ANNALS OF THE RHEUMATIC DISEASES

AN ANALYSIS OF 388 CASES OF RHEUMATOID ARTHRITIS

By J. G. SCLATER

RHEUMATOID arthritis is described as a polyarticular disease which is characterised by pain and swelling of the small and medium-sized joints of the body. The onset is usually insidious, but it may be acute, and muscular wasting not only around the affected joints but also throughout the body is a striking feature. The incidence is stated to be greatest in the age period 20 to 40, and females are more frequently affected than males.

It is a common experience, however, to find that this description by no means covers a great many of the cases of rheumatoid arthritis. For example, a man aged 65 to 70 may present an arthritis affecting wrists and metacarpal-phalangeal joints associated with muscular wasting. If such a clinical picture had been presented by a woman of 35 there would be no hesitation in making a diagnosis of rheumatoid arthritis, but can rheumatoid arthritis occur in a man of 70? Or again, a woman shortly after the menopause may develop pain, swelling and limitation of movement, with muscular wasting, in both knees, and a diagnosis of menopausal arthritis may be suggested. A year later, however, the wrists and fingers may show the characteristic changes of rheumatoid arthritis, and the original diagnosis may have to be changed. Other variations such as the disease remaining mono-articular for some months before other joints become affected, or where stiffness in the region of the joints is more striking than actual pain and swelling, make the diagnosis of rheumatoid arthritis in some cases uncertain and difficult.

Accordingly, in any analysis of cases of arthritis of the rheumatoid type it is essential that the criteria on which the diagnosis is made are clearly stated.

In this series a case was considered to be an arthritis of the rheumatoid type if it showed the following features:

- 1 The presence of persistent swelling of the peri-articular tissues in the region of more than one joint.
2. The involvement, either primarily or subsequently, of the wrist, metacarpal-phalangeal joints, or interphalangeal joints.

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3. The presence of muscular wasting.
4. Radiological evidence, where available, compatible with a diagnosis of rheumatoid arthritis.
5. The absence of evidence that the arthritis was specific (*e.g.*, tuberculous, gonococcal) in origin.

On these grounds 388 cases which had been admitted to hospital during the period 1935-40 were chosen. The records were obtained from the following sources:

Royal Infirmary, Edinburgh	169 cases
Municipal Hospitals, Edinburgh	119 "
Royal Infirmary, Aberdeen	100 "
<hr/>	
Total	388

154 cases were under the care of Professor Davidson (35 from his wards in the Royal Infirmary, and 119 cases from the medical unit of the Municipal Hospitals, Edinburgh). They were examined personally by the author. The 100 cases from the Royal Infirmary, Aberdeen, were investigated by Dr. J. J. R. Duthie while carrying out research on the chronic rheumatic diseases under Professor Davidson. The remaining 134 cases were treated in the Royal Infirmary, Edinburgh, and were selected because the data in the case records were sufficiently detailed to give the requisite information required for the investigation.

It has to be noted that the hospitals in which these cases were treated admit children under the age of twelve only in exceptional circumstances, and thus no case of rheumatoid arthritis occurring before this age is included in this survey.

The analysis was undertaken to obtain information on the following points:

1. Sex incidence.
2. Age of onset.
3. Incidence of a history of preceding infection.
4. Incidence of a chronic focus of infection.
5. The relationship of pregnancy, childbirth, and the menopause to the onset of the disease.
6. Occupation of the affected person.
7. Joint (or joints) first involved.
8. The relationship between the duration of the disease and its severity on admission to hospital.

1. SEX INCIDENCE

In the 388 cases 270 (69·5 per cent.) were females, 118 (30·5 per cent.) were males—*i.e.*, a ratio of 2·3 females to 1 male. (From Table II. it can be seen that while there is a small preponderance of females over males in Scotland it cannot account for the higher incidence of the disease in females.)

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The ratio of 2·3 to 1 is in keeping with the figures obtained in the surveys by Munroe, Osgood and Pemberton, and Comroe, but is lower than those given by Copeman and Bach.

