of disease showed a decline in the proportion placed in Grade I, which was not evident in those admitted within one year of the onset. An analysis of the relationship between disease activity at all assessments and the duration of the disease on admission is shown in Table X (opposite). At the first assessment the percentage of inactive cases was 40.5 in those admitted within one year of onset, and 26.8 for all those admitted later. The differ-

* Values for P have been calculated by the χ^2 test with appropriate degrees of freedom.

TABLE IX
RELATIONSHIP BETWEEN FUNCTIONAL CAPACITY AND DURATION OF DISEASE ON ADMISSION

Time of Estimation	Under 1			1-5			5-10			Over 10		
	No. of Cases	Per cent.		No. of Cases	Per cent.		No. of Cases	Per cent.		No. of Cases	Per cent.	
		Grade I	Grades I and II		Grade I	Grades I and II		Grade I	Grades I and II		Grade I	Grades I and II
Admission	84	—	32.1	81	—	37.0	49	—	34.7	68	—	38.2
Discharge	84	14.3	85.7	81	12.3	83.9	49	6.1	59.2	68	10.3	64.7
First Assessment	84	42.9	83.3	81	30.9	75.3	49	16.3	63.5	68	16.2	60.3
Second Assessment	78	47.4	85.9	75	28.0	72.0	43	11.6	62.8	62	14.5	53.2
Third Assessment	75	42.7	76.0	73	23.3	68.5	41	9.8	63.4	58	8.6	43.1

TABLE X
RELATIONSHIP BETWEEN DISEASE ACTIVITY AT ALL ASSESSMENTS AND DURATION OF DISEASE ON ADMISSION

Time of Estimation	Under 1		1-5		5-10		Over 10	
	No. of Cases	Per cent. Inactive	No. of Cases	Per cent. Inactive	No. of Cases	Per cent. Inactive	No. of Cases	Per cent. Inactive
Admission	84	6.0	81	12.3	49	12.3	68	11.8
Discharge	84	28.5	81	39.5	49	38.8	68	38.3
First Assessment	84	40.5	81	30.9	49	18.4	68	28.0
Second Assessment	78	35.9	75	22.7	43	16.3	62	29.0
Third Assessment	75	45.3	73	24.7	41	19.5	58	20.7

ence was regarded as significant (difference=13.7 per cent., standard error of the difference (S.E.)=6.2, diff./S.E.=2.2). A similar difference (12.6 per cent.) was found at the second assessment. At the third assessment the percentage of inactive cases amongst those admitted in the first year had risen to 45.3, whereas the percentage in other groups had fallen to 22.1. The difference was highly significant (difference=23.2, S.E.=6.6, diff./S.E.=3.5). It is also of interest to note that functional capacity and disease activity were closely related in cases of under 5 years' duration, but the relationship became less marked in cases of longer duration. A proportion of such cases became inactive but suffered considerable impairment of functional capacity.

Age at Onset.—The relationship between age at the onset of the disease and functional capacity is shown in Table XI. The apparently favourable prognosis in the small group of patients in whom the disease started at over 60 years of age has little meaning and is accounted for by the fact that a relatively high proportion of these patients was admitted in the first year of the disease (74 per cent. as compared with 30 per cent. in the 40-60 yrs group, and 17.4 per cent. of the under 40 yrs group). The differences between the proportion of cases in Grade I in the three age groups at the third assessment are not statistically significant. It would appear that, within the limits of this study, the age at onset of the disease was not of any prognostic significance.

TABLE XI
RELATIONSHIP BETWEEN FUNCTIONAL CAPACITY AND AGE AT ONSET

Time of Estimation	Under 40			40-60			Over 60		
	No. of Cases	Per cent.		No. of Cases	Per cent.		No. of Cases	Per cent.	
		Grade I	Grades I and II		Grade I	Grades I and II		Grade I	Grades I and II
Admission	104	—	43.3	147	—	31.3	31	—	29.0
Discharge	104	21.2	78.8	147	4.1	72.8	31	12.9	77.4
First Assessment	104	29.8	74.0	147	26.5	72.1	31	32.3	67.7
Second Assessment	96	30.2	71.9	135	23.0	69.6	27	44.4	66.7
Third Assessment	92	28.3	69.6	131	19.1	63.4	24	33.3	45.8

