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A PROSPECTIVE STUDY OF REITER'S SYNDROME

AN INTERIM REPORT ON THE FIRST 82 CASES*

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Between 1957 and 1963 a prospective study of Reiter's syndrome has been in progress at the Rheumatism Research Centre, Manchester Royal Infirmary. The aims of the study were to determine whether treatment of the genito-urinary disorder had any influence on the course of the disease, and to collect data regarding the clinical and laboratory characteristics of the syndrome at its presentation and during its evolution.

For the purposes of the study Reiter's syndrome was defined as an inflammatory polyarthritis in males with infection of the lower genito-urinary tract or a history of such infection; patients with evidence of infection of the gastro-intestinal tract, or a history of such infection, were included provided they also came within this definition. Other manifestations of the complete syndrome, affecting the eye, skin, etc., were not required for inclusion of a patient in the study. The criteria were subsequently relaxed to allow the inclusion of two female patients.

Material

In all 83 patients originally entered the study, but one was later withdrawn when the original diagnosis of Reiter's syndrome proved to be incorrect. Most of the patients were referred directly from venereal disease clinics, but some were referred by other hospital departments, and particularly by local orthopaedic surgeons who had been informed about the study beforehand.

Methods

(1) Treatment

Most of the patients were admitted directly to a special ward in Ladywell Hospital, Salford, under the care of a consultant venereologist (A.J.G.) for treatment. A few patients were admitted to the study as out-patients, chiefly on account of their refusal to enter hospital.

All patients were given symptomatic treatment with aspirin 60 gr. daily, with sedation as required. The side-effects of aspirin were relatively few and and in most cases easily controlled; patients with a history of gastric or duodenal ulceration were given antacids concurrently with aspirin. Several patients received phenylbutazone for short periods in doses of 300 to 400 mg. daily. One patient with an exceptionally severe attack was given corticosteroids for about 2 weeks. Affected joints were aspirated and splinted when indicated, and strict rest in bed was prescribed for patients with active arthritis in the weight-bearing joints; static muscle contractions and postural and breathing exercises during the period of rest in bed were followed by graduated weight-bearing exercises.

Alternate patients with a first attack of polyarthritis of less than 6 months' duration were allotted either to the Treatment or to the Control group. Those in the Treatment group were given oxytetracycline 500 mg. four times daily for 5 days, with daily prostatic massage for 14 days. Patients whose first attack of polyarthritis began more than 6 months before entry were allotted alternately to Treatment or Control groups in the same way.

(2) Assessments

The initial examination and investigation of the genito-urinary system was normally carried out at Ladywell Hospital by the venereologist in charge of in-patient treatment (A.J.G.): he alone knew the groups in which individual patients were placed, so that all assessments made by the other observers were blind in this respect.

Each patient was seen at the Rheumatism Research Centre as soon as possible after admission for the initial examination of the locomotor system and for the specified investigations, and thereafter monthly until discharged from hospital. This part of the

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initial examination and all the follow-up assessments were conducted by a rheumatologist (A.J.P.: originally Dr James Sharp) who advised on the general management of each case. Genito-urinary examinations and investigations were carried out by the second venereologist (S.M.L.) at the follow-up assessments and initially also for those entering the study as out-patients. Most patients were also examined independently on at least one occasion by an ophthalmologist at the Royal Eye Hospital, Manchester. Follow-up assessments were made at 1, 3, 6, 12, 18, and 24 months.

Laboratory Investigations

On Entry: Haemoglobin; total and differential white cell count; erythrocyte sedimentation rate (E.S.R., Westergren); sensitized sheep-cell agglutination test (S.C.A.T., Ball, 1950); stool culture for dysenteric organisms; electrocardiogram; radiographs of hands, feet, calcaneum, pelvis, chest, and cervical spine; chemical testing, microscopy, and culture of urine; microscopy of urethral discharge, if any, and of prostatic secretion; Wassermann reaction, Price's precipitation reaction, and gonococcal complement-fixation test.

At Each Follow-up Assessment: Haemoglobin, total white cell count, E.S.R., S.C.A.T.

At 3, 6, and 12 Months and then Yearly: Radiographs of hands, feet, and calcaneum (and of pelvis at 12 months only).

Results

General Characteristics

Age at Onset.—The highest incidence of the attacks studied, taking the series as a whole, was in the age group 25–34 (Table I).