2. AGE AT ONSET

In Table I. is given the age of onset in ten-year periods in the two sexes.

TABLE I.—AGE OF ONSET BY AGE AND SEX

<i>Age.</i>	<i>Male.</i>		<i>Female.</i>		<i>Total.</i>	
	<i>No. of Cases.</i>	<i>Per-centage.</i>	<i>No. of Cases.</i>	<i>Per-centage.</i>	<i>No. of Cases.</i>	<i>Per-centage.</i>
12-14	1	0·8	10	3·6	11	2·8
15-24	11	9·3	50	18·4	61	15·7
25-34	28	23·8	45	16·6	73	18·8
35-44	31	26·3	76	27·7	107	27·6
45-54	27	22·9	56	21·6	83	21·4
55-64	18	15·2	26	9·6	44	11·3
65-74	2	1·6	7	2·6	9	2·3
Total	118	99·9	270	100·1	388	99·4

AVERAGE OF ONSET

<i>Males.</i>	<i>Females.</i>	<i>Both.</i>
42	39	40

From the above table it can be seen that:

(a) The average age of onset in males was 42, in females was 39, and in the whole series 40.

(b) The general trend of the age of onset of both males and females corresponds fairly closely, 73 per cent. of the male cases and 66 per cent. of the female cases occurring in the age period 25 to 54.

(c) 49 per cent. of the cases occurred between the age period 35 to 54.

(d) The percentage of cases with the age of onset between the ages 12 to 24 is more than twice as high in the females as in the males; this is in keeping with the clinical impression that when rheumatoid arthritis occurs in the young the female is much more likely to be affected.

Before considering whether those figures have any significance in relation to the pathogenesis of the disease it is necessary to take into account the distribution of the total population in similar age periods. Table II. gives the distribution of both sexes of the population of Scotland in the relevant age periods for the year 1938. The figures were obtained from the Annual Report of the Registrar-General for

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Scotland, 1938, and the year 1938 was chosen as being the middle year of the period 1935-40. The figures for the whole of Scotland had to be taken, as there are no figures for such areas as the east and south-east or north-east of Scotland, the main areas from which the cases under discussion were drawn. This is justifiable, as there is no indication that the age period distribution of the population in these areas is in any way different from the distribution in Scotland as a whole.

TABLE II.—ESTIMATED POPULATION OF SCOTLAND BY AGE AND SEX, 1938

<i>Age.</i>	<i>Both Sexes.</i>	<i>Males.</i>	<i>Females.</i>
15-24	859,100	430,900	428,200
25-34	804,300	391,800	412,500
35-44	666,200	309,600	356,600
45-54	554,300	252,900	301,400
55-64	468,900	219,400	249,500
65-74	290,200	133,400	156,800
Total	3,643,000	1,738,000	1,905,000

It might be argued that the variation of the population in each age group would account for the variation in the number of cases found in these groups as in Table I. Starting from this hypothesis for any given number of total cases the expected number in each age group can be calculated.

Table III. compares the number of cases actually present against the "expected" number in each age group in both sexes.

TABLE III.—COMPARISON BETWEEN THE NUMBER OF FOUND AND EXPECTED CASES BY AGE AND SEX

<i>Age.</i>	<i>Male.</i>		<i>Female.</i>		<i>Total.</i>	
	<i>Found.</i>	<i>Expected.</i>	<i>Found.</i>	<i>Expected.</i>	<i>Found.</i>	<i>Expected.</i>
15-24	11	29	50	58	61	87
25-34	28	26	45	57	73	83
35-44	31	21	76	49	107	70
45-54	27	17	56	41	83	58
55-64	18	15	26	34	44	49
65-74	2	9	7	21	9	30

Applying the chi-square test of significance to these figures it can be shown that the variation between the number of expected and found cases is significant. This means that some factor or factors other than the age distribution of population must be present to account for the number of cases in each group.