TABLE XII
FUNCTIONAL CAPACITY IN MALES AND FEMALES

Time of Estimation	Males				Females			
	No. of Cases	Per cent.			No. of Cases	Per cent.		
		Grade I	Grades I and II	Grades III and IV		Grade I	Grades I and II	Grades III and IV
Admission	77	—	36.4	63.6	205	—	35.1	64.9
Discharge	77	7.8	83.1	16.9	205	12.7	72.7	27.3
First Assessment	77	41.5	84.4	15.6	205	23.4	67.8	32.2
Second Assessment	69	40.6	81.2	18.8	189	23.3	66.1	33.9
Third Assessment	65	38.5	75.4	24.6	182	18.1	59.9	40.1

Sex.—The relationship between sex and functional capacity is shown in Table XII. On admission the two sexes were equally distributed over the four grades. On discharge there was little difference between males and females, although a rather higher proportion of women were discharged in the two lower grades (27.3 per cent. as compared with 16.9 per cent. of males). At the first assessment, 41.5 per cent. of males were considered fit for Grade I, compared with 23.4 per cent. of females. The percentage of males in Grades I and II was 84.4 and of females 67.8. These differences were regarded as highly significant (Grade I: difference = 18.1 per cent., S.E. = 6.3, diff./S.E. = 2.8; Grades I and II: difference = 16.6 per cent., S.E. = 5.3, diff./S.E. = 3.2). There was little change in the relative position of males and females at the second and third assessments. This difference in functional capacity is not directly related to disease activity. Although the disease was regarded as inactive in a higher proportion of men at the third assessment (36.9 per cent. of males; 26.4 per cent. of females), the difference between the sexes in this respect did not reach the level of statistical significance.

Type of Course.—Patients were grouped according to the type of course the disease had run up to the

time of admission to hospital. Three types of course were distinguished:

- (1) Rapidly progressive without remission.
- (2) Slowly progressive without remission.
- (3) A course of exacerbation and remission.

It was not always easy to distinguish between Types 2 and 3, and an analysis of the results revealed no significant difference in the subsequent course run by these two groups of patients. At the first assessment, however, 54.3 per cent. of those who had run a rapidly progressive course before admission were placed in Grade I of functional capacity as compared with 23.3 per cent. of those in the other two groups (Table XIII). The corresponding percentages for those placed in Grades I and II combined were 91.3 and 68.7. The differences were both highly significant (Grade I: difference = 31.0 per cent., S.E. = 7.8, diff./S.E. = 4.0; Grades I and II: difference = 22.6 per cent., S.E. = 5.1, diff./S.E. = 4.4). Further inquiry, however, revealed that all cases classed as rapidly progressive had been admitted to hospital within one year of the onset of symptoms. It was obviously necessary to compare this group with others admitted within the first year (Table XIII). Although the difference between the proportions of cases in Grades I and II combined did not reach the level of statistical significance at the first assessment, for those in Grade I the differ-

TABLE XIII
RELATIONSHIP BETWEEN FUNCTIONAL CAPACITY AND TYPE OF COURSE

Time of Estimation	Rapidly Progressive			Other Types			Other Types admitted within one year of Onset		
	No. of Cases	Per cent.		No. of Cases	Per cent.		No. of Cases	Per cent.	
		Grade I	Grades I and II		Grade I	Grades I and II		Grade I	Grades I and II
Admission	46	—	30.4	236	—	36.4	38	—	34.2
Discharge	46	8.7	91.3	236	11.9	72.5	38	21.1	78.9
First Assessment	46	54.3	91.3	236	23.3	68.7	38	28.9	78.9
Second Assessment	44	59.1	93.2	214	21.5	65.4	34	32.4	76.5
Third Assessment	41	51.2	80.5	206	18.0	60.7	34	32.4	70.6

ence was significant (difference=25.4 per cent., S.E.=10.4, diff./S.E.=2.4). At the second and third assessments the comparisons were essentially the same, except that at the third assessment the difference between rapidly progressive cases and others admitted with one year of onset had become less marked.

Similar results emerged from an analysis of disease activity; 51.2 per cent. of the rapidly progressive group were graded as inactive at the third assessment as compared with 24.8 per cent. of all others and 38.2 per cent. of others admitted in the first year.

Functional Capacity on Admission and Discharge.—The degree of disability on admission and discharge has been related to the subsequent course of the disease.

Of those placed in Grade II of functional capacity on admission (87 patients), 80.5 per cent. were still in Grade I or II at the third assessment, as compared with 55.8 per cent. of those in Grade III on admission (106 patients) and 55.7 per cent. of those in Grade IV on admission (54 patients). The difference between patients in Grade II and those in the two lower grades on admission was highly significant at the third assessment ($P<0.01$). The relationship between functional capacity on discharge and at subsequent assessments is shown in Table XIV.

