Reiter's Disease, Ankylosing Spondylitis and Rheumatoid Arthritis Occurring Within a Single Family

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A family is reported in which three brothers had respectively, ankylosing spondylitis, Reiter's disease, and Reiter's disease followed by rheumatoid arthritis; the father had atypical spondylitis following stigmata of Reiter's disease. The literature of Reiter's disease affecting more than a single family member is reviewed.

Several authors have suggested that rheumatic diseases are prevalent in families of patient's with Reiter's disease (RD) (1–4). Moreover, RD has occasionally affected more than one member of a family (1, 2, 5–14). Preliminary results of a family study of relatives of patients with RD have disclosed evidence of a link between RD and psoriasis and also between RD and ankylosing spondylitis (AS) (15).

I have encountered a family in which two sons and possibly the father had RD, and a third son, classical AS. This may be the first report of RD and AS, respectively, affecting different siblings (Fig 1). The family is also noteworthy in that definite rheumatoid arthritis has appeared in one case following RD.

Case 1

The patient, MLH, Ann Arbor VA Hospital, No 10913, a 46-year-old mechanic, was admitted in 1962 because of cervical lymphadenopathy.

From 1939 to 1954 he noted attacks of low back pain lasting several days. During this 15-year period he had morning stiffness for one hour, but no lassitude, weight loss or weakness. He was never disabled from working and sought no medical treatment for his spinal symptoms. From 1953 to 1955 he had recurrent brief attacks of pain at the lumbo-dorsal junction and the right lower anterior thoracic area. After 1955 he had no further pain, but became aware of progressive restriction of spinal motion and dorsal kyphosis. He had no history of conjunctivitis, urethral discharge, or pain in peripheral joints.

Physical examination showed a nontender, movable mass in the right cervical area with several 1–2 cm satellite nodes. He had pronounced dorsal kyphosis, loss of lumbar lordosis, and marked forward protrusion of the head (Fig 2). There was severe limitation of motion in the cervical spine, and the lumbar spine was virtually fixed. Chest expansion was 3 cm. The peripheral joints were normal. The sedimentation (Wintrobe) rate was 10 mm/hr.

Radiographs of the spine (Fig 3A) showed advanced changes of AS. Biopsy of cervical node was diagnostic for Hodgkin's disease, from which he died in 1966.

Comment. When admitted in 1962 for Hodgkin's disease, the patient presented the characteristic spinal deformity and immobility of advanced AS.

Case 2

The patient, KMH, Ann Arbor VA Hospital, No. A13182, a 46-year-old truck driver who is a brother of MLH, was admitted on December 2, 1963, because of polyarthritis of two weeks duration.

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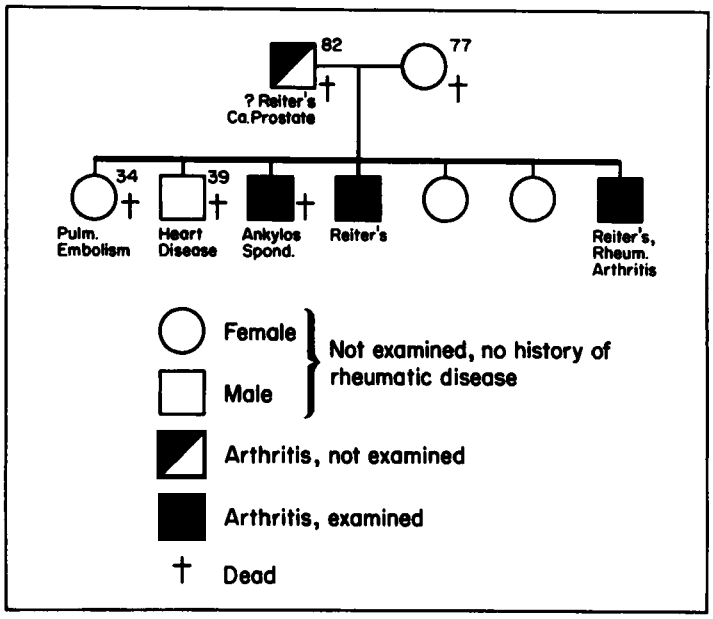


Fig 1. Pedigree of the H family.

