THE COURSE OF REITER'S SYNDROME

BY

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Reiter's syndrome in its fully developed form is characterized by an association of non-specific urethritis, arthritis, conjunctivitis, and a number of less constant features (Reiter, 1916). Cases of urethritis and arthritis alone have a course indistinguishable from the full syndrome and are therefore included in this study. This leads to difficulties in nomenclature which will be resolved only when the aetiology of this condition becomes known.

Clinical descriptions of individual attacks are many, but the natural history of the syndrome has received little attention and much remains unknown. Ford (1953), in an interesting paper, describes the history of 21 selected cases, the criteria being recurrent or chronic arthritis over a period of five years or more. It is my aim to record some observations on a large group of consecutive patients, many of whom have been followed for several years.

Present Study

This is based on the experience gained from 185 consecutive patients (182 male, 3 female) with Reiter's syndrome who attended the venereal disease clinic at St. Mary's Hospital, London, from 1942 to 1956 inclusive. A few had their first attack elsewhere, and in some the disease started before this study began. I saw 125 cases personally, and the rest were studied from their medical records. Of the 185 cases, 87 had arthritis associated with genital infection and 98 showed additional features, especially eye and skin involvement. Most of the patients received some form of treatment which might have influenced the natural course of the disease, but there is no good evidence that any current therapy can essentially alter the progress of Reiter's syndrome (Fowler and Knight, 1956).

Incidence in Hospital.—The incidence of the syndrome in relation to the total number of urethral infections seen in males at this clinic over the same period was 0.8% (22,010 cases of urethritis and 182 males with Reiter's syndrome). As the study is confined to hospital patients it is not thought that it necessarily reflects the incidence of the syndrome as it may occur in the general population. Apart from genital infections, bacillary dysentery has been associated with this syndrome, and it is of interest that similar incidence figures have been noted (Paronen, 1948).

Basic Data

The small number of females confirms the general experience that they are only exceptionally affected. In cases occurring after dysentery there is a much higher incidence in women (Paronen, 1948). Both white (164) and coloured (21) patients were affected, though the condition seemed to be less severe in coloured patients.

The social class and civil state of the patients are shown in Table I. Table II shows that the majority of patients in this series were sexually promiscuous and that casual sexual relationship prior to the onset of the genital infection leading to Reiter's syndrome was the rule. In two patients non-specific urethritis (N.S.U.) and arthritis was said to follow their first sexual contact.

Table III deals with the history of genital infection; it is apparent that a number of patients have a past history of venereal urethritis. Of the 16 who presented themselves with several features of the syndrome but no evident urethritis, 12 were found to have chronic persistent prostaticitis and all gave a past history of gonorrhoea.

TABLE I.—Social Class (Registrar-General's Classification) and Civil State of 185 Patients

No.	Class					Civil State			
	I	II	III	IV	V	Single	Married	Divorced	Widowed
	3	5	55	80	42	107	68	7	3

TABLE II.—Sexual Background (Obtained from Personal History and Past Record of Venereal Disease)

Sexual Habits		Sexual Contacts before Onset of Reiter's Syndrome with	
"Promiscuous" ..	112	Wife/husband ..	17
Not promiscuous ..	41	Friend ..	25
No intercourse ever ..	2	Stranger/prostitute ..	99
Data incomplete ..	30	Homosexual ..	4
		"None" ..	2
		Data incomplete ..	38

TABLE III.—Frequency of Past and Present Lower Urogenital Infection (in 185 Patients with Reiter's Syndrome)

	Before 3 Months of Onset of Reiter's Syndrome	Within 3 Months of Onset of Reiter's Syndrome
Gonorrhoea	74	26
with residual N.S.U.	—	67
N.S.U.	8	71
Haemorrhagic cystitis with N.S.U.	2	5
Urethritis of unknown diagnosis	11	—
No urethritis	90	16*

* 12 of these patients had asymptomatic chronic prostatitis.

The attacks which were closely associated with gonorrhoea were of special interest because of the now generally accepted view that the important aetiological factor is a non-gonococcal element rather than a gonococcal one (Harkness, 1949). In 67 patients penicillin apparently cleared the gonococci, leaving a residual urethritis which was followed by arthritis and sometimes by other symptoms of the syndrome. In 26 further cases no post-gonococcal urethritis followed penicillin; nevertheless a typical attack of arthritis, with or without conjunctivitis, developed a few days later and did not respond to penicillin. There seemed to be no clinical difference between attacks preceded by N.S.U., gonorrhoea with N.S.U., or gonorrhoea alone, and the significance of these findings is uncertain.

The age of onset ranged from 15 to 59 years, and 82% of attacks occurred between 20 and 40 (Table IV). The frequency of the principal signs and symptoms is recorded in Table V.