TABLE I
AGE AT ONSET OF ATTACKS STUDIED

Age Group	Number of Cases	
	First Attack	Whole Series
15–24	15	19
25–34	24	32
35–44	10	17
45–54	9	11
55–64	1	3
Total	59	82

In 59 patients studied during their first attack, the predominance of the younger age groups is even more striking, since there were 39 patients between 15 and 34 years of age compared with twenty between 35 and 64 (Table I); the age distribution of patients studied during a second or later attack was broadly similar.

Race.—78 of the 82 patients were of European origin; only four (4·9 per cent.) were Negroes (Table II) and in these four the disease was mild. The small proportion of coloured men seems significant in view of the fact that 21 per cent. of all patients with non-gonococcal urethritis (NGU) in the Manchester area in 1961 were coloured, and suggests that NGU is less frequently complicated by Reiter's syndrome in the Negro than in white Europeans.

Marital Status.—47 (57 per cent.) of the patients were single, separated, divorced, or widowed, and 35 (43 per cent.) were married; 34 (41 per cent. were single.

Sex.—There were two females, neither of whom had severe attacks, and one of these was the consort of one of the eighty males.

Occupation.—Thirteen patients followed itinerant occupations which involved regular travelling and nights spent away from home.

First Hospital Attendance.—63 patients were referred from venereal disease clinics, and the remainder from other hospital departments.

Diagnosis.—Seven patients were diagnosed as having gonorrhoea on bacteriological evidence; a further thirteen patients with bacteriologically-confirmed gonorrhoea also had non-gonococcal urethritis which was noted after successful treatment of gonococcal infection. In 61 patients a diagnosis of NGU was made, and in one there was no evidence of active urethritis.

Previous History.—In 23, 5, and 28 cases respectively there was a previous history of gonorrhoea, gonorrhoea with NGU, and NGU; for the 59 patients with a first attack of Reiter's syndrome the

TABLE II
DISTRIBUTION OF CASES BY VARIOUS CHARACTERISTICS

Race		Marital Status		Sex	Occupation		Source		Diagnosis	
White	78	Married	35	Male 80	Itinerant	13	VD Clinic	63	Gonorrhoea	7
Negro	4	Single	34	Female 2	Non-itinerant	69	Other	19	Gonorrhoea and NGU	13
		Other	13						NGU	61

corresponding figures were 15, 2, and 12. A previous history of dysentery was given by six patients but in none of these did it bear any obvious relation to the onset of Reiter's syndrome. Fourteen patients gave a history of accidental trauma involving one or more joints subsequently affected during their attack of Reiter's syndrome, and in four it seemed possible that occupational trauma had determined the onset of arthritis in certain joints. Apart from the former attacks of Reiter's syndrome, the previous history of rheumatic complaints was unremarkable. There was no striking previous history of allergy, migraine, eczema, or hay-fever.

Interval between Onset of Urethritis and of Other Symptoms.—In nearly three-quarters of the cases (58) the interval was between 0 and 15 days (Table III). In eleven cases the interval exceeded 15 days and in one it was uncertain. In a further eleven cases other symptoms of the syndrome preceded recognition of urethritis.

TABLE III

INTERVAL BETWEEN RECOGNITION OF ONSET OF URETHRITIS AND ONSET OF OTHER SYMPTOMS

Days	0–3	4–7	8–11	12–15	16+	No Data	Other Symptoms First
Number of Cases	13	15	18	12	11	1	11

Initial Symptoms Other than Urethritis.—In three cases, one of which was a first attack, the initial symptom was a mild non-specific diarrhoea lasting less than a week; in a further eight cases, of which six were first attacks, the presenting symptom was arthritis or conjunctivitis. We believe that in these eleven cases the NGU was so mild that it escaped recognition by the patient even though it was readily apparent on examination.

Presentation of Arthritis.—It was sometimes difficult to be certain which joint was first affected, but in at least three out of four patients it was an ankle or a knee or one of the joints in the feet. The finger and wrist joints were first affected in only seven cases, and some other joint or joints in nineteen; the arthritis presented in two or more joints simultaneously in only six cases. Four patients were not able to remember clearly which joint was first affected.

Clinical Picture on Entry into the Study

One of the objects of the study was to investigate the frequency with which various features might be expected at a patient's first attendance, since many patients are seen before the full syndrome has developed. The interval between the onset of symptoms and entry into the study varied between 3 days and 6 months, with an average of about 3 weeks, but this figure could not always be determined with accuracy.