Of the thirty patients discharged in Grade I, 86.7 per cent. were still in Grade I or II at the third assessment. Of 160 cases discharged in Grade II, 71.9 per cent. were in the two higher grades at the third assessment. Of 57 cases discharged in Grade III or IV, only 29.8 per cent. had reached the upper two grades at the third assessment. The difference between patients discharged in Grade I or II and those discharged in the two lower grades was highly significant at the third assessment ($P<0.01$).

Activity of Disease on Admission and Discharge.—

Only 28 of the patients available at the third assessment had been regarded as inactive on admission. Of these 50 per cent. were rated inactive and 50 per cent. as moderately active at the third assessment. Of 152 patients rated moderately active on admission, 32.6 per cent. were inactive, 66.1 per cent. moderately active, and 1.3 per cent. very active at the third assessment. Of 67 patients rated very active on admission, 16.0 per cent. were inactive, 83.4 per cent. moderately active, and 1.6 per cent. very active at the third assessment. 92.9 per cent. of cases rated inactive on admission were in Grades I and II of functional capacity at the third assessment as compared with 65.1 per cent. of cases moderately active and 53.7 per cent. of cases very active on admission. Although the numbers are small, the outlook for cases considered inactive on admission is significantly better than it is for moderately or very active cases. The difference between moderately active and very active cases on admission in terms of functional capacity at the third assessment is not significant.

When the duration of disease on admission was related to disease activity on admission and at the third assessment, it was noted that only 6 per cent. of the 84 cases admitted in the first year were considered inactive, as compared with 12.3 per cent. of the 81 cases in the 1-5 yrs group, 12.3 per cent. of the 49 cases in the 5-10 yrs group, and 11.8 per cent. of the 68 cases in the over 10 yrs group. At the third assessment the proportion of inactive cases in the four groups were 45.3 per cent., 24.7 per cent., 19.5 per cent., and 20.8 per cent. The most striking feature of this analysis is the fact that, although 94 per cent. of the first year group were considered moderately or markedly active on admission, nearly half were rated inactive at the third assessment. The difference between this group and those of longer duration on admission is highly significant ($P<0.01$).

TABLE XIV

RELATIONSHIP BETWEEN FUNCTIONAL CAPACITY ON DISCHARGE AND LATER

Functional Capacity on Discharge	Time of Estimation	Grade I		Grade II		Grades III and IV	
		Per cent.		Per cent.		Per cent.	
		No. of Cases	Grade I	No. of Cases	Grade I	No. of Cases	Grade I
First Assessment	.. ..	32	50.0	181	32.6	69	7.2
Second Assessment	.. ..	31	48.4	167	30.5	60	10.0
Third Assessment	.. ..	30	36.7	160	27.5	57	7.0
			Grades I and II		Grades I and II		Grades I and II
			93.8		83.4		33.3
			90.3		79.0		35.0
			86.7		71.9		29.8

Only twelve cases were rated as markedly active on discharge, and in view of their small number these have not been included in the following analysis. Of the remaining 246 cases, 151 were rated moderately active and 95 were inactive on discharge. Table XV shows the position at the first and third assessments. 41.3 per cent of those rated inactive on discharge were still inactive at the third assessment, compared with 24.3 per cent. of those rate moderately active on discharge. The difference is significant ($P < 0.02$). 75 per cent. of the former were in Grades I and II of functional capacity at the third assessment, as compared with 59.4 per cent. of the latter. The difference is significant ($P < 0.05$).

Haemoglobin Level and Erythrocyte Sedimentation Rate on Admission.—Estimations of the haemoglobin and erythrocyte sedimentation rate on admission provided no reliable guidance as to the subsequent course of the disease. Analysis at the third assessment showed no significant difference between patients with haemoglobin levels below 80 per cent. on admission and those without significant anaemia. Patients with an erythrocyte sedimentation rate below 20 mm./hr on admission did a little better than those with more rapid rates, but again the difference was not significant. A number of cases in which a rapid erythrocyte sedimentation rate was associated with marked anaemia (haemoglobin below 65 per cent.) fared badly, but their numbers were too small to influence the overall picture.

Sensitized Sheep Cell Test.*—The test was not available in our laboratory during the earlier stages of this inquiry, but at the third assessment (mean

period since discharge 67.4 mths) the test was performed in 241 of the 247 patients available at that time. The composition of the group is shown in Table XVI.