TABLE IV.—Age of Onset of Reiter's Syndrome

Age in Years	No.	Age in Years	No.	Age in Years	No.
15-	8	30-	41	45-	9
20-	34	35-	26	50-	2
25-	51	40-	12	55-59	2

TABLE V.—Frequency of Principal Manifestations

Genital infection:	No. Affected
N.S.U.	71 (38.4%)
Gonorrhoea with N.S.U.	67 (36.2%)
Acute haemorrhagic cystitis with N.S.U.	26 (14.0%)
Chronic prostatitis without N.S.U.	5 (2.7%)
Joint and tendon involvement:	12 (6.5%)
Polyarthritis	161 (87.0%)
Monoarthritis	14 (7.5%)
Arthralgia	10 (5.5%)
Sacroiliitis	16 (8.6%)
Achilles tendinitis	24 (12.9%)
Other	13 (7.0%)
Plantar fasciitis	40 (21.6%)
Eye lesions:	60 (32.3%)
Conjunctivitis	21 (10.8%)
Iritis	5 (2.7%)
Keratitis	38 (20.5%)
Balanitis	37 (20.0%)
Cystitis (non-haemorrhagic)	26 (14.0%)
Keratoderma blennorrhagica	11 (5.9%)
Stomatitis	5 (2.7%)
Thrombophlebitis of legs	3 (1.6%)
Subcutaneous nodules	1 (0.5%)
pericarditis	1 (0.5%)

Latent Period

In a limited number of patients the periods between the relevant intercourse and the onset of urethritis on the one hand and between the onset of urethritis and the next manifestation of the syndrome were recorded, but as the data depend entirely on the patients' veracity and good memory, the figures should be treated with some reserve (Table VI).

TABLE VI.—*Latent Periods*

	No. of Cases	Mean Time (Days)
Sexual intercourse to onset of gonorrhoea ..	50*	6
Onset of gonorrhoea to onset of arthritis ..		12.7
Sexual intercourse to onset of N.S.U. ..	30	13.3
Onset of N.S.U. to onset of arthritis ..		14

* All these cases developed post-gonococcal N.S.U.

The duration of first attacks in 165 cases ranged from 3 weeks to 18 months (mean: 3.8 months), and in the remaining 20 cases the disease showed no clear-cut remission from the start for three or more years.

Follow-up

Eighty patients were observed for less than one year, mostly because they defaulted. In the majority of defaulters the attacks were mild, and it is possible that most of them did well subsequently; but even if one assumes the some-

TABLE VII.—*Follow-up of Patients with Reiter's Syndrome*

Duration (Years)	No. of Patients with	
	Single Attack	Multiple Attacks
<1 year ..	73	7
1- ..	3	42
5- ..	2	28
10- ..	2	12
15- ..	1	10
20- ..	—	4
25+ ..	—	1
Total ..	81	104

30 cases of Reiter's syndrome followed for 10 years or more from the onset, showing recurrences of arthritis (26 cases) and the influence of fresh urethral infections on the course of the illness.

what improbable event that all of them were cured, there are still over 50% of the total series known to have had repeated attacks or continued activity over a number of years. These findings give a less favourable picture than is sometimes suggested and emphasize the need for a long observation period (Table VII).

In all, 30 patients could be followed for 10 years or more from the onset of their illness, and, although attempts have been made to see as many patients as possible over a prolonged period, it is certain that this group is not representative of the whole series but is biased in containing the more seriously and chronically involved cases. Nevertheless, the study of these patients proved especially rewarding, as it demonstrated several interesting features (see Diagram). It can be seen that reinfection with venereal urethritis, be it gonococcal or non-gonococcal in nature, did not inevitably lead to further arthritic attacks. There was, in fact, no obvious reason why some episodes of urethritis in the same patient were followed by arthritis and others were not. No clinical difference in the character of the urethritis was found. The Diagram shows also that some later attacks of arthritis were not always preceded by urethral infection, unlike the first attacks in this group. Another interesting observation brought out by this long-term study is the extreme variability of the intervals between attacks; these were as short as three months or as long as 18 years.

Multiple Attacks

More than one attack of arthritis occurred in 104 patients. A total of 304 attacks were recorded in this group, the frequency distribution of which is shown in Table VIII.

TABLE VIII.—*Frequency Distribution of Multiple Attacks in 104 Cases with Reiter's Syndrome*

No. of Attacks	No. of Cases	No. of Attacks	No. of Cases
2 ..	54	6 ..	1
3 ..	24	7 ..	1
4 ..	14	8 ..	1
5 ..	8	9 ..	1
		Mean:	2.9 attacks

Forty-eight patients claimed that one or more of the later episodes were "unprovoked," as there had been no sexual intercourse during the preceding two to three months. In 22 of these attacks urethritis was absent, and in a further two instances non-specific urethritis appeared only after the onset of arthritis. On assessment, most of these attacks were considered to be relapses. Apart from the notable absence of urethritis in some of these cases, there was an unusually high incidence of iritis and sacroiliitis. In the whole series there were 21 cases with iritis, and 17 of these occurred in patients with probable relapses; of the total of 16 cases with sacroiliitis, 9 were found in this selected group. In contrast, rather more patients had subsequent attacks following the pattern of their first one—that is, sexual intercourse—urethritis—joint and other changes. A few cases showed both types of attacks at different times. Apart from the difficult problem of relapse versus reinfection, it was noted that with repeated attacks recovery became less complete.