He was well until November 15, 1963, when he experienced gradual onset of pain and swelling of the right hand, the right knee, the right foot, and the metacarpophalangeal (MCP) joints.

Physical examination showed scaling and redness of the periumbilical skin and of the glans penis. Soft swelling, increased warmth, and tenderness were noted at the following joints: right first and second MCP's, right knee, and right third and fifth metatarsophalangeals (MTP's). Oral temperature was 99.8 F. The white blood count was 13,000/cu mm, hemoglobin 13.8 g/100 ml, and sedimentation rate (Wintrobe) 65 mm/hr. The urine sediment showed numerous leukocytes per high power field. Three serum uric acid determinations were normal, the bentonite flocculation test for rheumatoid factor was negative, the antistreptolysin 0 titer was 50 Todd units, and three lupus erythematosus cell preparations were negative.

Twenty-five milliliters of slightly turbid fluid of decreased viscosity was aspirated from the right knee; this contained 15,400 white blood cells/cu mm, 83% of which were polymorphonuclears. Culture of this fluid and two subsequent aspirates from the right knee were negative for bacteria.

X-rays of the involved joints were normal except for slight sclerosis of the cortical margin of both sacroiliac joints.

On the third hospital day, a urethral discharge was detected, culture of which showed gonococcus, a diphtheroid, and hemophilus influenza. He gave a history of possible hypersensitivity to penicillin, so he was treated with tetracycline from December 4 to 14. This was followed by clearing of the urethral discharge but by no apparent change in the course of the arthritis and low grade fever.

On December 11, pain, warmth, and swelling appeared in the right 1st MTP, and soon thereafter, pain and stiffness in the mid-dorsal spine. Several days later, pain and warmth occurred at the left knee.

On December 13, the first of several asymptomatic, erythematous superficial lesions appeared on the tongue and palate (Fig 4A and B), and the lesions on the glans penis assumed a circinate, papular form.

Joint pain was partially relieved by 300 mg of phenylbutazone daily. By December 19, he was able to walk with a cane, was discharged to continue convalescence at home.

The periumbilical lesions, balanitis, and oral lesions cleared by January 15, 1964. His peripheral

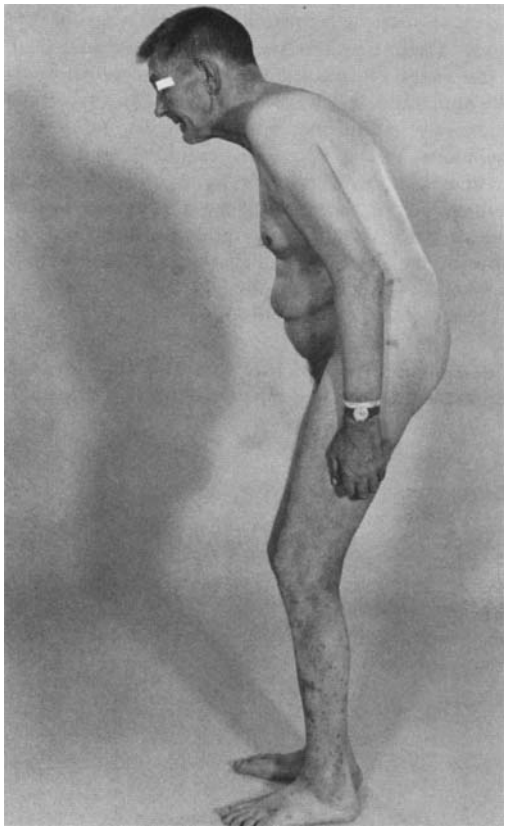


Fig 2. MLH, erect standing, showing characteristic posture of ankylosing spondylitis.

joint pain and swelling subsided slowly during the next six months, but were replaced by severe low back pain and stiffness persisting for several months. He was able to return to work 18 months after onset of his illness, free of symptoms except for mild lumbar pain and morning stiffness.

