ARTHRITIS ASSOCIATED WITH GONORRHOEA*†

BY

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Keefer and Spink (1937) recorded the outstanding clinical features of gonococcal arthritis as manifested by patients attending the Boston City Hospital over a 5-year period just before the sulphonamide and penicillin era. By careful documentation of the clinical course in 140 cases, determination of serum antibody titres to Neisseria gonorrhoeae and analysis of 112 joint effusions, the authors were able to provide a description of the clinical characteristics of gonococcal arthritis which has never been bettered. Subsequently, many descriptions of arthritis following gonorrhoeal infections have appeared in the literature, but most have added no new information and many have only served to spread confusion concerning our knowledge of certain clinical entities. It is now apparent that the mode of presentation and the ensuing course of post-gonococcal arthritis may fall anywhere within a spectrum ranging from acute sepsis in a single joint to a chronic disabling polyarthritis. Wright (1963), for example, reviewed the records of patients who had initially been diagnosed as having gonococcal arthritis at the Johns Hopkins Hospital, and found that some of them later manifested a clinical course that was characteristic of Reiter’s syndrome. In contrast, Ford (1961) was not able to find any patients with true suppurrative arthritis following gonococcal infections and claimed that “post-gonococcal arthritis is Reiter’s syndrome”.

The time appears opportune, therefore, to present clinical data obtained on a number of patients, examined personally by us, at the Boston City Hospital during the past 4 years. Each patient presented with culture-proven gonorrhoea and a related episode of arthritis. Not only did these cases afford us the unique opportunity to compare our findings with observations made over three decades ago in the same hospital, but they provided clinical information which should add perspective to the controversy that has arisen regarding the relation of post-gonococcal arthritis to Reiter’s syndrome and post-venereal arthritis.

Material and Methods

26 patients at the Boston City Hospital over a 4-year period from February, 1962, to April, 1966, formed the basis of this study. Certain clinical characteristics and synovial fluid findings were analysed in each case and the patients were classified into three groups:

I. Definite gonococcal arthritis: Gonococci recovered on culture of synovial fluid (Table II).

II. Probable gonococcal arthritis: Gonococci not recovered from synovial fluid but found on culture from the genito-urinary tract or blood. In addition, arthritis occurred shortly after known gonorrhoea and cleared promptly on antibiotic therapy (Table III).

III. Polyarthritis of unknown aetiology: An episode of arthritis associated with culture-proven gonorrhoea (gonococci cultured from the genito-urinary tract or blood). The arthritis showed an atypical response to specific anti-gonococcal treatment (Table IV).

Results

Classification.—Of the 26 patients studied, there were ten cases of definite gonococcal arthritis, eleven of probable gonococcal arthritis, and five of polyarthritis of unknown aetiology associated with gonorrhoea. In Group II, two patients had received a single dose of penicillin before admission to hospital. In Group III, two patients demonstrated the triad of arthritis, urethritis, and conjunctivitis, and these features plus their clinical course were considered typical of Reiter’s syndrome.

Age, Sex, and Race.—The age of the patients upon presentation ranged from 16 to 62 years; the majority were young individuals and the mean age was only 31 years. There were thirteen males and thirteen females, all five in Group III being male. Four women were pregnant and all were in the third trimester when they developed arthritis associated with gonorrhoea. Sixteen of the 21 patients with definite or probable gonococcal arthritis were Negro and five were Caucasian. Four of the five patients in Group III were Caucasian.

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Clinical Aspects

(a) Fever and Chills.—Fever was considered to be present if the body temperature was recorded as greater than 100° F. The majority of patients in all groups were febrile at the time of admission. The presence or absence of chills depended on the patient’s description of his symptoms so that the documented incidence of this finding probably represents an underestimation of its true frequency. Nevertheless, it is of interest that no patients in Group III complained of chills, whereas this was not an infrequent finding in Group I (30 per cent.) and Group II (54 per cent.).

(b) Interval between First Manifestation of Gonorrhoea and Onset of Arthritis.—This was difficult to measure because of inadequate history in some cases. However, in three persons with definite gonococcal arthritis who were able to supply this information precisely, the average interval was 10 days (4, 9, and 17). In five cases of probable gonococcal arthritis whose histories were deemed reliable, the average interval was 7 days (0, 3, 7, 7, and 14). The five cases in Group III averaged a 7-day “lag” between urethritis and the onset of arthritis (4, 4, 7, 7, and 13).