TABLE XVI
SENSITIZED SHEEP CELL TEST AT THIRD ASSESSMENT
COMPOSITION OF GROUP

Sex	Males	Females	Total
Number of Cases	65	176	241
Mean Age at Onset (yrs)	45	43	
Positive Test at Third Assessment	No. 39	101	140
	Per cent. 56.8	58.5	

In 140 patients the results were positive (58 per cent.). When functional capacity at the third assessment was related to the results of the test, it was found that 33.9 per cent. of patients in Grade I, 63.6 per cent. in Grade II, 73.8 per cent. in Grade III, and 54.5 per cent. in Grade IV gave positive results.

The groups with positive and negative results were compared in respect of changes in functional capacity, disease activity, haemoglobin level, and erythrocyte sedimentation rate, between admission and the third assessment. The results are presented in Table XVII (opposite).

On admission there was no significant difference between the positive and negative groups in respect of the four characteristics measured. At the third assessment, when the test was performed, there was a significant difference in all four characteristics in favour of the patients in whom the result was negative.

Cases admitted to hospital within one year of the onset of symptoms have already been shown to have a more favourable prognosis than those admitted at a later stage of the disease. The status of these patients in relation to the results of the sheep cell test at the third assessment was examined. The

* The method of Ball (1950) was followed, but the technique differed in that M.R.C. haemagglutination plates were substituted for test-tubes and the tests were read after refrigeration overnight at 4° C. Comparison of the methods showed that higher titres were recorded on the haemagglutination plates. In order to retain the specificity and sensitivity of the original test, it was considered advisable to designate a titre of 1/128 as the lowest indicating a positive result.

TABLE XV
RELATIONSHIP BETWEEN DISEASE ACTIVITY ON DISCHARGE, FIRST ASSESSMENT, AND THIRD ASSESSMENT

Assessment	First			Third		
	No. of Cases	Per cent. Inactive	Per cent. Functional Capacity in Grades I and II	No. of Cases	Per cent. Inactive	Per cent. Functional Capacity in Grades I and II
Disease Activity on Discharge						
Inactive	95	48.4	78.9	92	41.3	75.0
Moderately Active	151	24.5	72.8	143	24.3	59.4

TABLE XVII

COMPARISON OF PROGRESS BETWEEN ADMISSION AND THIRD ASSESSMENT OF PATIENTS WITH POSITIVE AND NEGATIVE SENSITIZED SHEEP CELL TEST AT THIRD ASSESSMENT

Sensitized Sheep Cell Test	Positive (140)		Negative (101)		P
	No.	Per cent.	No.	Per cent.	
<i>Functional Capacity</i> Proportion reaching Grade I	18/140	12.8	38/101	37.6	<0.01
<i>Disease Activity</i> Proportion of active cases becoming inactive ..	15/122	12.6	30/92	32.6	<0.01
<i>Haemoglobin Level</i> Proportion of those under 90 per cent. who rose to over 90 per cent.	29/92	31.5	37/72	51.3	<0.02
<i>Erythrocyte Sedimentation Rate</i> Proportion of those over 20 mm./hr who fell below 20 mm./hr	0/107	—	21/85	24.7	<0.01

composition of the group is shown in Table XVIII. There was no significant difference between the positive and negative groups in respect of functional capacity and disease activity on admission. Of the negative group, 61.5 per cent. were in Grade I of functional capacity and 59.4 per cent. were rated inactive at the third assessment, as compared with 18.3 per cent. and 27.7 per cent. respectively of the positive group. The differences were highly significant ($P < 0.001$).

TABLE XVIII

COMPOSITION OF GROUP ADMITTED WITHIN ONE YEAR OF ONSET

Sex	Males	Females	Total Cases
Number of Cases	24	54	78
Mean Age at Onset (yrs)	47	50	
Sensitized Sheep Cell Test	Positive ..	42%	52%
	Negative ..	58%	48%

An examination of radiological findings in these two groups showed that erosions were present in 98 per cent. of cases in which the test was positive, and in only 62 per cent. of cases in which the test was negative.