Films of the sacroiliac joints on September 21, 1964 showed minimal erosions as well as the previously noted slight juxta-articular sclerosis of the joint margins (Fig 3B).

Comment. Although he had gonococcal urethritis, the patient also developed mucocutaneous lesions regarded pathognomonic for RD (16). Arthritis of peripheral joints and the low back was unaffected by antibiotic therapy and pursued a course characteristic for RD.

Case 3

The patient, WLH, a 39-year-old clerk, brother of MLH and KMH, was examined on June 16, 1964 and related the following history. In 1937, at age 12, he developed acute pain and swelling of his feet and skin lesions near his toes. His joint pain improved after several weeks, though mild chronic pain continued in his feet for some years. In 1948 he had nonspecific urethral discharge followed shortly by iritis and a severe attack of pain and swelling in the feet. He was unable to walk for more than three months, but recovered completely except for mild chronic foot pain as previously. In 1959, acute urethritis and balanitis appeared. These lasted several weeks without any flare of joint symptoms.

When seen on June 16, 1964, the patient reported the recent onset of occasional mild arthralgia of the hands, elbows, shoulders, knees, ankles, and in one wrist, as well as chronic slight pain in the lumbar spine. Morning stiffness of one hour was present. On physical examination, he was a well-developed male who did not appear ill. No heart murmur was heard. The skin and nails were normal. The peripheral joints were normal except for bony

swelling and subluxation at the MTP joints with marked lateral deviation of all the toes. The spinal range of motion was normal except for minimal loss of cervical and lumbar flexion. Chest expansion was 6 centimeters. The serum uric acid was 5.1 mg/100 ml. The latex fixation test for the rheumatoid factor was positive at a titer of 1:5120. Radiographs showed obliteration of the sacroiliac joints bilaterally (Fig 3C) and severe valgus deformity of the metatarsals with varying degrees of subluxation at all the MTP joints; the bones of the feet were well mineralized and without characteristic rheumatoid erosions. Films of the spine were normal.

When seen again in 1967, he reported 12 months of painful swelling of his hands and wrists and increased pain in the shoulders and knees. Examination showed synovial swelling of the wrists and proximal interphalangeal and MCP joints of the hands. There was also swelling and increased heat at the knees. No subcutaneous nodules were found. The spine and feet were unchanged. The sedimentation rate (Wintrobe) was 23 mm/hr, lupus erythematous cell preparation negative and latex fixation test again positive at a titer of 1:5120. Radiographs of the hands showed bony erosions at several MCP joints and mild demineralization. Films of the spine were unchanged. Reexamination in 1970 showed identical physical findings and some progression of the MCP erosions.

Comment. In 1964 the positive test for the rheumatoid factor was discounted, and a diagnosis

