REITER'S SYNDROME IN FIRST COUSINS*

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Stecher (1955) has pointed out that the train of events is always the same in establishing a familial hereditary element in disease. Once the diagnostic criteria of a condition have been established, individual family reports follow. When these reach sufficient numbers, they are assembled and analysed with a view to finding the nature of the underlying genetic factors.

Hereditary factors are now well recognized as playing a part in nearly all rheumatic conditions. Many people who are genetically "at risk", however, do not develop these diseases. In gout, for example, it is now established that hyperuricaemia is genetically controlled, and dominant in males. (Smyth, Cotterman, and Freyberg, 1948; Stecher, Hersh, and Solomon, 1949). Infective, psychological, and metabolic factors influence the way in which the gene precipitates attacks. West (1949), who studied the aetiology of ankylosing spondylitis from many angles (geography, sex, occupation, etc.), reached the conclusion that the familial incidence of the disease was greater than might be expected on grounds of chance alone. Romanus and Ydén (1955) considered the hereditary factor in spondylitis to be an autosomal dominant, not sex-linked, and with incomplete penetrance, *i.e.* not all those genetically prone actually develop the disease. Hersh, Stecher, Solomon, Wolpaw, and Hauser (1950) placed the penetrance level in males at 70 per cent. Romanus (1953) stated that irrefutable signs of prostatovesiculitis could be found in a high proportion of men with spondylitis, and believed the infection to be significant in causation. Stecher (1955), in studying 224 families of patients with rheumatoid arthritis, found 250 cases in 1,054 brothers and sisters, which is about half of what might be expected if the disease were inherited as a single factor dominant. Analysing his figures in conjunction with an adequate randomized series showing the incidence as 0.58 per cent. in the general

public, he came to the conclusion that the degree of penetrance was about 50 per cent., conditioning factors, endogenous and/or environmental, determining the level. Wilson, Schweitzer, and Lubschez (1943) did much to establish a familial link in rheumatic fever. Stevenson and Cheeseman (1956), in their study of 462 Belfast families, showed the chances of rheumatic fever to be greatly increased in sibships whose parents revealed a history of the disease. Their figures suggest a penetrance level of about 50 per cent.

Although there is still much doubt regarding the existence of a rheumatic diathesis, close investigation of families with rheumatism show that many different forms may exist among related people. Dawson and Tyson (1935) have shown a familial association between rheumatic fever and rheumatoid arthritis. Riecker, Neel, and Test (1950), studying the inheritance factors in rheumatic disease, quoted Robecchi as saying that 30 per cent. of the immediate relatives of cases of Still's disease have some form of rheumatism.

Present Observations

Reiter's syndrome consists of multiple arthritis, iritis, or conjunctivitis and keratoderma blennorrhagica, following or in conjunction with a non-gonococcal urethritis. The cause of non-gonococcal urethritis is unknown, but it is widely recognized as an infective condition of coital origin. It is known as a relapsing condition (Morton and Read, 1957). Some 3 to 4 per cent. of men with non-gonococcal urethritis develop complete or incomplete Reiter's syndrome. Although in many cases, the arthritis clears completely, both clinically and radiologically, the recurrence of urethritis is commonly accompanied by recurrence or exacerbation of the syndrome. Lydon (1957) has pointed out the resemblance between Reiter's syndrome and rheumatoid arthritis. Romanus and Ydén (1955) are in no doubt that spondylitis and non-specific

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prostate-vesiculitis are inseparably associated. It would also seem significant that section studies of the skin in psoriasis (a condition now often clinically associated with arthritis) resemble in every detail the microscopic appearance of the skin from cases of keratoderma blennorrhagica (Auckland, 1951). There is little doubt therefore, that Reiter's syndrome is genetically a rheumatic condition, and like other rheumatic conditions, may show a familio-hereditary factor.

The incidence of non-gonococcal urethritis in males in England and Wales has averaged 12,600 per annum since venereal disease clinics first made separate returns of the condition in 1951 (Ministry of Health, 1957).