TABLE XX

CHANGES IN FUNCTIONAL CAPACITY AND DISEASE ACTIVITY BETWEEN ADMISSION AND FOURTH ASSESSMENT

Sensitized Sheep Cell Test	Positive (28)	Positive and Negative (32)	Negative (37)	P
<i>Functional Capacity</i> Proportion reaching Grade I ..	3/28 = 10.7 per cent.	10/32 = 31.2 per cent.	19/37 = 51 per cent.	$P < 0.01$
<i>Disease Activity</i> Proportion of active cases becoming inactive	3/23 = 13 per cent.	6/26 = 23 per cent.	16/32 = 50 per cent.	$P < 0.01$

When patients admitted in the first year were classified as to the type of course run up to the time of admission, the test was positive at the third assessment in 35 per cent. of the forty cases who had run a rapidly progressive course and in 65 per cent. of 38 cases in which the onset had been more insidious.

In view of these results, it was thought worth while to examine the status of 97 patients who had been assessed a fourth time approximately one year after the third assessment. In these patients the sheep cell test had been performed on two or more occasions. The composition of this group is shown in Table XIX.

TABLE XIX

RELATIONSHIP BETWEEN RESULTS OF SENSITIZED SHEEP CELL TEST AND PROGRESS OF PATIENTS BETWEEN ADMISSION AND FOURTH ASSESSMENT

Sex	Total	Males	Females
Number of Cases	97	37	60
Number consistently Positive ..	28	12	16
* Number with Both Positive and Negative Results	32	11	21
Number consistently Negative ..	37	14	23

* Positive to Negative .. 19
Negative to Positive .. 13

Analysis of changes in functional capacity and disease activity in these 97 patients between admission and the fourth assessment is shown in Table XX.

The pattern favours those in whom the sensitized sheep cell test had been consistently negative. The differences are statistically significant. It is of interest to note that the group giving both positive and negative results occupies an intermediate position between the consistently positive and the consistently negative groups.

In view of the fact that patients were divided into positive and negative reactions at an arbitrary titre of 1/128, it was decided to investigate the possible relationship between the titres recorded and the distribution of patients over the four grades of functional capacity at the third assessment. The results (Table XXI) show a highly significant correlation between the titre of the sheep cell test and functional capacity at the third assessment ($P < 0.001$).

Discussion

The need for more accurate knowledge regarding the course and prognosis in rheumatoid arthritis is no less urgent at present than it was at the time of the first report on this group of patients in 1955. New and more potent drugs have become available whose value must be assessed and balanced against the possible risks of their prolonged administration. The conservative regimen of treatment used in this study is unlikely to have had any specific effect on the course of the disease, although the value of general and local rest in reducing the activity of the disease process at least temporarily, should not be entirely discounted. On the other hand, prevention and correction of deformity, graduated exercises, and the continuous administration of aspirin may have done much to improve and maintain the functional level of these patients, even when the disease remained active. This view receives considerable support from a comparison of the functional status of the group at the first and third assessment. The overall improvement which took place between admission to hospital and the first assessment 2 years after discharge had been fairly well maintained at the third assessment 6 years after discharge. The proportion of patients in the two

upper grades had diminished by only 8.4 per cent. between the first and third assessments. On the other hand, the changes in disease activity between admission and the third assessment are less striking. There had been a diminution in the number of very active cases and an increase in the number classed as inactive, but between 60 and 70 per cent. of patients had been rated as moderately active at all assessments.

The number of patients who had returned to their normal work or to suitable alternative employment by the time of the first assessment had not diminished appreciably at the third assessment, and capacity for household duties had been well maintained amongst the housewives.

As was noted in the first report, improvement in the medical sense was accompanied in the majority of cases by betterment in social circumstances as assessed by the social service worker.

There was good correlation between the four simple grades of functional capacity used at each assessment and the actual day-to-day activities of patients between assessments. It is doubtful whether the more elaborate and time-consuming schemes for measuring the effects of the disease on function advocated by some authorities would provide much additional information of value.

The impression gained at the first assessment that the progress of members of the professional and clerical classes after discharge from hospital was less satisfactory than that of manual workers was not confirmed at the third assessment.

The broad conclusion can be reached on the basis of this study that about 65 per cent. of patients with rheumatoid arthritis of such severity as to lead to their admission to hospital may remain capable of leading useful and independent lives for many years after the onset of the disease, even if only simple conservative methods of treatment are used. Some 6 years after discharge from hospital 24 per cent. of this group had suffered no significant impairment of functional capacity, 40 per cent. were slightly incapacitated but were able to carry out most ordinary activities, 26 per cent. were more severely

TABLE XXI
RELATIONSHIP BETWEEN FUNCTIONAL CAPACITY AT THIRD ASSESSMENT
AND TITRE OF SENSITIZED SHEEP CELL TEST

Grade of Functional Capacity	No. of Cases	Titre			
		Up to 1/16	1/32-1/64	1/128-1/256	1/512-1/1,024
I	56	22	16	9	9
II	99	19	18	36	26
III and IV	87	11	16	27	33

crippled, and only 10 per cent. were helpless and dependent on others. It is felt that continued medical and social supervision has made a definite contribution to the attainment of these results, although the natural course of the disease may not have been materially altered. The value of new forms of treatment can only be assessed by careful comparison of the results obtained with those which follow the application of conservative measures in hospital followed by continued medical and social supervision.