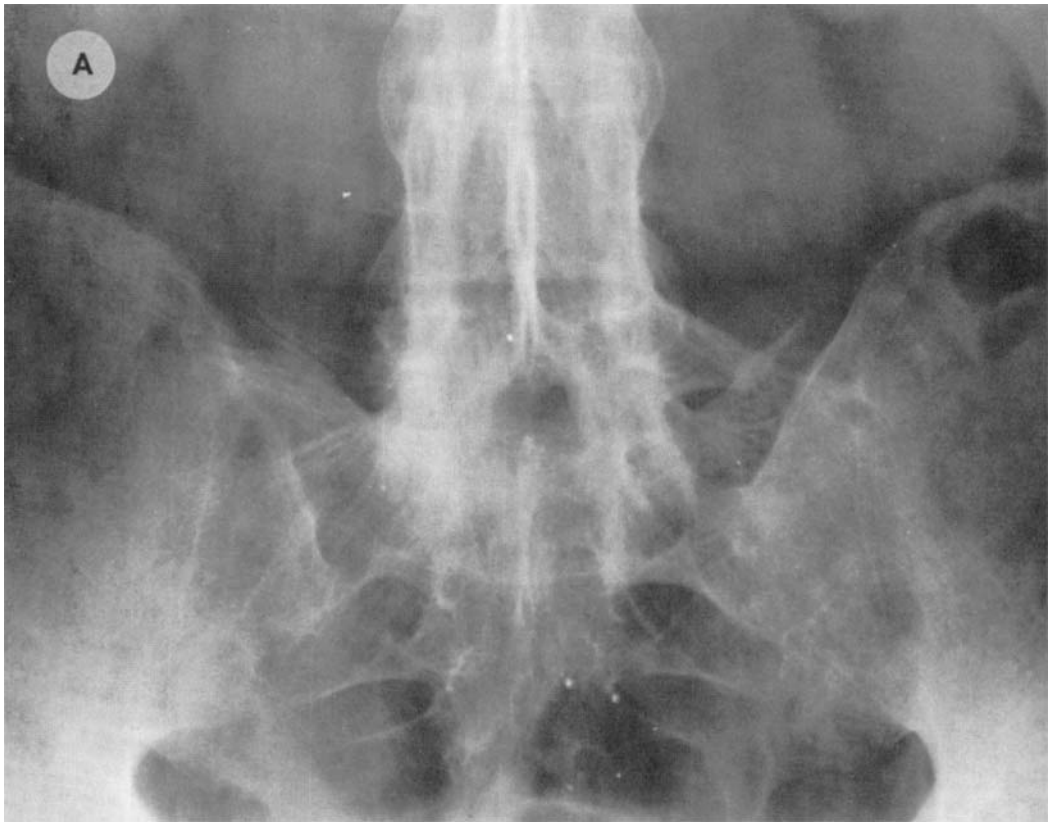
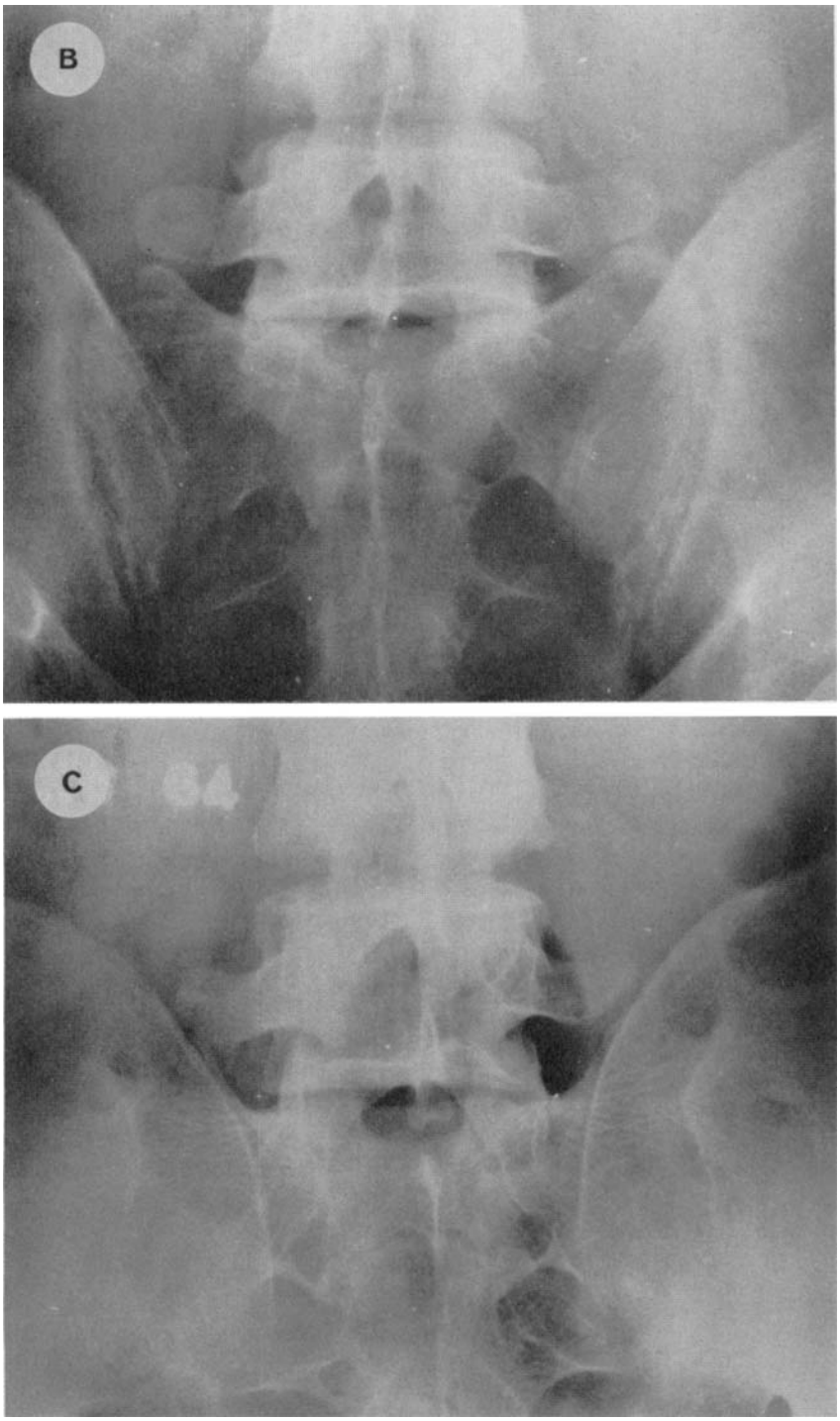