With Reiter's syndrome occurring in only 3 to 4 per cent. of these, the total number of cases is small, and the chances of demonstrating a familio-hereditary factor are somewhat remote and so far undocumented. It therefore seems important to report an example of Reiter's syndrome in first cousins (Figure).

- A) History of rheumatic fever
 (B) Case 2 as described.
 (C) Rheumatic fever at ages 14 and 21; died with mitral stenosis, at age 35.
 (D) Case 1 as described.
 (E) Congenital bilateral contracture fifth finger; arthritis (? septic) after scarlet fever at age 5.

X = Male

O = Female

Case Reports

Case 1, an unmarried man aged 36 (III, 6 in Pedigree Chart), was first seen on July 25, 1955, complaining of an urethral discharge of 3 days' duration. He stated that he had last had intercourse 3 months previously. His past history revealed that he had had acute urethral gonorrhoea in 1943. In 1947, he had had non-gonococcal

urethritis with arthritis in the right knee and right ankle. In 1950 he had had burning micturition without urethral discharge, multiple arthritis, bilateral iritis, and keratoderma blennorrhagica of the feet, which necessitated hospitalization for 8 months.

Examination.—There was a purulent urethral discharge, Gram-stained specimens of which failed to show any organisms. The urine was hazy in both glasses of the two-glass urine test. The Wassermann reaction and Kahn test were negative and the gonococcal complement-fixation test doubtful.

Treatment.—Oral terramycin 250 mg. 6-hrly was started immediately and 2 days after the initial visit the urethral discharge was much less and the urine showed a haze in the first glass only.

The patient complained of low backache, and he had mild iritis (right eye). The terramycin therapy was continued in conjunction with 20 gr. aspirin four times a day, and he was advised to rest.

After 3 days the urethral condition showed no new change. There was bilateral iritis, and arthritis of the right knee and metacarpophalangeal and interphalangeal joints of the left thumb. Terramycin therapy was replaced by aureomycin therapy, which cleared the

urethritis completely within a few days, aspirin was continued, and the patient was admitted to hospital.

Laboratory Findings.—There was slight polymorphonuclear leucocytosis. The erythrocyte sedimentation rate (E.S.R.) was 15 mm. in the first hour (Wintrobe). Radiologically the fourth lumbar vertebra showed some early lipping, and the right knee showed some early lipping and loss of joint space. The electrocardiogram was normal. On August 10, 12 days after the start of the illness the E.S.R. rose to 27 mm. in the first hour.

The left knee then became affected, and the patient developed hyperkeratotic lesions of the glans penis, scrotum, and soles

of both feet. All aspects of the condition worsened gradually, in spite of treatment, but the patient eventually recovered after a course of bi-weekly intravenous T.A.B. fever therapy. Altogether he required nearly 4 months in hospital. He was seen at intervals over the next year and finally discharged in November, 1956.

Recurrence.—In March, 1957, this man attended again with a recurrence of urethral discharge. He denied any new sexual exposure. The urethritis responded promptly to aureomycin and the patient was confined to bed for 2 weeks. He did not develop any rheumatic manifestations on this occasion, or within the ensuing 6 months.

Case 2, a married man aged 37 (III, 4 in Pedigree chart), was the first cousin of Case 1, the mothers of the two

men being sisters (II, 3 and 7). He reported first on March 26, 1957, complaining of urethral discharge, low backache, and pain with swelling in the first interphalangeal joint of the right index finger. All the symptoms were of one week's duration. He admitted extra-marital intercourse on three occasions with the same consort during the previous month. There was no past history of genito-urinary infection.

Examination.—There was a purulent non-gonococcal urethritis, arthritis in the right index finger, mild bilateral iritis, and hyperkeratotic lesions of the glans penis and coronal sulcus. The E.S.R. was normal and the Wassermann reaction, Kahn test, and gonococcal complement-fixation test were all negative.