Precipitating Factors

A careful search was made for precipitating factors other than urethral infection. None were identified with certainty, but some experiences are worth recording. In four patients with previous Reiter's syndrome, diarrhoea occurred as a result of food-poisoning (2 cases) and antibiotic therapy for an unrelated condition (2 cases), and was followed within one to five days by a new attack of arthritis. This is of interest because of the known association of a similar syndrome with acute dysentery. In three patients second attacks of the full syndrome followed within two to seven days after urogenital surgery or instrumentation (hydrocele operation, dilatation of a urethral stricture, and salpingectomy for chronic non-specific salpingitis). In six cases one

attack was preceded by tonsillitis. In all these instances the first attack followed venereal urethritis, and the possibility of the above conditions being associated by chance only with the later episodes cannot be ruled out.

Predisposing Factors

In the last 109 cases systematic inquiry regarding "rheumatic diseases" in parents, siblings, and offspring was undertaken; of these, 14 (12.9%) gave a clear account of rheumatoid arthritis in their families, compared with 9 (2.2%) in a control group of 400 cases attending with uncomplicated N.S.U. or gonorrhoea (Boyd, Oates, and Csonka, 1958). These findings suggest that there may be a hereditary predisposition to the arthritic manifestations of Reiter's syndrome.

There was only one known instance of Reiter's syndrome occurring in more than one member of a family in the entire series. It concerned two brothers who lived in different parts of England and who developed severe attacks within three months of each other. A common sexual source was denied.

Once a patient has suffered from this syndrome it seems likely that sooner or later the condition will recur. It is open to question whether this is due to a change brought about by the first attack or whether the increased susceptibility is inherent in the patient. A similar problem presents itself in rheumatic fever, in which both predisposition and infection with a specific organism play their part and where the prevention or early treatment of haemolytic streptococcal infection is successful in stopping further attacks. Whether a similar policy would be as beneficial in the management of patients with a history of previous attacks of Reiter's syndrome has not yet been adequately explored.

Dissociation of Symptoms

Many patients showed a rapid evolution of the classical features of the syndrome in a matter of days or weeks, as described in the literature, but some differed by a marked dissociation in the time of appearance of the cardinal symptoms—for example, one patient presented himself with non-specific urethritis and arthritis; nine years later he was seen with another similar attack, but with additional conjunctivitis for the first time. Another patient had recurrent episodes of urethritis and circinate balanitis over a period of two years; at the end of this time he developed severe arthritis and conjunctivitis. Yet another had urethritis and arthritis on three occasions; and on the fourth, nine years after the first attack, he developed iritis as well, which became the dominant feature of his recurrent active phases. In general, iritis was especially prone to make a late appearance, and keratoderma blennorrhagica was also a late-comer on occasion. The record in this series is held to date by a man whose first attack of urethritis and arthritis was followed by a symptom-free interval of 18 years, when he contracted venereal urethritis once more, and this was associated with arthritis and also conjunctivitis. These experiences lend support to the view that the various components of the disease need not occur simultaneously and that the "incomplete" syndrome is essentially of the same nature as the more fully developed one. This last point was probably demonstrated by two of our patients who gave the same female contact as source of their urethritis; this was followed in the one case by arthritis only and in the other by the full triad.

Sequelae

No deaths were attributed to the syndrome. The long observation period allowed a study of the late changes, and the more important of these are summarized in Table IX. Most of the patients with recurrent iritis had also one or more of the other listed sequelae, such as foot deformities or sacroiliitis, and the total number of individuals with some measure of permanent damage was 28. In addition to this group with well-defined changes there were a further six patients who were handicapped by a mild-to-moderate

activity in various joints for periods of two to three years but who have not shown residual joint damage so far.

TABLE IX.—*Sequelae*

	No. of Cases	Remarks
Recurrent iritis	21	In 8 cases this became the dominant feature of the illness, with some visual loss
Foot deformities (pes valgus, pes cavus, subluxation of toes, periostitis of heels)	23	
Ankylosis of peripheral joints	8	The joints involved were: toes (4), hip (2), knees (2), elbow (1), tarsal joints (1)
Sacroiliitis	16	One patient showed also spinal involvement; the rest were limited to the sacroiliac joints

Summary

This paper records 185 patients with arthritis following genital infection, mostly venereal urethritis, who attended St. Mary's Hospital, London, over the past 15 years.

There were 182 males and 3 females in this consecutive series; 87 cases had arthritis only and 98 showed additional features, especially eye and skin involvement.

More than one attack occurred in 104 patients, and some of the later episodes appeared to arise independently of sexual contacts and may have been relapses.

The follow-up period in 30 cases extended for 10 years or more. Not every fresh urethral infection led to further attacks of arthritis. The intervals between attacks varied from a few months to 18 years. Possible predisposing and precipitating factors are discussed.

A dissociation of symptoms was noted in some cases when eye or skin lesions were not seen until years after the first attack. This suggests that the initial "incomplete" form of the syndrome is essentially of the same nature as the fully developed one.

Sequelae included sacroiliitis, deformed and chronically painful feet, ankyloses of peripheral joints, and visual disturbances resulting from recurrent iritis.

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