Fig 3. Radiographs of lower back: **A.** MLH, showing obliteration of the sacroiliac joints and "bamboo spine." **B.** KMH, showing minimal erosions of the sacroiliac joints and juxta-articular sclerosis. **C.** WLH, showing obliteration of the sacroiliac joints.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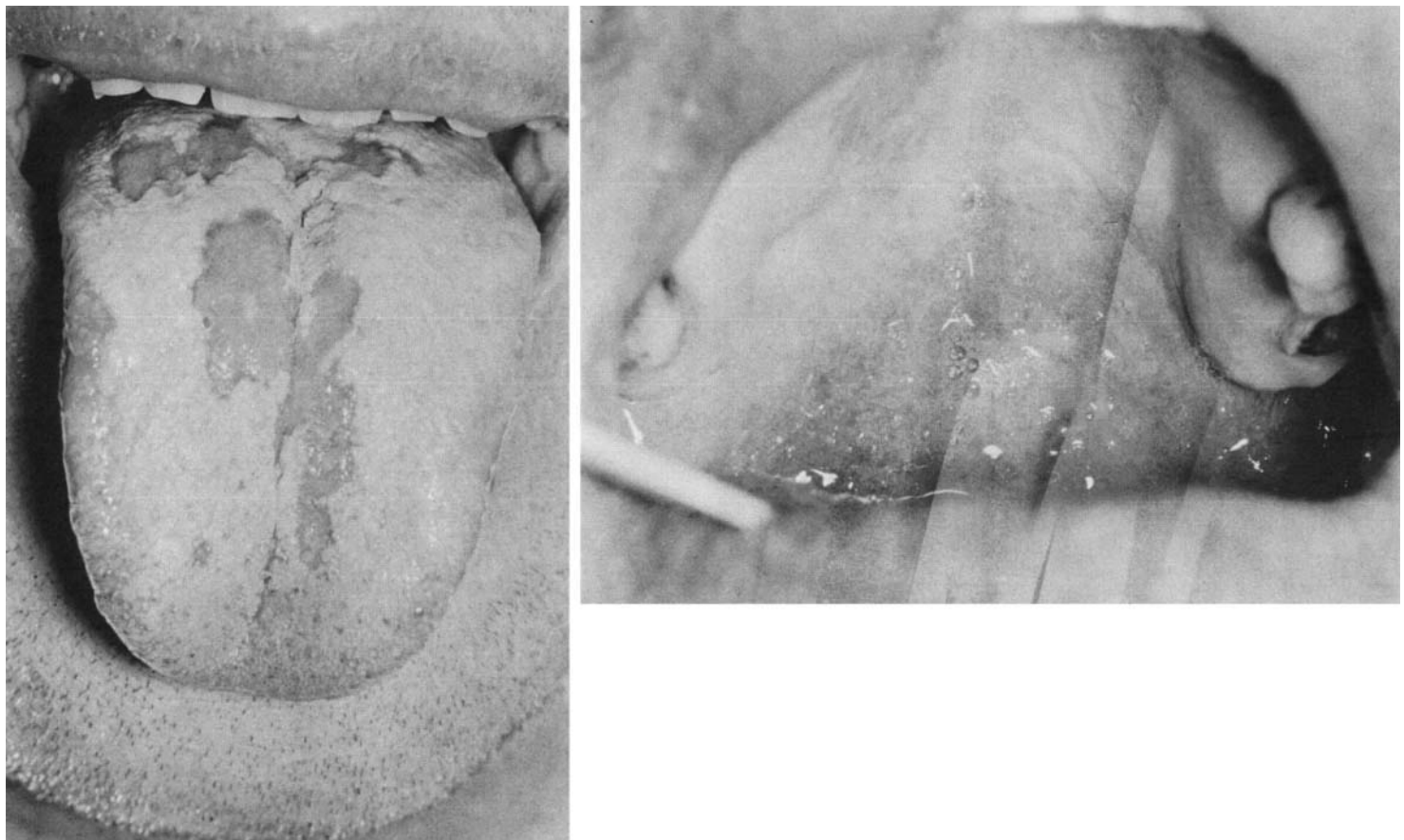