Symptoms Other than Arthritis and Urethritis.—The frequency with which various symptoms were observed at the first examination is shown in Table IV; symptoms such as conjunctivitis, which had sometimes already resolved by this time, were included when the evidence for their occurrence was unequivocal.

TABLE IV

SYMPTOMS OTHER THAN ARTHRITIS AND URETHRITIS ON ENTRY TO THE STUDY (82 cases)

Symptom	No. of Cases	Symptom	No. of Cases
Backache ..	51	Conjunctivitis	32
Non-specific pains	18	Iritis	3
Sore throat ..	16	Circinate balanitis	33
Mucosal lesions (mouth) ..	20	Keratodermia blennorrhagica	27
Tongue lesions ..	13	Nail lesions	5

Backache was one of the most constant symptoms. Although in some cases it was clearly due to active arthritis of the sacro-iliac or spinal joints, in others there was no definite evidence of arthritis, and in such cases it was often mild and usually transient. The various oro-genital lesions were sometimes at too early a stage of development for certain recognition at the first examination, but the accuracy of the initial observations was usually substantiated during follow-up; minimal lesions of this type appear to be important diagnostic features. Ulceration of the buccal mucosa was most often seen opposite the molar teeth or on the palate, and occasionally on the fauces and alveolar margins; the ulcers were whitish, shallow, often oblong, up to a centimetre in length, were not conspicuously painful, and were usually surrounded by a small areola of injection. There was often a diffuse injection of the entire faucial and posterior palatal area and an associated mildly-tender upper cervical lymphadenopathy. The tongue was often covered with a thick yellowish fur; the typical tongue lesion might appear as a small and sharply-defined unfurred area or, when more advanced, as multiple pink islands of denudation surrounded by the paler normal or furred mucosa. Circinate balanitis, keratodermia blennorrhagica, or conjunctivitis had appeared in more than one-third of the patients by the time of the initial examination.

Circinate balanitis was never seen in the circumcised unless some portion of prepuce remained. Iritis was rarely seen at the first examinations. In several cases early nail lesions were seen which took the form of a painless red swelling at the base of the nail fold, superficially resembling paronychia, with a yellow segment of thickening and fragmentation affecting at this stage only the white of the nail.

Active Skeletal Lesions (Table V).—Active arthritis, periostitis, or soft tissue lesions were not diagnosed unless there was pain spontaneously or on movement, tenderness, or warmth in addition to fluid, swelling, or thickening. Although the general picture of the arthritis was usually asymmetrical, more than half the patients had bilateral arthritis of some joint, usually of the knee, ankle, or tarsus. Evidence of periostitis was most often found on the calcaneum, especially at the attachment of the plantar fascia or Achilles tendon; it was also found in the region of the knee, elbow, and wrist joints and on the pelvis. Most of the recurrent cases had some residual joint damage from previous attacks, and the same joints tended to be involved again. The preponderance of arthritis in the lower limbs and the relative sparing of the upper limbs is striking. Although sometimes the cervical or lumbar regions of the spine were involved as a whole, more often one or two segments appeared to be mainly affected. Severe arthritis of the knee joints was sometimes associated with gross lateral and antero-posterior instability, but this tended to recover within weeks in contrast to the much longer duration of such changes in rheumatoid arthritis.

TABLE V

ACTIVE SKELETAL LESIONS AT FIRST EXAMINATION (82 cases)

Joint	No. of Cases	Joint	No. of Cases
Foot:		*Hand:*	
Terminal interphalangeal	0	Terminal interphalangeal	1
Proximal interphalangeal	9	Proximal interphalangeal	6
Metatarso-phalangeal	32	Metacarpophalangeal	15
Tarsal	43		
Ankle	26	*Wrist* and intracarpal joints	15
Knee	48	*Elbow*	4
Hip or Shoulder	12	Temporo-mandibular	1
Spine: cervical	10	Sterno-clavicular	4
thoracic	11	Acromio-clavicular	8
lumbar	15	Manubrio-sternal junction	0
Sacro-iliac: one	10	Costo-chondral junctions	2
both	6		
Bilateral arthritis of one or more joints			47
Tenosynovitis			4
Periostitis			36

Laboratory Investigations on Entry into the Study

The results of the routine investigations are summarized in Table VI. In most cases the E.S.R. (Westergren) was in the middle range, but in a number of severe cases the value was above 100 mm./hr; severe cases also showed a mild anaemia and usually a moderate leucocytosis. The sensitized sheep-cell agglutination test (S.S.C.A.T.) and the stool culture were negative in all cases.