(c) Patterns of Joint Involvement.—Most patients in Groups I and II complained of arthralgia in many joints at the onset of their disease when they were also complaining of fever and chills, anorexia, and malaise. However, joint involvement was considered to be present only if pain on motion or tenderness plus soft tissue swelling or joint effusion was found by the examiner. The pattern of joint involvement in almost every case was similar, i.e. arthritis in two or more joints, usually asymmetric and often confined to several large joints especially the knees, ankles, or wrists. True monoarticular arthritis was the exception rather than the rule and in only one case in Group I and one case in Group II did it appear that no more than one joint was affected throughout the entire clinical course (Table I). Four of the five patients in Group III demonstrated multiple joint involvement, while in the fifth only the left ankle was affected.

The particular joints affected in patients with definite or probable gonococcal arthritis is illustrated in Fig. 1. The high incidence of knee involvement in Group I was striking (8 of 10 patients). Other joints affected in this Group were wrist (4), elbow (4), and ankle (3). Small joints such as the interphalangeals and metacarpophalangeals were spared in most instances. The eleven patients in Group II

<table>
<thead>
<tr>
<th>Group</th>
<th>Joint Involvement</th>
<th>Total</th>
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<tbody>
<tr>
<td>I.   Definite gonococcal arthritis</td>
<td>Polyarthritis 6</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Mono-arthritis 1</td>
<td></td>
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<tr>
<td></td>
<td>Poly→Mono-arthritis 3</td>
<td>10</td>
</tr>
<tr>
<td>II.  Probable gonococcal arthritis</td>
<td>Polyarthritis 10</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Mono-arthritis 1</td>
<td></td>
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<tr>
<td></td>
<td>Poly→Mono-arthritis 0</td>
<td>11</td>
</tr>
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Fig. 1.—Affected joints in gonococcal arthritis.
most commonly showed wrist involvement (6), followed by knee (5) and shoulder (3). Predilection for larger joints was also demonstrated in Group III: knee (4 of 5), ankle (4), and shoulder (1).

(d) Tenosynovitis, Fasciitis, and Skin Changes.—Intense redness of the skin and increased heat and swelling of the tissues adjacent to the affected joints was frequently observed in patients with definite and probable gonococcal arthritis. Tenosynovitis was also common, but its true incidence could not be ascertained with accuracy since its presence was not always documented when the patient was first seen. In contrast, no evidence of tenosynovitis was obtained for the patients in Group III. Two of these, however, had keratoderma blennorrhagica and three had demonstrable pain and tenderness localized to the plantar fascia of the soles of the feet.

(e) Therapy.—During the acute flares of the disease complete immobilization of affected joints was maintained. All 26 patients were treated with therapeutic doses of systemic penicillin (ranging from 1 to 6 million units/day) except for Case 25 in Group III who was said to be allergic to penicillin and was given tetracycline, 2 g./day for 6 days. Two patients (Cases 9 and 11) received initial intra-articular injections of 50,000 units penicillin. The duration of treatment was also variable as several patients had been started on penicillin before admission and others left hospital against advice before completion of what was deemed adequate therapy. Length of treatment, however, averaged 11 days in Group I, 13 days in Group II, and 12 days in four patients in Group III.

By the criteria of the study, the temperature fell to normal in Groups I and II after the institution of penicillin therapy, with dramatic alleviation of their symptoms, especially joint discomfort, within 48 hours and often within 12 hours. It was noted, however, that in nineteen cases who were followed closely by us, signs of joint involvement, especially painless effusions, persisted for from 4 to 21 days after starting antibiotic therapy. Furthermore, in these patients no relationship was discernible between the delay in starting specific penicillin treatment and the time necessary to effect a complete cure (Fig. 2). Although subsequent follow-up in most of the patients was limited, there was no instance of residual joint deformity or disability in Group I and II, nor did we encounter strains of gonococci that proved resistant to the amounts of penicillin outlined above.

The arthritis in the two patients with Reiter's syndrome was non-remitting by comparison, and both required several months before improvement was observed. One eventually appeared to clear substantially after phenylbutazone therapy and the other after moderate doses of prednisone. In the other three patients in Group III remission was finally achieved after many months.

Laboratory Findings

(a) Blood.—Initially, peripheral white blood cell counts revealed a mild leucocytosis in patients from all groups (mean 12,700 cells/cu. mm. in Group I, 13,500 in Group II, and 11,000 in Group III). Differential counts were not strikingly different from group to group but there was a slight predominance of polymorphonuclear leucocytes in the peripheral blood smears in Groups I and II compared with Group III (75 versus 64 per cent.).