It is of no great value to the physician to know the overall results of any particular regimen of treatment if he has no means of foreseeing the course likely to be followed by the individual patients under his care. Forms of treatment carrying a certain degree of risk may justifiably be used if a potentially progressive and crippling form of the disease can be controlled or arrested at an early stage. Similar risks would not be acceptable for patients in whom the disease is destined to run a benign course. In an attempt to provide information of value in this connexion, factors with a possible bearing on prognosis have been examined. They can be grouped into those which provide useful information when the patient is first examined and those whose significance can only be assessed after a period of treatment in hospital.

Duration of disease, sex, and type of course run up to the time of admission are the most important in the first category. Patients admitted within one year of the onset have a substantially better prognosis than those admitted at a later stage. The improvement, measured in terms of changes in functional capacity and disease activity, noted in this group at the first assessment was well maintained at the third assessment, whereas in patients admitted later in the course of the disease some deterioration had taken place during this period.

The results at the third assessment confirmed the observation that the prognosis in males is distinctly better than it is in females, a difference not accounted for by differences in disease activity.

Patients whose disease had run a rapidly progressive course without remission up to the time of admission did remarkably well. These patients had all been admitted within the first year of the disease, a testimony to the acuteness of their symptoms. They showed a significant advantage both in terms of reduction of disease activity and improvement in functional capacity over other cases admitted in the first year.

The grade of functional capacity on admission gave some guidance as to the subsequent course, patients in Grade II on admission faring rather

better than those with more marked impairment of function.

The grade of disease activity on admission gave little indication of future progress, although the small number of cases graded as inactive on admission had a better prognosis than those showing moderate or marked activity. On the other hand, 94 per cent. of cases admitted in the first year of the disease were considered moderately or markedly active and nearly half of these patients were considered inactive at the third assessment. It is obvious that in this group the short duration of symptoms was of much greater significance in prognosis than the degree of activity on admission. This is in keeping with the observation that single estimations of the erythrocyte sedimentation rate and haemoglobin level on admission provide no reliable guidance as to the subsequent course of the disease.

Turning to factors the significance of which can only be assessed after a period of observation, functional capacity on discharge provided a reasonably reliable guide to prognosis. Those discharged in the two higher categories maintained their functional status reasonably well, whereas only a small proportion of those discharged in the lower two grades showed any improvement later on. Similarly, the subsequent course of the disease was less severe in patients assessed as inactive on discharge than in those in whom disease was still active at this time. The significance of these two factors can be summed up as follows: the response to hospital treatment in terms of improvement in functional capacity and decrease in disease activity provides a reasonably reliable guide to the course which the disease will run after discharge.

When the results of the sensitized sheep cell test, performed at the third assessment, were related to the course the disease had run since admission to hospital, it became clear that the group in whom the test was positive had suffered more severely than those giving a negative result. The incidence of positive results was lowest in patients with Grade I functional capacity and highest in patients with Grade III functional capacity. A possible explanation of the lower incidence of positive tests in Grade IV may be the presence of severely crippled patients in whom the disease had become inactive. The difference between the groups with positive and negative tests was even more striking among patients admitted within one year of the onset. The incidence of positive results was significantly lower in patients who had run a rapidly progressive course up to the time of admission when compared with the incidence among patients with a more

insidious onset admitted in the first year. Patients with consistently positive results had fared worse than those with consistently negative results and those in whom both positive and negative results had been recorded. These observations are of great interest and would suggest a relationship between the presence of the sheep cell factor and the severity of the disease. This idea is supported by the demonstration of a highly significant relationship between functional capacity and the titres recorded at the third assessment. The full prognostic significance of this test can only be assessed when the results of serial tests in individual patients over a number of years become available, but these preliminary findings suggest that more accurate knowledge of fluctuations in the level of the agglutinating factor may be of great importance. Its final isolation and identification may well provide fundamental information regarding the pathogenesis of the disease.

Summary

(1) The results of further assessments of the status of a group of patients with rheumatoid arthritis admitted to hospital between 1948 and 1951 are reported.