TABLE VI

LABORATORY FINDINGS

Investigation		Number of Cases
Erythrocyte Sedimentation Rate (Westergren: mm./1 hr):	Below 10	12
	10–60	42
	Above 60	27
Haemoglobin (g./100 ml.):	Below 13·0	12
	13·0 or Higher	70
White Blood Cells (per cu. mm.)	Below 5,000	0
	5–10,000	51
	Above 10,000	31
Sensitized Sheep-cell Agglutination Titre More than 1 : 16		0
Electrocardiogram. Abnormal		2
Stool Culture. Abnormal		0

Of two patients with abnormal electrocardiograms, one had a minor irregularity of no apparent significance while the other had the typical changes of acute pericarditis during the course of an extremely severe attack.

Radiological Changes on Entry into the Study

The number of patients with radiological bone changes is shown in Table VII. As expected, a greater proportion of the patients with recurrent attacks than of those with first attacks showed changes attributable to Reiter's syndrome; 15 per cent. of patients with a first attack already had minor but definite changes at the time of their first examination. The changes seen in early cases consisted of localized osteoporosis, cortical erosion, or periosteal

TABLE VII

NUMBER OF PATIENTS WITH RADIOLOGICAL CHANGES ON ENTRY INTO THE STUDY (81 cases)

Site	First Attack	Recurrence	Total
Calcaneum	12	14	26
Feet	11	9	20
Ankles	3	1	4
Sacro-iliac joints	3	7	10
Hands	1	4	5
Other Joints	4	3	7
Bilateral Changes	7	9	16

new bone formation at the attachment of muscles or ligaments or on the shafts of long bones near their articulations. In cases with a history of previous attacks, more advanced changes were seen, typically in the form of large calcaneal spurs, and occasionally there was gross joint destruction with subluxation or ankylosis. The relatively frequent presence of changes in early cases is rather surprising, but it should be emphasized that in some cases these were minimal and not easily seen without close scrutiny.

Effects of Treatment

The effects of treatment were assessed by analysing the severity and duration of the attacks in the Treatment and Control groups; the results are summarized in Table VIII. 45 patients (20 treated, 25 control) attended regularly for follow-up until all signs of active disease had vanished. A further nine (5 treated, 4 control) attended regularly up to the point at which the disease had almost remitted but still showed minimal evidence of activity; these patients, who had mild inflammation in one or two joints with a normal E.S.R., or a raised E.S.R. without clinical evidence of active disease, are included with those followed to complete recovery in the analysis. Of the remaining 28 patients (14 treated, 14 control) who defaulted, most were seen on at least two occasions and many on three or more occasions; since they still showed active disease, even though it was clearly well past its zenith, they are not included in the analysis of the duration of attacks, but are included, when the data seemed adequate, in other parts of the analysis.

TABLE VIII

EFFECTS OF TREATMENT

Group	Treatment	Control
Mean duration of attack in cases followed to recovery (wks)	24·8 (25 cases) (range 6–92)	26·3 (29 cases) (range 3–78)
Mean number of joints affected at first visit	5·3 (39 cases)	4·7 (42 cases)
Mean number of new joints affected after first visit ..	1·98 (38 cases)	1·81 (41 cases)
Maximum number of joints affected at any one visit ..	6·0 (38 cases)	5·5 (39 cases)
Mean duration of extra-articular lesions (wks)	8·5 (24 cases)	10·0* (32 cases)
Number of cases developing new non-arthritic lesions after first visit	4	9
Number of cases having later recurrences	4	5

* This figure drops to 8·0 if one exceptional value of 90 weeks is excluded.

Bone and Joint Lesions.—Serial estimates of the severity of arthritis based on subjective responses are unsatisfactory as a means of comparison, and the most useful measure proved to be the number of individual joints showing active arthritis at each examination. Because it is difficult to distinguish clinically between individual joints in the spine, the cervical, thoracic, and lumbar regions were classed as three single joints. The carpo-metacarpal, intracarpal and wrist joints, and the tarso-metatarsal and intratarsal joints were similarly classed as two single joints, but the ankle joints were kept separate. Periosteal tenderness usually subsided as the arthritis improved, but its duration proved unhelpful in gauging recovery from the acute attack, since tenderness over calcaneal spurs sometimes persisted long after all other evidence of active disease had disappeared; in such cases it seems probable that the persistence of symptoms was mechanical rather than inflammatory in origin.