(b) Synovial Fluid.—Joint fluid aspiration was attempted as early as possible in all cases and analyses of the fluids were performed in our laboratory. All specimens were implanted on chocolate agar as well as blood agar and cultured anaerobically in the Clinical Laboratory of the Boston City Hospital. In many instances serial synovial fluid analyses were obtained. The results of these studies are presented in detail in Tables II, III, and IV (opposite and overleaf).

The initial mean synovial fluid white blood cell counts were clearly higher in Group I (58,500 cells/cu. mm.) and Group II (39,500 cells/cu. mm.) than in Group
III (8,160 cells/cu. mm.), but differential counts were similar in all three categories. Mucin clot formation in acetic acid was generally “poor” or “fair” in all groups, although there were three exceptions (Cases 13, 15, and 25) where clot formation was “good”. The joint fluid sugar/blood sugar differential was elevated in two (Cases 1 and 9), but too few values were recorded to enable evaluation of its clinical usefulness. Perhaps the most unusual and unexplained joint fluid finding was the low white cell count obtained on fluids withdrawn simultaneously from both knees of Case 4, which both yielded
positive cultures for gonococci. Joint aspirations performed on all patients in Group I after penicillin therapy had been instituted yielded negative cultures for infectious organisms.

**Discussion**

Arthritis in association with gonorrhoea occurs more frequently than might have been expected in this era of readily available antibiotics. Although our series of 26 patients is far smaller than that of Keefer and Spink (1937), who discovered 140 cases with gonococcal arthritis in the same institution from 1931 to 1935, it should be noted that we included only those patients in whom the diagnosis was confirmed by culture of gonococci from joint fluid, genito-urinary tract secretions, or blood. Intentionally, we have not reported the findings on thirty persons who were seen over the same period of time and in whom the clinical features and synovial fluid abnormalities were presumably due to gonorrhoea, although the aetiological agent could not be identified for various reasons. In some, for example, post-venereal urethritis or cervicitis and arthritis had received prompt treatment with penicillin before admission to hospital. Efforts to culture organisms from joint effusions or genito-urinary discharges in these cases invariably yielded negative results despite a strong clinical impression that they initially had contracted gonorrhoea. Statistics to support the view that the incidence of gonococcal arthritis is not significantly decreasing, at least in large municipal institutions, has come from studies at the Parkland Memorial Hospital, Dallas, where 115 patients with definite or probable gonococcal arthritis were seen during a 6-year period from 1958 to 1964 (Hess, Hunter, and Ziff, 1965).

Despite the continuing high frequency of new cases, penicillin therapy does alter the morbidity associated with gonococcal arthritis. Our study revealed that 21 of the 26 patients with gonococcal arthritis recovered completely, whereas the majority of those seen at Boston City Hospital before the introduction of penicillin developed chronic synovitis, which in turn often led to residual deformity. The beneficial effects of penicillin were so dramatic in our series that we have been prompted to conclude that most patients who present with arthritis associated with gonorrhoea have, in fact, a true suppurative arthritis responsive to antibiotic therapy and unlikely to pursue a chronic course. The similarities that were noted between patients in Group I (where joint fluid cultures were positive) and Group II (where joint fluid cultures were negative) further suggested that, in a presumptive case of gonococcal arthritis, marked improvement following penicillin is almost as reliable a diagnostic criterion as successful culture of the gonococcus from the joint fluid.

If one accepts our evidence based on clinical findings that 21 of 26 patients were correctly diagnosed as having suppurative arthritis due to gonorrhoea, then the series is large enough to make certain useful conclusions regarding the natural history of this disease. The majority of patients with gonococcal arthritis are young adults, although exceptions occur; there was one 69-year-old woman in our series.

Not represented in our series are children (Holt, 1905; Fink, 1965) and newborn infants (Parrish, Console, and Battaglia, 1940), who occasionally develop gonococcal arthritis. Our data also support recent observations by Grabar, Sanford, and Ziff (1960), that females are more commonly affected than males in contrast to the pre-antibiotic era when men with gonococcal arthritis often outnumbered women by as much as three to one.
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(Wehrbein, 1929; Lees, 1932; Keefer and Spink, 1937).