Treatment.—Oral terramycin 250 mg. 6-hrly, and 20 gr. aspirin four times a day were started immediately. The patient refused to enter hospital, and was ordered to rest at home. After 2 days his general condition was much improved, and there was some improvement in the genito-urinary condition; 6 days after his initial attendance, he still had slight muco-purulent urethral discharge with a pus haze in both glasses of the two-glass urine test. Terramycin was replaced by aureomycin therapy in the same dosage, and the discharge cleared. Aspirin was continued, but 3 weeks after his initial attendance there was no change in his joint condition, and he was admitted to hospital.

Laboratory Findings.—The E.S.R. was 18mm. in the first hour.

There was no leucocytosis. Radiologically, the first interphalangeal joint of the right index finger showed definite cartilage loss, and there was evidence of osteoporosis of the base of the middle phalanx. In spite of further treatment he developed arthritis of the right elbow and right shoulder joint, with limitation of movement and some muscle wasting. The E.S.R. rose to 25 mm. in the first hour.

The electrocardiogram was normal, and the sensitized sheep cell agglutination test for rheumatoid arthritis was negative.

Progress.—There was no improvement with aspirin or bi-weekly intravenous T.A.B. fever therapy, but real comfort and improvement followed the start of Butazolidin 100 mg. three times daily. The patient was discharged after 6 weeks, and has been under constant care ever since, but is making only a slow recovery.

Discussion

There is no doubt that the diagnosis in each case was non-gonococcal urethritis, complicated by Reiter's syndrome. The occurrence of a comparatively rare rheumatic disorder like Reiter's syndrome in first cousins is noteworthy. Coincidence is difficult to exclude, but several factors support the idea of a familio-hereditary element.

The fairly common finding of different types of rheumatism in the family of the two men concerned is shown in the pedigree, and adds support to the suggestion that Reiter's syndrome has a familio-hereditary element.

Summary

(1) The occurrence of Reiter's syndrome in first cousins is reported; other members of the family had had different rheumatic conditions.

(2) If other observers find further familial cases, especially in brothers or in fathers and sons, the importance of an inheritance factor in the development of Reiter's syndrome, as in some other rheumatic conditions, may be established.

REFERENCES

- Auckland, G. (1951). *Brit. J. vener. Dis.*, **27**, 143.
 Dawson, M. H., and Tyson, T. Lloyd (1935). *Proc. Amer. Ass. for Study and Control of Rheum. Diseases*, **2**, 132.
 Hersh, A. H., Stecher, R. M., Solomon, W. M., Wolpaw, R., and Hauser, H. (1950). *Amer. J. hum. Genet.*, **2**, 391.
 Lydon, F. L. (1957). *Brit. med. J.*, **1**, 1303.
 Ministry of Health (1957). Report for 1955, Pt. 2., Appendix C, Cmd 16, p. 254.
 Morton, R. S., and Read, L., (1957). *Brit. J. vener. Dis.*, **33**, 223.
 Riecker, H. H., Neel, J. V., and Test, A. (1950). *Ann. intern. Med.*, **33**, 1254.
 Romanus, R. (1953). *Acta med. scand.*, **145**, Suppl. 280.
 — and Ydén, S. (1955). "Pelvo-Spondylitis Ossificans", trans. J. Whitehouse. Munksgaard, Copenhagen.
 Smyth, C. J., Cotterman, C. W., and Freyberg, R. H. (1948). *J. clin. Invest.*, **27**, 749.
 Stecher, R. M. (1955). *Med. Clin. N. Amer.*, **39**, 499.
 —, Hersh, A. H., and Solomon, W. M. (1949). *Ann. intern. Med.*, **31**, 595.
 Stevenson, A. C., and Cheeseman, E. A. (1956). *Ann. hum. Genet.*, **21**, 139.
 West, H. F. (1949). *Ann. rheum. Dis.*, **8**, 143.
 Wilson, M. G., Schweitzer, M. D., and Lubschez, R. (1943). *J. Pediat.*, **22**, 468.