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From Tables I. and II. can be calculated the relative incidence of the disease in each age group. This allows a direct comparison to be made of the incidence in one age group with another, thus eliminating the factor of the variation of the population in these groups. With the figures at my disposal a true incidence rate cannot be given, as neither the population of the districts from which the cases are drawn nor the number of all the cases of rheumatoid arthritis occurring in these districts is known. Therefore the calculation of such a "relative" incidence rate per 1,000,000 persons in each age group is the most satisfactory method available.

TABLE IV.—THE RELATIVE INCIDENCE RATE PER 1,000,000 BY AGE AND SEX

<i>Age.</i>	<i>Male.</i>	<i>Female.</i>	<i>Total.</i>
15-24	25·5	116·4	71·0
25-34	71·5	109·3	90·8
35-44	100·1	213·1	160·6
45-54	105·2	185·8	149·7
55-64	83·9	104·2	93·8
65-74	15·0	44·6	34·5

From Table IV. it can be seen that:

(a) In the males the highest incidence occurs between the ages 35 to 54, but that there is no great difference in any age group from 25 to 64.

(b) In males the disease is as common between the ages 55 to 64 as between 25 to 34, and three to four times more common as between the 15 to 24.

(c) In females the incidence is doubled between the ages 35 to 54 as compared with the age period 25 to 34 and 55 to 64.

(d) In females the incidence of the disease between 55 to 64 is almost as great as in either of the age periods 15 to 24 or 25 to 34. Thus the widely accepted clinical view that rheumatoid arthritis is mainly a disease of young women is not supported by these findings.

(e) If the disease does occur before the age of 25 the incidence is four to five times greater in the female than the male.

3. INCIDENCE OF A HISTORY OF PRECEDING INFECTION

In this analysis only those infections which occurred within two months prior to the onset of symptoms were considered significant. The types of infection met with were upper respiratory tract infection, sinusitis, teeth abscesses, pyelitis, phlebitis, etc.

Table V. shows the distribution of a history of preceding infection by age and sex.

TABLE V.—DISTRIBUTION OF A HISTORY OF PRECEDING INFECTION BY AGE AND SEX

Age.	Males.			Females.			Total.		
	No. of Cases.	Pre- ceding Infection.	Per Cent.	No. of Cases.	Pre- ceding Infection.	Per Cent.	No. of Cases.	Pre- ceding Infection.	Per Cent.
12-14 ..	1	1	(100)	10	1	10·0	11	2	18·0
15-24 ..	11	1	9·1	50	13	26·0	61	14	23·0
25-34 ..	28	3	10·7	45	13	28·8	73	16	36·4
35-44 ..	31	5	16·1	76	17	22·4	107	22	20·5
45-54 ..	28	2	7·1	56	12	21·4	83	14	16·9
55-64 ..	18	3	16·6	26	1	4·0	44	4	9·1
65-74 ..	2	0	—	7	0	—	9	0	—
Total ..	118	15	11·8	270	57	21·0	388	72	18·3

A definite history of preceding infection was obtained in only 15 cases out of 118 males (11·8 per cent.) and in 57 out of 270 females (21 per cent.). The incidence was fairly evenly distributed in both sexes throughout the age periods 25 to 54, a period which includes 70 per cent. of the cases. This even distribution is more striking when both male and female cases are considered together. The maximum incidence of a history of preceding infection occurs in the age period 25 to 34.

On the other hand, after the age of 55 the incidence of a history of preceding infection is much lower than for the whole group, 4 out of 53 (7·5 per cent.); while the incidence in the age period 12 to 34 is 42 out of 145 cases (30 per cent.).

These findings are of some interest, since they support to some extent the view that in young persons infection is of greater ætiological importance than in the old.

However, an incidence of a history of preceding infection of only 18·3 per cent. is small, and accordingly it is unwise to draw definite conclusions from these figures.

4. THE INCIDENCE OF FOCAL SEPSIS

Table VI. gives the number of cases in which a focus of infection was found, by age and sex.