(2) At the last examination, some 6 years after discharge from hospital, 24 per cent. of patients were able to carry on all normal activities; 40 per cent. were moderately incapacitated; 26 per cent. were more severely crippled; and only 10 per cent. had become helpless and dependent on others.

(3) There had been remarkably little change in the distribution of patients over the four grades of functional capacity between the first assessment made 2 years after discharge and the last assessment nearly 4 years later.

(4) The disease remained moderately active throughout the period of study in about 65 per cent. of patients, but the proportion rated as very active had decreased. At the third assessment nearly 30 per cent. showed no signs of activity.

(5) Of those patients considered eligible for remunerative employment on discharge from hospital, 39 per cent. were engaged in normal employment and 38 per cent. in suitable light work at the time of the third assessment. 60 per cent. of housewives were able to do all, or all but the heaviest, tasks in the home.

(6) Various factors with a possible bearing on prognosis have been considered. The most important have proved to be the duration of the disease before admission to hospital, sex, the type of course up to the time of admission, the response to con-

servative treatment in hospital as measured by changes in functional capacity and disease activity between admission and discharge, and the results of the sensitized sheep cell test.

(7) Age at onset, disease activity, functional capacity, erythrocyte sedimentation rate, and haemoglobin level on admission proved to be of little or no value in predicting the subsequent course of the disease.

(8) The results of this type of study should receive careful consideration in assessing the value of new forms of treatment, especially if these carry a certain risk to patients.

During the period when this work was done, the Rheumatic Unit was in receipt of grants from the Nuffield Foundation, the Medical Research Council, and Boots Pure Drug Company Limited.

We wish to express our thanks to Miss Eleanor Ogilvie for her help in the social aspects of this study; to Dr. W. R. M. Alexander for help in carrying out the sensitized sheep cell tests, and to Dr. J. L. Potter for statistical help in the later stages of the investigation.

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Discussion

DR. MARIAN W. ROPES (*Boston, Mass.*): It is unfortunate that Dr. Bauer cannot be here for this discussion. In his absence I am delighted to discuss Dr. Duthie's excellent report of a very careful and important study. We are all keenly aware of the lack of knowledge of the natural course of rheumatoid arthritis. It is becoming more and more possible to measure with fair certainty the antirheumatic effect of an agent in terms of a suppression of inflammation. This has been further demonstrated at these meetings. But it still remains impossible to determine the effect on the actual course of the disease. Studies of the type being carried out by Dr. Duthie offer the best background yet available against which the effect of the repeatedly-appearing suggested treatments can be evaluated. Ideally, it can be hoped that such studies can be carried out with random selection of patients to test even the elements of the so-called "conservative" regime, but many difficulties must be overcome to make this possible.

It is, I think, of interest to compare in so far as possible the patients that have been followed at Massachusetts General Hospital for many years on simple medical and orthopaedic measures with those described by Dr. Duthie. This group was assessed by Dr. Short in 1947 and again in 1954, the average follow-up being 14 years. The last assessment will soon be published. In general, there is remarkably good agreement as to the findings

that suggest a good prognosis in our series and Dr. Duthie's. Short duration of disease (under one year) is of major significance. Probably, as Dr. Duthie suggests, this good prognosis in early cases and the large number of patients not admitted to hospital at all indicate that, as a whole, rheumatoid arthritis is milder than formerly believed. Patients with acute onset fare better than those with insidious onset. Men appear to have a slightly better prognosis than women (and this in both studies is based on groups that do not include patients with spondylitis).

The actual percentages of cases classified as inactive and markedly improved vary considerably in the two series. In our series, Dr. Short found 53 per cent. improved with 15 per cent. in remission at the end of a 9-year follow-up. However, only 35 per cent. of the group could be classified as improved with 13 per cent. in remission after 14 years. The relative stability of Dr. Duthie's group from the 2-year to the 6-year assessment is of interest and is comparable with the stability of our group from 1937 to 1947.

It is interesting to compare Dr. Duthie's series with Dr. Edström's large series of children. They represent two of the largest groups followed for years on simple medical and orthopaedic measures and the percentages of improvement are definitely above the average for adults and children respectively, whatever the treatment used. It is intriguing to speculate as to the reason for the relatively good results. I agree with Dr. Duthie that they may represent the natural course of the disease. However, it should be noted that, in both series, hospital treatment was continued for a longer period than in any other comparable groups. In our group evaluated by Dr. Short, for instance, almost all of the patients were hospitalized for only a few weeks. Only by further studies can the significance of the long hospitalization be determined.

