

# REITER'S SYNDROME FOLLOWING *Shigella flexneri* 2a

## A SEQUEL TO TRAVELER'S DIARRHEA REPORT OF A CASE WITH HEPATITIS

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*Shigella flexneri* 2a was isolated from a patient with Reiter's syndrome (RS) following a family outbreak of traveler's diarrhea. Among 3 members at risk, only the patient was positive for HLA-B27. Data from 3 similar families support the hypothesis that susceptibility to RS is genetically transmitted. It is urged that every effort be made to culture and subtype *Shigella* and other enteric pathogens in RS following diarrhea. Concurrently, the patient had hepatitis, interpreted as a parallel enteric infection.

Clusters of Reiter's syndrome (RS) have occurred during land-based (1) and ship-board (2) epidemics of *Shigella* dysentery and among recruits arriving in a zone where dysentery is prevalent (3). There are several accounts of 2 or more individuals within a household who developed features of RS following diarrhea (4,5).

This is the fourth report of RS following family outbreaks of traveler's diarrhea acquired in Mexico (6-9), and the second such family with proved shigellosis. HLA typing showed the B27 antigen in the present

patient with RS, but not in the 2 accompanying family members.

Because the patient developed probable infective hepatitis during his illness, hepatic involvement in RS has also been reviewed.

### CASE REPORT

The patient (II-3, Figure 1), a 39-year-old executive of Norwegian ancestry, developed fever and persistent diarrhea 24 hours after eating a meal including raw oysters served on the first day of his arrival in Mexico in March 1973. He was accompanied by his wife (II-6) and son (III-1), age 11, who became ill at the same time with diarrhea and vomiting that lasted 24 hours without sequelae. On day 15 purulent conjunctivitis appeared, lasting 2 weeks. On day 16, the patient was seen at the University of Michigan Medical Center because of persistent diarrhea and fever up to 40°C. A stool specimen obtained at sigmoidoscopy contained *giardia lamblia*; bacterial culture was negative for pathogens. Metronidazole for 24 days, average 875 mg/d, resulted in the disappearance of the parasite, but diarrhea and fever persisted. On day 33, pain appeared in the low back, neck, and ribs, soon followed by pain and swelling of the ankles, knees, hands, and wrists. A repeat stool culture on day 33 was also negative, but a stool cultured on day 36 grew out *S. flexneri* 2a. On day 40, scleral icterus and dark urine were noted, and bilirubinuria was demonstrated. During this period the aspirin intake was 3.3 g/d and serum salicylate was 16.8 mg/dl.

On day 53, when the patient was transferred to the Ann Arbor Veterans Administration Hospital, physical examination showed a well-developed icteric man in moderate pain whose temperature was 38.5°C. A tender liver, 10 cm in total height, and circinate balanitis were noted. There was tenderness over the spine, limitation of head turning and lumbar

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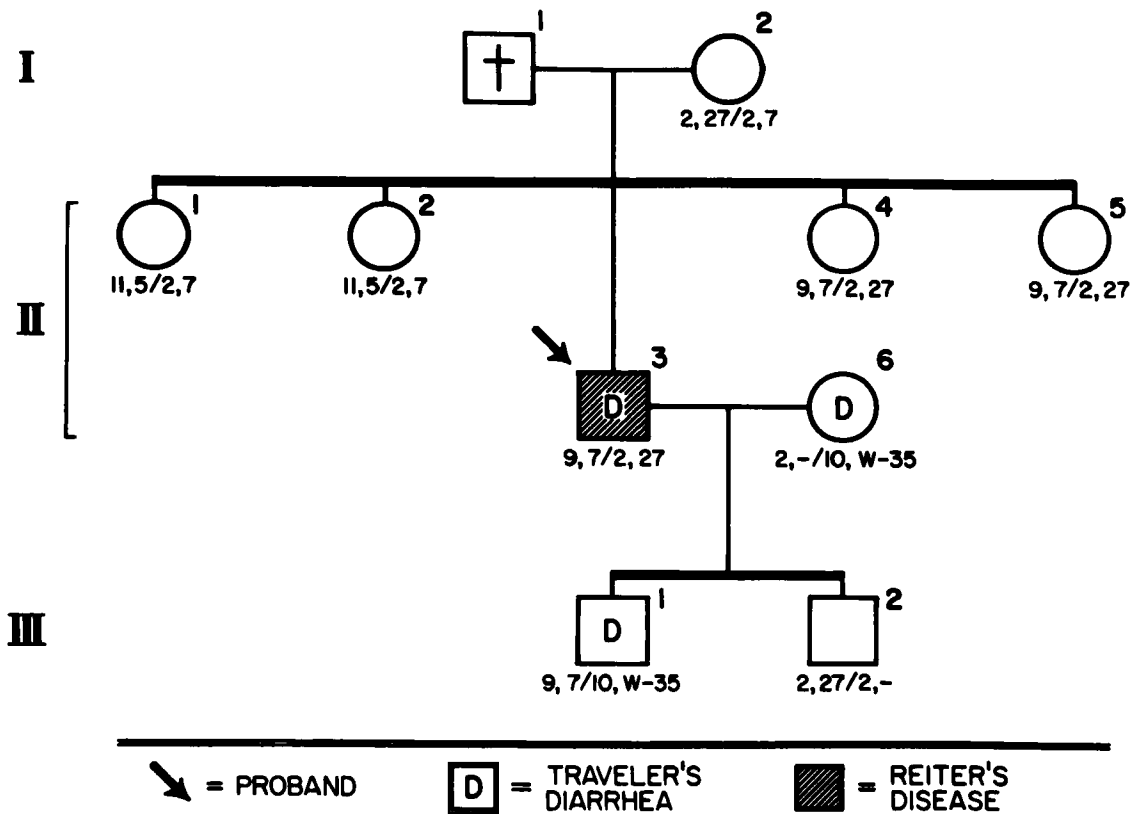