Fig 4. KMH, oral lesions: **A (left).** tongue, geographic loss of papillae, **B (right).** erythematous lesions of hard and soft palates.

of RD was made because of Reiter's triad occurring in 1948, recurrent urethritis and balanitis, and ankylosis of the sacroiliac joints. However, it became clear by 1967 that definite rheumatoid arthritis was superimposed upon the earlier findings, though not necessarily superseding the original diagnosis of RD.

Case 4

AMH, the father of the index case, was born in 1871 and died in 1959. Extensive information was available from his original Army and Veterans Bureau medical records.

In 1898, during service in Georgia, he had acute diarrhea, followed by gross hematuria, swelling and pain in the knees, and pain in the hands, shoulders, and hips. The joint symptoms subsided after several weeks, but chronic pain in the knees and shoulders remained. At an examination in 1903 for disability rating purposes, a balanitis was noted, and the shoulders were found to be limited in motion. A pension was awarded for arthritis.

Pain in the back and in numerous peripheral joints continued. In 1936, at another rating examination, the patient presented with dorsal kyphosis, a flattened lumbar lordosis, paravertebral muscle tenderness, and spinal limitation of motion. Radiographs (unfortunately not available for current review) revealed "increased density of bone in both sacroiliac joints." A diagnosis of "chronic spinal arthritis" was made.

By 1940, rheumatic complaints had largely disappeared and the patient felt relatively well. In 1955, cancer of the prostate was discovered, and a transurethral resection with bilateral orchidectomy was performed. An electrocardiogram revealed first degree heart block.

A radiograph done in 1956 showed minor irregularity and sclerosis of the left sacroiliac joint compatible with the changes of degenerative disease. Radiographs of the spine in 1956 did not reveal any other lesions suggesting ankylosing spondylitis, except for a syndesmophyte at the C5–6 interspace (Fig 5) and squaring of two lumbar vertebrae. He died in 1959 with multiple osteoblastic metastases in his ribs and pelvis. An autopsy confirmed metastatic carcinoma of the prostate. There was evidence of coronary artery disease, and fibrotic areas were noted in the endocardium and muscle of the left ventricle. Slight stenosis of the mitral valve with thickened leaflets and a single small marginal vegetation were found. No abnormality of the aortic valve or proximal aorta was noted.