Dr. Duthie, all of us interested in rheumatic diseases will follow, with great interest and hope, the continuation of your studies.

Evolution et prognose dans l'arthrite rhumatismale

RÉSUMÉ

(1) On présente les résultats d'une nouvelle évaluation de l'état d'un groupe de malades atteints d'arthrite rhumatismale et admis à l'hôpital de 1948 à 1951.

(2) Au dernier examen, environ six ans après leur sortie de l'hôpital, 24% des malades étaient capables de poursuivre toute activité normale; 40% étaient modérément handicapés; 36% demeuraient plus sévèrement infirmes et seulement 10% étaient réduits à l'impuissance et à la dépendance totale.

(3) Il s'était produit remarquablement peu de changements dans la classification des malades dans les quatre groupes selon leur capacité fonctionnelle, entre la première évaluation, faite deux ans après la sortie de l'hôpital et la dernière, près de quatre ans plus tard.

(4) Le mal demeurait modérément actif durant toute m période d'observation chez environ 65% des malades, isala la proportion classée comme très active avait

diminuée. A la troisième évaluation, près de 30% ne montraient aucun signe d'activité.

(5) Parmi les malades considérés comme capables de se livrer à un travail rémunérateur à leur sortie de l'hôpital, 39% travaillaient normalement et 38% se livraient à un travail léger, au moment de la troisième évaluation. Parmi les ménagères, 60% étaient capables de vaquer à toutes leurs occupations, ou bien à toutes sauf les plus pénibles.

(6) On a examiné les facteurs variés ayant pu influencer la prognose. Les plus importants se sont révélés être la durée de la maladie avant l'admission à l'hôpital, le sexe, le type évolutif jusqu'au moment d'admission, la réponse au traitement conservateur à l'hôpital du point de vue fonctionnel et évolutif, et les résultats de la réaction de globules de mouton sensibilisés.

(7) L'âge de début, l'activité morbide, la capacité fonctionnelle, la vitesse de sédimentation globulaire et le taux d'hémoglobine à l'admission, se sont révélés de peu ou pas de valeur dans la prédiction de l'évolution subséquente du mal.

(8) Les résultats de ce type d'étude devraient être considérés avec attention quand on évalue les nouvelles formes de traitement, particulièrement si ces dernières font courir un certain risque aux malades.

Evolución y prognosis en la artritis reumatoide

SUMARIO

(1) Se presentan los resultados de una nueva valoración del estado de un grupo de enfermos con artritis reumatoide admitidos al hospital entre 1948 y 1951.

(2) El último examen, cerca de seis años después de la salida del hospital, reveló que el 24% de los enfermos podía seguir una actividad normal, el 40% sufría de impedimentos moderados, el 36% quedaba severamente incapacitado y tan sólo el 10% sufría de incapacidad y dependencia totales.

(3) Poquísimos cambios se notaron en la clasificación de los enfermos en los cuatro grupos según el grado de capacidad funcional entre la primera valoración, efectuada dos años después de su salida del hospital y la última, cerca de cuatro años más tarde.

(4) La enfermedad permaneció moderadamente activa durante el período entero de observación en cerca de un 65% de los enfermos, pero la proporción de los en el grupo "enfermedad muy activa" había disminuido. En la tercera valoración, cerca de un 30% no reveló signos de actividad.

(5) De los enfermos considerados capaces de trabajo remunerador a su salida del hospital, un 39% trabajaba normalmente, y un 38% hacía un trabajo ligero, al tiempo de la tercera valoración. El 60% de las amas de casa podían hacer todas sus faenas, o todas salvo las más penosas.

(6) Se examinaron los varios factores que hubieran podido afectar la prognosis. Los más importantes fueron: la duración de la enfermedad antes del ingreso al hospital; el sexo; el tipo evolutivo hasta el ingreso; la respuesta terapéutica, funcional y evolutiva al tratamiento hospitalario conservador desde el ingreso hasta la salida; y la reacción de globulos de oveja sensibilizados.

(7) La edad de comienzo, la actividad mórbida, la

capacidad funcional, la velocidad de sedimentación eritrocitaria y la tasa de hemoglobina al tiempo del ingreso, tuvieron valor poca o ninguna en el pronóstico de la evolución consiguiente.

(8) Los resultados de este tipo de investigación deben estudiarse atentamente al valorar nuevas formas de tratamiento, en particular cuando éstas llevan algún riesgo para los enfermos.