Fig 1. Family tree of a patient affected with Reiter's syndrome following an outbreak of traveler's diarrhea.

flexion, as well as swelling of the following peripheral joints: ankles, left great toe interphalangeal, right wrist, second and third metacarpophalangeals, second (finger) proximal interphalangeal, and third and fourth metatarsophalangeals. A stool culture was negative.

He was treated with 3 g of aspirin per day, occasional propoxyphene, and physical therapy. The patient refused a liver biopsy. The icterus cleared and the patient was discharged on day 70.

During the combined hospitalizations, the following serum studies were normal or negative: rheumatoid factor; antinuclear antibody; immunoelectrophoresis; febrile agglutinins; complement fixation for *Endamoeba histolytica*, *Salmonella*, and *Trichinella spiralis*; hepatitis-associated antigen, HB<sub>e</sub>Ag; and antibodies of HB<sub>e</sub>Ag. A blood smear for malaria parasites was negative. A muscle biopsy, electromyogram, electrocardiogram, and X rays of the spine and peripheral joints were normal. Synovial fluid aspirated from a knee showed a poor mucin clot, leukocyte count of 32,000/mm<sup>3</sup>; differential count of 80% polymorphonuclear cells and 20% mononuclear cells; negative culture for microorganisms; total protein of 4.8 g/dl; and total hemolytic complement of 20 units. Concurrently serum run total hemolytic complement and protein were 93 units (normal: 104-188) and 5.5 g/dl respectively. Abnormal serum hepatic studies reached peak values as follows: glutamic oxalacetic transaminase (normal: 5-25 units) 1430, day 53; glutamic pyruvic transaminase (nor-

mal: 5-25 units) 1840, day 54; alkaline phosphatase (King-Armstrong units, normal: 4-12) 20.6, day 19; total bilirubin (mg/dl, normal: up to 1.2) 9.3, day 55; and prothrombin time (control: 10.5), 19.8 seconds, day 49.

Outpatient drug therapy was limited to intermittent phenylbutazone. The arthritis remained disabling for 6 months. At 18 months he was free of symptoms; physical examination of the peripheral joints and spine as well as the serum oxalacetic transaminase, bilirubin, and prothrombin time were normal.

At this time the patient's mother (I-2) and siblings (II-1, 2, 4, and 5) were seen and tissue-typed. Though all had recurrent low back pain, none had physical signs of spondylitis. None had had peripheral arthritis or heel pain. X-ray films of the spine were not available.

## DISCUSSION

Four reports of RS following outbreaks of diarrhea among North American tourist families visiting Mexico are summarized in Table 1. RS never occurred in both parents. Of 10 children with diarrhea, 5 developed RS. The data from these 4 families support the hypothesis that susceptibility to RS is genetically transmitted. Children appear to develop this post-

Table 1. *Reiter's Syndrome Following Family Outbreaks of Traveler's Diarrhea*

Reference No.	No. Traveling	Family Members with Diarrhea	Family Members with RS	Signs of RS*	Stool Culture
6.	6	Father, 2 sons	Father Son Son	U, A, back pain C, A, U, iritis C, U, A	Neg <i>Shigella flexneri</i> 2 Neg
7.	5	Parents, 3 children	Mother Child Child	Not specified Not specified Not specified	Neg† Neg† Neg†
9.	6	Parents, 4 children	Son	Pyuria, C, A, mouth lesions	No pathogens
Present report	3	Parents, son	Father	C, A, balanitis, back pain	<i>Shigella flexneri</i> 2a
Total	20	17 (7 parents, 10 children)	8 (3 parents, 5 children)		

\* U: urethritis; A: arthritis; C: conjunctivitis.

† Personal communication (8).

dysenteric, probably postshigellosis form of RS as readily as do their parents.

Among the 3 members of the present family who traveled together, the HLA-B27 antigen was present only in the patient with RS; thus its occurrence was in keeping with the strong association previously reported between B27 and RS, whether postvenereal (10) or postshigella (11).