With respect to the clinical aspects of gonococcal arthritis, it should be remembered that, although the articular symptoms usually appear about 10 days after the onset of urethritis, the interval may be either considerably shorter or, as claimed by others (Hench, Bauer, Fletcher, Ghrist, Hall, and White, 1935; Keefer and Spink, 1937), inordinately delayed, so that the relation seems obscure. A history of fleeting joint pains, anorexia, malaise, fever, and particularly chills, before the appearance of joint swelling or effusions in large joints should arouse immediate suspicion of gonococcal arthritis. The study emphasized that the most common mode of presentation of gonococcal arthritis is a polyarthritis, a little appreciated fact. Involvement of more than one joint in sixteen of the 21 cases with suppurative arthritis due to gonococci contrasts with the characteristic monoarticular arthritis seen in other forms of bacterial arthritis (Cartier, Martin, and Kelly, 1959). Other systemic manifestations, such as bacterial endocarditis, pericarditis, and meningitis, which were seen quite frequently in the pre-antibiotic era were not encountered in our series.

Laboratory findings in patients with gonococcal arthritis were as anticipated, raised white blood cell counts (predominantly polymorphonuclears) being the rule. Special serological studies to measure antibody response to gonococcal infection were not carried out in this study. Hess and others (1965), however, using an immunofluorescent technique, recently found that nineteen of 22 patients with definite and probable gonococcal arthritis (a group similar to our 21 cases) and seventeen of 35 patients with presumptive gonococcal arthritis (a group similar to the thirty cases from Boston City Hospital not included in our study because of negative cultures from either joint fluid or genito-urinary tract) had significant rises in titre of antibodies to gonococci. In agreement with others, we found that synovial fluid white blood cell counts greater than 30,000 cells/cu. mm. were usually associated with positive joint fluid cultures, while counts below this value were characteristically negative (Ropes and Bauer, 1953; Ward, Cohen, and Bauer, 1960). Serial synovial fluid analyses proved most helpful in following the resolution of the infectious process, particularly after the institution of systemic penicillin therapy. Because of the sensitivity of the organisms and the excellent penetration of penicillin from blood into the synovial spaces, intra-articular injection of penicillin was not recommended. Indeed, the local administration of crystalline penicillin may provoke an inflammatory response and may therefore interfere with a valuable means of assessing the response to specific antibiotics. In none of the patients with definite gonococcal arthritis was the initially good response to penicillin therapy followed by a chronic synovitis as sometimes happens in cases of septic arthritis due to pneumococcal and meningococcal infections (Argen, 1964; Pinals and Ropes, 1964; Cohen and Kim, 1966).

The present study enabled us to make some observations regarding the relationship between gonococcal arthritis and Reiter's syndrome. The original study from Boston City Hospital did not allow for distinction between these two conditions; the study, in fact, predated the first American report of Reiter's syndrome by Bauer and Engelman (1942). It should be noted, however, that four of the 140 cases developed keratoderma blennorrhagica, a condition now considered characteristic of Reiter’s syndrome and only casually related to gonorrhea (Kulka, 1962). In our series five patients were encountered, whose arthritis, though directly associated with gonorrhea, did not respond dramatically to penicillin and continued to pursue a more chronic course. Two had unequivocal Reiter's syndrome and the others presumably had a similar diagnosis although conjunctivitis was not clinically apparent. The arthritis involved large joints and in this respect could not be distinguished readily from gonococcal arthritis until a poor response to penicillin became obvious. Synovial fluid analyses were clearly abnormal in Group III especially in the two cases with classical Reiter's syndrome although elevation of the white blood cell count was a less prominent feature than in Groups I and II. None of our cases presented with diarrhoea (common in European studies of Reiter's syndrome: Hancock and Mason, 1965) and all were ushered in with urethritis. We were unable to detect any instance in which gonorrhoea appeared to precipitate rheumatoid arthritis, as was postulated by Hench and Boland (1946) after a study of arthritis associated with gonorrhoea in military personnel. Finally, we found little evidence to support the contention that Reiter's syndrome may be in some fashion directly caused by gonorrhoeal infection, the findings in several patients suggesting that gonorrhoea and Reiter's syndrome may occur together as independent venereal diseases.

Summary and Conclusions

26 patients in whom an episode of arthritis was associated with culture-proven gonorrhoea were carefully studied with respect to age, sex, interval between onset of urethritis or cervicitis and arthritis, mode of presentation, pattern of joint involvement, response to penicillin therapy, and laboratory
findings, particularly synovial fluid analysis. In 21, the arthritis was suppurative, polyarticular, and responsive to penicillin therapy; in five it was non-suppurative, polyarticular, non-responsive to penicillin therapy, and inclined to pursue a sub-acute or chronic course. Two of these five patients with chronic arthritis appeared to have classical Reiter’s syndrome associated with gonorrhoea.

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