From the following table it can be seen that:

(a) A focus of infection was found in 147 out of 388 cases—i.e., 38 per cent.

(b) In the elderly patients of over 55 years of age the incidence of focal sepsis was 8 out of 53 cases (15 per cent.), while in persons younger than 25 focal sepsis was found in 34 out of 72 cases (47 per cent.).

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TABLE VI.—DISTRIBUTION BY AGE AND SEX OF CASES IN WHICH A FOCUS OF INFECTION WAS FOUND

Age.	Male.			Female.			Total.		
	No. of Cases.	Focal Sepsis.	Per Cent.	No. of Cases.	Focal Sepsis.	Per Cent.	No. of Cases.	Focal Sepsis.	Per Cent.
12-14 ..	1	1	(100)	10	4	40.0	11	5	45.0
15-24 ..	11	7	50.0	50	22	44.4	61	29	47.5
25-34 ..	28	12	42.8	45	26	57.7	73	38	52.0
35-44 ..	31	12	38.7	76	27	35.5	107	39	37.8
45-54 ..	27	9	33.3	56	19	34.0	83	28	33.7
55-64 ..	18	5	27.7	26	3	11.5	44	8	18.0
65-74 ..	2	0	—	7	0	—	9	0	—
Total ..	118	46	39.0	270	101	37.4	388	147	38.0

These findings and the deductions to be drawn from them correspond to those discussed under the incidence of a history of preceding infection.

The sites of infection were as follows:

Tonsils	97
Teeth	32
Sinuses	13
Uro-genital tract	11
Aural	4
Breast	3
Veins	3
Lung	3
Gall-bladder	1

The commonest sites for foci of infection were found to be the mouth and upper respiratory passages. This is in keeping with the age distribution of foci of infection shown in Table VI., for it is widely recognised that such infections are commoner in childhood and adolescence than in adult life.

Conclusions

An investigation into the part played by infection in the ætiology of rheumatoid arthritis is very difficult. In the case of a history of preceding infection, if a patient comes to hospital for the first time two to three years after the onset of the disease he may have forgotten a transient sore throat or cold which occurred three to four weeks before the onset of the disease. This delay, unavoidable in a disease usually insidious in onset, will tend to keep unduly low the number of cases giving a history of preceding infection.

As regards investigations into the foci of infection this delay has also to be considered, as infected tonsils or dental abscesses may have

been eradicated before the patient reports for treatment for the arthritis.

I can find no reference in the literature to the incidence of foci of infection in the normal healthy population. Without such a figure for comparison no conclusions can be drawn from the figures found in this investigation. If, however, infection were to play a major rôle in the pathogenesis of the disease one would expect a high incidence of infection in cases of rheumatoid arthritis, and the maximum incidence of such an infection should fall within the same age period as the maximum incidence of the onset of the disease.

The incidence of 18.3 per cent. for a history of preceding infection and of 38 per cent. for a focus of infection in this investigation appears to be too low to be significant.

Also the maximum incidence of the onset of rheumatoid arthritis was found between 35 to 54, whereas the maximum incidence of both a history of preceding infection and of a focus of infection was found between the ages 15 to 34.

Accordingly it would appear that if infection is important it is probably not the frequency or the severity of the infection that is significant, but perhaps some other factor such as the abnormal response of the patient to infection.

5. (a) THE RELATIONSHIP OF PREGNANCY TO THE ONSET OF ARTHRITIS

The relationship of pregnancy to the onset of arthritis was investigated by noting the number of cases in which the onset of the disease or a relapse occurred either during pregnancy or within six months of parturition.

In no case did arthritis manifest itself during pregnancy.

There were 27 cases in which symptoms developed within six months after parturition—*i.e.*, 10 per cent. of all female cases. As pregnancy occurred only in the period 20 to 40 in the cases investigated, the true incidence is 27 out of 107 cases—*i.e.*, 25 per cent.

However, in 25 of the 27 cases either a history of preceding infection was obtained or a focus of infection found.