Although stool cultures were obtained only from the RS patient, it is presumed that the acute diarrheal illnesses appearing simultaneously in all 3 family members shared the same etiology. Volunteers infected with a virulent strain of *Shigella flexneri* 2a have shown a spectrum of disease severity, including mild, brief illness (12).

RS, first reported in Mexico as late as 1961 (13), remains an uncommon disease in native Mexicans in spite of prevalent shigellosis (14). A low population frequency of HLA-B27 undoubtedly accounts in part for the apparent rarity of RS in Mexico. In Los Angeles a Mexican-American population has a B27 frequency of 4%, compared to a Caucasian frequency of 10% (15).

Although enteropathogenic *Escherichia coli* account for a large proportion of traveler's diarrhea in Central America, smoldering prolonged outbreaks of shigellosis, often yielding multiple other pathogens serially or simultaneously, are also characteristic of the area (16). *Shigella flexneri* 2a is also endemic in North

America, where it is second only to *Shigella sonnei* in the etiology of bacterial dysentery. The true prevalence of shigellosis is probably understated because symptoms may not suggest enteritis, rectal swabs are often omitted when stool samples are unavailable, and bacterial isolation techniques are imperfect (16). Family outbreaks not only can supply valuable genetic data and elucidate the spectrum of RS in children and adults, but also may increase the chances of recovering the instigating *Shigella* organism. At least with *Shigella sonnei*, the family unit can maintain the bacteria for weeks as various members and contacts develop clinical disease at intervals (17).

Although 28 years have passed since Paronen's monumental study of an epidemic of RS associated with *Shigella flexneri* dysentery (1), the present authors could find no report completely serotyping *Shigella* recovered from a patient with RS. Organisms recovered in the field or aboard ship obviously cannot be fully characterized, but whenever feasible, cultures should be sent to a sophisticated bacteriologic laboratory to define purported rheumatogenic strains of *Shigella*. At best, stool isolates are difficult to recover, because arthritis following shigellosis appears to have a latent period of a minimum of 11 days (2), during which the organism usually disappears from the stool. *Shigella flexneri* (type 2, but apparently not subtyped) was recovered in a family outbreak of RS, only because a parent on his own

initiative sent in a stool from his child during an episode of diarrhea, 10 days before onset of arthritis (6). The present case demonstrates the value of multiple stool cultures as late as a month after the onset of diarrhea.

Reactive arthritis or RS is said to follow infection by *Shigella dysenteriae* as well as *Shigella flexneri* species (18), but the few reports documented by cultures incriminate *Shigella flexneri* exclusively (1,6,19) or predominately (20). Because antibodies develop late and irregularly, serologic methods have little place in the diagnosis of acute bacillary dysentery. Nevertheless, serial testing for specific antibodies could facilitate diagnosis in RS, especially if forthcoming reports can establish that rheumatogenic *Shigellae* are confined to a particular species or subtype. Reactive arthritis, occasionally including other features of RS, has followed *Salmonella* (21) and *Yersinia enterocolitica* (22) infections, so that interest in enteric pathogens in RS cannot be limited to *Shigella*.

At the peak of his illness the current patient developed jaundice, hepatomegaly, and elevated liver enzymes. Review of liver disease associated with RS discloses hepatitis (jaundice) (1,23-26), salicylate hepatotoxicity (27), and amyloidosis (28-30). In the present patient, if one assumes simultaneous infections by a hepatitis virus and *Shigella flexneri*, the incubation period for the hepatitis would be 40 days, within the range for type A. Because hepatitis type A shares the epidemiologic pattern of enteric diseases, it is not surprising that an acute icteric illness occasionally may overlap postdysenteric RS. The fact that clinical hepatitis has been reported with RS only in cases presenting with diarrhea (1,23-26) supports this interpretation. In three epidemics of diarrhea associated with multiple cases of RS, hepatitis occurred in 3 of 322 (1), 2 of 310 (24), and 1 of 60 (23) patients with RS.

Finally, there are three case reports of minor hepatic histopathologic changes in RS, all in patients without history of diarrhea or icterus (27,31,32). Convincing evidence for aspirin hepatotoxicity was presented in the most recent of these reports (27), and salicylate toxicity could account for postmortem (31) and biopsy (32) findings in the remaining two. A study from Europe (33) demonstrated that serum alkaline phosphatase and the ratio of hepatic to bone alkaline phosphatase were higher in RS than in other inflammatory and degenerative articular diseases; the values in RS only slightly exceeded those in rheumatoid arthritis, and information about aspirin intake among the patients with RS was not included. Pending confirmation of a purported predilection for salicylate hepatotoxicity with

RS, liver enzymes should be monitored in patients receiving aspirin. In the present patient the signs of hepatitis resolved promptly, even while aspirin was continued.

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EDITOR'S NOTE: "Physical Features of Patients with Ankylosing Spondylitis" by Nourollah Parhami, which appeared on pp 1351-1352 of the November-December 1976 issue as a "Brief Communication," should have been published as a letter to the editor. The editors intend to publish all acceptable articles of similar length and import as letters.