Comments. Although it is presumptuous to read too much into old records, the onset of the joint disease was associated with hematuria and diarrhea, recognized manifestations of RD (4, 17), and balanitis was observed later. He had generalized spinal pain, deformity and sacroiliac roentgenographic changes noted by examiners some years after his acute polyarthritis. Curiously, both the clinical signs of spondylitis and roentgenographic evidence of sacroiliitis largely disappeared after 1940. Adequate studies of the sacroiliac joints were never obtained. Late in life, an isolated cervical lesion and suggestive squaring of lumbar vertebrae were noted.

At autopsy there was evidence of rheumatic mitral valvulitis. Atherosclerotic coronary artery disease probably accounted for the A–V block and fibrotic left ventricular changes.

DISCUSSION

Early reports of enhanced familial prevalence of AS have been supported by subsequent population studies, though the genetics involved have been controversial, with results suggesting multigenic causation (18).

Surveys for AS have been carried out on two levels: a) prevalence of overt clinical disease, b) prevalence of radiographic signs of bilateral sacroiliitis. Both lines of approach have supported familial aggregation of AS. Thus the prevalence of overt clinical disease in various populations is 0.1-0.2%, and among relatives of affected subjects, 4% (18). Similarly, bilateral sacroiliitis has been found in 3.7% of controls and 16% of first degree relatives (18). Studies have been handicapped because females should not be subjected to pelvic radiographs until past the childbearing age, and because there is no other specific laboratory test for this disease.

By the criterion of radiographic evidence, the three sons, but not the father, would be included as positive for sacroiliitis. However, only a single inadequate view of the sacroiliac joints taken late in life is available in the father's case.

It is tacitly assumed that radiographic signs of sacroiliitis are permanent if not progressive, and there is evidence that the prevalence of these signs is not affected by age (18). However, in my experience, a rare patient may show blurring of joint margins and severe juxtaarticular sclerosis early in his course, only to lose the sclerosis some years later without progression of his minor erosive changes. The minimal, stationary, erosive disease in such cases may be disclosed only by frontal oblique views or tomography. The father's disease cannot be definitely classified on the basis of findings late in his life, though the notation years earlier of sacroiliac sclerosis, back pain, and limitation of spinal motion point to spondylitis. The presence of a typical syndesmophyte at the C 5–6 interspace provides additional evidence.

Cervical involvement, with a large "skip area" of normal intervening spine has been a feature of the spondylitides of psoriasis and RD (19), sometimes regarded as variants of AS. Surveys for AS are handicapped by nosological disagreement about these variants, both of which are associated with sacroiliitis that may be indistinguishable from that of AS (19). In general, the spondylitis of RD follows a mild, abortive, and nondeforming course (20) as has prevailed in cases 2, 3, and 4 of this report. A