Of these 27 cases 15 had further pregnancies subsequent to the onset of the arthritis. In only three cases did subsequent child-bearing produce deterioration of the arthritis. In the other twelve there were no data stating whether or not the arthritis improved during pregnancy.

Conclusions

Although these figures are too small to draw any certain conclusions, they indicate that pregnancy does not appear to play any specific rôle in the ætiology of rheumatoid arthritis.

5. (b) THE RELATIONSHIP OF THE MENOPAUSE TO THE ONSET OF ARTHRITIS

The changes in the metabolism of the body and the psychological outlook of the person associated with the menopause occur over a wide period both before and after the cessation of menstruation.

In this analysis all cases which developed arthritic symptoms in the period two years before to two years after the cessation of menstruation were noted.

Nineteen such cases were found—i.e., 7 per cent. of all female cases. In the series the menopause occurred only in the period 35 to 54; thus the true incidence was 19 out of 132 cases—i.e., 14·4 per cent.

In 11 of those cases either a history of preceding infection was obtained or a focus of infection found.

Conclusions

From the above data the figure $\frac{4}{20}$ gives an approximation of the chance association between the onset of arthritis and the cessation of menstruation. The actual percentage of 14·4 per cent. is lower than what might have been expected by coincidence, and this would indicate that the menopause does not tend to precipitate the onset of rheumatoid arthritis.

6. OCCUPATION

The undernoted figures are based on the 288 cases drawn from the Edinburgh hospitals:

Domestic duties	..	..	..	..	..	..	165
Casual labouring work	..	..	..	..	..	..	13
Retail trade	..	..	..	..	..	..	13
Ploughman	..	..	..	..	..	..	10
Miner	..	..	..	..	..	..	9
Engineer	..	..	..	..	..	..	9
Typist	..	..	..	..	..	..	9
Joiner	..	..	..	..	..	..	8
Baker	..	..	..	..	..	..	4
Distillery worker	..	..	..	..	..	..	4
Printer	..	..	..	..	..	..	4
Mason	..	..	..	..	..	..	4
Railway worker	..	..	..	..	..	..	3
Bricklayer	..	..	..	..	..	..	3
Sailor	..	..	..	..	..	..	3
Schoolgirl	..	..	..	..	..	..	3
Nurse	..	..	..	..	..	..	3
Commercial traveller	..	..	..	..	..	..	2
Waitress	..	..	..	..	..	..	2
Car conductor	..	..	..	..	..	..	2
Plumber	..	..	..	..	..	..	2
Painter	..	..	..	..	..	..	2
Laundry worker	..	..	..	..	..	..	2
Blacksmith	..	..	..	..	..	..	1
Not stated	..	..	..	..	..	..	8

The only point of interest in the above list is the great predominance of cases carrying out domestic duties. This is not surprising considering that 195 of the 288 cases were females and the great majority of women of the hospital class in the age period 25 to 54 are occupied with domestic duties.

7. SITE OF COMMENCEMENT OF THE DISEASE AS INDICATED BY THE FIRST JOINT AFFECTED

TABLE VII.

<i>Joint Affected.</i>	<i>Male.</i>		<i>Female.</i>		<i>Total.</i>	
	<i>No. of Cases.</i>	<i>Per Cent.</i>	<i>No. of Cases.</i>	<i>Per Cent.</i>	<i>No. of Cases.</i>	<i>Per Cent.</i>
Fingers	24	26	75	38	99	35
Knees	17	18	50	26	67	21
Wrists	13	14	25	13	38	13
Feet	9	10	21	11	30	11
Ankles	18	19	10	5	28	10
Shoulders	8	9	5	2	13	5
Elbows	3	3	7	4	10	4
Hips	1	1	2	1	3	1

From the above table it can be seen that the disease started in the fingers in 38 per cent. of the females as compared with 26 per cent. of the males. If the hypothesis is accepted that the joints most likely to be affected are those submitted to the greatest strain, then the higher incidence of the disease starting in the interphalangeal and metacarpal-phalangeal joints in the female might be explained.