Arthritis was the feature of the syndrome which lasted longest; resolution of arthritis marked the completion of recovery from the individual attack, except for one patient in whom iritis first appeared 8 months from the onset. The mean duration of attack, from the onset of the presenting symptom to the resolution of the arthritis, was almost the same in the treatment and control groups, being less than 24·8 weeks in 25 treated cases and less than 26·3 weeks in 29 control cases. The mean number of joints affected at the first examination was 5·3 in the whole treatment group and 4·7 in the whole control group.

The mean numbers of joints becoming freshly involved after the first visit were 1·98 and 1·81, and the maximum number of joints actively affected at any one visit was six in the treatment group and 5·32 in the control group. The duration and extent of the arthritis were virtually the same in the two groups, and it is clear that the treatment given for the genito-urinary infection had no appreciable effect on the course of the syndrome.

In only twenty out of 77 cases was a larger number of joints actively affected at follow-up assessments than at the initial examination, and this was nearly always at the first or second month. The picture therefore emerges of an asymmetric inflammatory polyarthritis affecting predominantly the lower limb joints, evolving rapidly to its maximum severity within a few weeks, or at the most within a month or two, of the onset of the disease, lasting at its height for up to 2 months but usually less, and gradually remitting, with an occasional minor recrudescence, over 3 or 4 months to complete or almost complete recovery.

The clinical picture of the arthritis in Reiter's syndrome contrasts sharply with that of rheumatoid arthritis, in which the onset is usually less abrupt, the number of joints affected tends to increase over weeks or months rather than days, the course is prolonged for months or years, and permanent joint damage is common.

Other Lesions.—Urethritis rarely persisted more than a few weeks after admission to hospital, and conjunctivitis had usually almost cleared up before the first examination at the Rheumatism Research Centre. As with the urethritis, all the other characteristic types of lesion were most often seen in greatest profusion at the initial examination; only in thirteen cases (4 treated, 9 control) were new lesions seen at follow-up examinations. Geographical denudation of the tongue and superficial ulcers of the buccal mucosa had usually resolved by the time of the assessment after one month, but circinate balanitis, which usually appeared at the same time, tended to last longer. Keratodermia blennorrhagica sometimes continued to spread for a number of weeks while the arthritis remained at its height but usually started to clear up rapidly soon after the circinate balanitis had healed.

The average time during which extra-articular lesions were present after the onset of the attack was 8·5 weeks in the treatment group and 10·05 weeks in the control group; if one exceptional value of 90 weeks is excluded, however, the average time in the control group falls to 8·0 weeks. There was therefore no significant difference in the duration of the extra-articular lesions in the two groups. Nine out of 32 patients in the control group developed new lesions after the first visit compared with four out of 24 in the treatment group, but it is doubtful whether this represents a real difference, since in every other respect, including the incidence of later recurrences, the two groups behaved similarly.

Discussion

The results provide no evidence that treatment of the genito-urinary component of Reiter's syndrome with oxytetracycline and prostatic massage has a beneficial influence on the course of the disease, nor on the other hand that such treatment is attended by any harmful effects; the possibility remains that treatment either with tetracycline or with prostatic massage alone might have yielded a different result but this seems unlikely.

The incidence of keratodermia blennorrhagica was somewhat higher and the incidence of iritis lower than would have been expected from the published data (Hancock, 1960). These differences from the published figures may be more apparent than real, since the results given here relate only to a single attack of the syndrome in each patient; and whereas keratodermia is seen most frequently during a first attack, the incidence of iritis, often a very late complication, increases with the length of follow-up. Radiological evidence of bone lesions in early cases was more frequent than expected, probably because unusual care was taken to search for such lesions. Although there are minor differences in detail, the observations reported here are generally in close accord with those of Csonka (1958), Hancock (1960), and Harkness (1950).

Summary

An account is given of the presenting features and the course of Reiter's syndrome.

A controlled trial of treatment with oxytetracycline and prostatic massage in 82 cases is described.

The specified treatment had no influence on the course of the disease.

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Étude prospective du syndrome de Reiter
Rapport intérimaire des premiers 82 cas

Résumé

On décrit les premiers symptômes et le cours de la maladie dans le syndrome de Reiter; on rapporte un essai clinique contrôlé du traitement de 82 malades par l'oxytétracycline et le massage prostatique.

Ce traitement n'eut aucun effet.