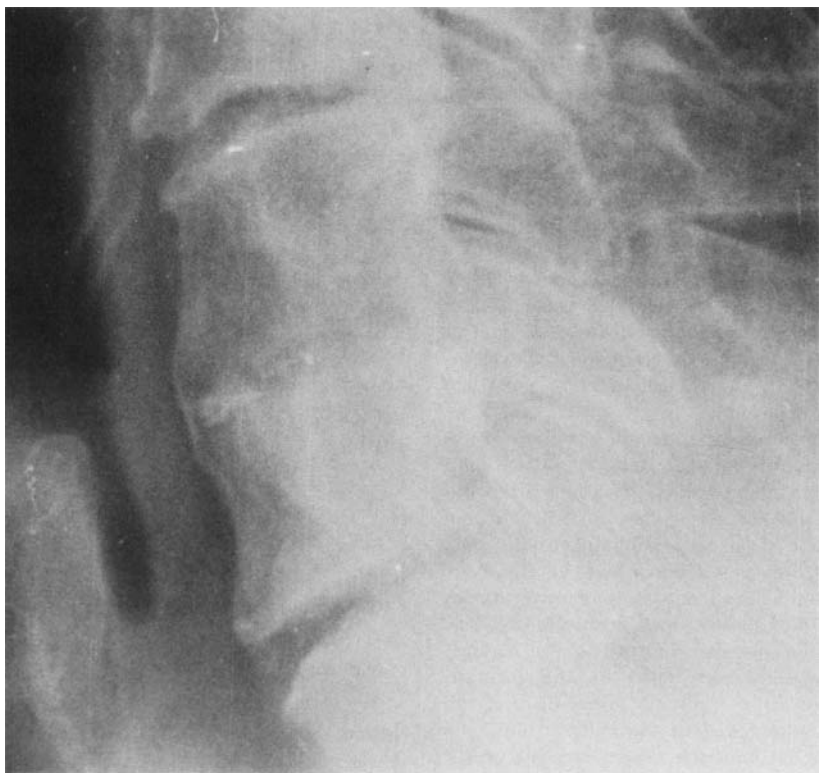

Fig 5. AMH, lateral radiograph of cervical spine, showing loss of disc space and anterior syndesmophyte bridging C5 and C6.

promising approach, that may bring some order to this confused area, is Lawrence's population study, which has confirmed familial interrelationship among AS, RD and psoriasis (15).

When the family is viewed in terms of RD, two brothers satisfy definite criteria, and there are reasons for speculating that the father also had this disease. Published reports of RD affecting more than one member of a family are summarized in Table 1. Five of these deal with RD following dysentery, often epidemic, and involving children and adults of both sexes nearly simultaneously within a household (5–7, 9–10). Similar experience was briefly noted by Paronen in his study of 344 patients with RD appearing during an epidemic of Shigella dysentery. He found a family with RD in five of seven siblings and two other families with more than one case of RD (1). Occasional shipboard epidemics of dysentery and RD have involved unrelated individuals living at close quarters (21, 22). Indeed, reports of family outbreaks of RD include a brother-in-law (8) and spouse (9) as secondary cases.

Five other families, with which this report might be grouped, had involvement of post-pubertal boys or men without a history of dysentery (8, 10–13). The onsets of RD among different members of these families were sometimes widely separated in time and place.

In contrast to the well-known interrelationship between RD and AS, follow-up

Table 1. Reiter's Disease Affecting More Than One Member of Family: Summary of Literature

	Index case					Secondary case(s)				
Author(s)	Year	Sex	Age	Diarrhea	Triad*	Relationship	Age	Diarrhea	Triad	Interval†
Koster, Jansen	1946	M	15	+	+	Brother	11	0	0	14 days
						Brother	3	0	0	15 days
Glauner	1947	M	15	+	+	Brother	10	+	+	not given
Schoeneich	1950	F	13	+	+	Brother	7	0	+	3 days
Fabregoule	1951	M	40+	+	+	Wife	40+	+	0	simultaneous
						Son	16	+	0	simultaneous
Davies, Haverty, Boatwright	1969	M	39	+	0	Son	11	+	+	3 days
						Son	7	+	+	few days
Trier	1950	M	adult	0	0	Bro-in-law	—	0	+	1 month
						Brother	37	0	0	20 months
Morton	1958	M	36	0	+	First cousin (male)	27	0	+	10 years
Gough	1962	M	adult	0	0	Son	15	0	+	not given
Mowat, Nicol	1968	M	29	0	+	Brother	21	0	+	27 months
Csonka	1969	M	31	0	+	Brother	34	0	+	9 months
		M	27	0	+	Brother	25	0	+	6 months
Good	This report	M	23	0	+	Brother	46	0	+	17 years

* Triad = polyarthritis plus at least 2 of urethritis, mucocutaneous involvement, and ocular involvement (conjunctivitis or acute iritis).

† Interval between onset index case to onset secondary case(s)

study has shown no overlap between RD and rheumatoid arthritis (20). The coexistence of RD and rheumatoid arthritis, as in Case 3 of this report, is most unusual, there being but a single published case of this combination, (23).

Close followup of this family may provide a unique opportunity to learn more about AS and its variants. I hope to obtain sacroiliac radiographs of the two living female siblings when they are past the menopause and to begin observation of the children of this sibship during their young adulthood.

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