The frequency with which the arthritis started in joints other than the fingers and wrists is considerably higher (52 per cent.) than a study of the literature would lead one to expect.

8. THE RELATIONSHIP BETWEEN THE DURATION OF THE DISEASE AND ITS SEVERITY

The 288 cases admitted to the Edinburgh hospitals were used in this investigation.

The cases were divided according to the state of the disease into the following groups:

GROUP 1.—Peri-articular swelling with stiffness, but only little limitation of movement.

GROUP 2.—Peri-articular swelling with more marked limitation of movement than in Group 1, but no evidence of ankylosis, and still in employment.

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GROUP 3.—Fixation of joints, flexion deformities, and inability or great difficulty in continuing in employment.

GROUP 4.—Gross deformities with patient either bedridden or severely crippled.

According to this classification the cases were distributed as follows :

Group 1	..	..	..	..	..	34 (11.9 per cent.)
„ 2	..	..	..	..	..	116 (40.3 „)
„ 3	..	..	..	..	..	109 (37.5 „)
„ 4	..	..	..	..	..	29 (10.1 „)

The average duration of the disease in each group was :

Group 1	..	..	..	..	..	1.3 years
„ 2	..	..	..	..	..	2.4 „
„ 3	..	..	..	..	..	5.0 „
„ 4	..	..	..	..	..	7.0 „

47.5 per cent. of the cases fell into Groups 3 and 4. Thus nearly half the cases were crippled before hospital treatment was started.

This is brought out more strikingly in Table VIII., in which the cases were divided according to the duration of the disease into :

- Up to 6 months.
- Between 6 months and 1 year.
- 1 to 3 years.
- 4 to 6 years.
- 7 to 9 years.
- 10 years and over.

The cases in each of these divisions were then placed in their respective groups according to the severity of the disease, as shown in Table VIII.

TABLE VIII.

Duration of Disease.	No. of Cases.	Group 1.		Group 2.		Group 3.		Group 4.	
		No.	Per Cent.	No.	Per Cent.	No.	Per Cent.	No.	Per Cent.
Up to 6 mths.	37	14	38	16	43	6	16	1	3
6 months to 1 year ..	30	10	33	16	53	3	10	1	3
1 to 3 years ..	107	8	7	50	47	40	37	9	9
4 to 6 years ..	50	0	—	16	32	28	56	6	12
7 to 9 years ..	20	0	—	6	30	9	45	5	45
10 years and over ..	44	2	4.5	12	27	23	52	7	16

From this table it can be seen that :

(a) During the first year of the disease 83.6 per cent. of the cases are in either Group 1 or 2.

- (b) By 1 to 3 years only 54 per cent. are in Group 1 or 2.
 (c) After the disease has lasted for ten years or more only 31·5 per cent. fall into the first two groups.

Conclusions

From these figures it can be said that as a general rule the longer the disease has existed the more severe it is. The outlook for patients in Groups 3 and 4 is very much worse than for those in Groups 1 and 2, and the importance of early and thorough treatment is obvious.

SUMMARY

1. A survey of 388 cases of rheumatoid arthritis is reported.
2. In this series the disease was found to be two to three times more common in females than males.
3. The maximum incidence of age of onset occurs between 35 and 54 (49 per cent.). In males and females the incidence between the ages of 55 and 64 is approximately the same as between 25 and 34 (Table IV.).
4. A history of preceding infection was obtained in 72 cases out of 388 (18·3 per cent.).
5. The incidence of focal sepsis was 147 out of 388 cases (38 per cent.).
6. No case of arthritis developed during pregnancy, while 27 cases of the 107 patients in the child-bearing period age (25 per cent.) occurred within six months of parturition.
7. Nineteen cases out of 132 (14·4 per cent.) between the ages 35 to 54 developed symptoms of arthritis within two years of cessation of menstruation.
8. The disease had been present for five years or more in 47·6 per cent. of the cases when first seen. The degree of crippling was found to be closely related to the duration of the disease.

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