A Brief History of Stoll-Brodie-Fiessinger-Leroy Syndrome (Reiter's Syndrome) and Reactive Arthritis with a Translation of Reiter's Original 1916 Article into English

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Abstract: While not the only form of reactive arthrits, Reiter's syndrome is the eponym given to a form of reactive arthritis associated with with the classice triad of conjuntivitis, urethritis, and inflammatory arthritis. Although in popular use, the term Reiter's syndrome has become clouded, not only because of the variable pathophysiology of reactive arthritis, but also because of Reiter's own past as an early member of the Nazi party and his prominent role in the German health system during the Thrid Reich, including involvement with involuntary medical procedures and experiments in Nazi concentration camps. As is often the case, the eponym attached to the syndrome does not honor the original describers of the disease, although doubtless Reiter's account remains the classic description. We offer a brief historical review of the disease, and complete it with a translation into English of Reiter's original publication.

Keywords: Reiter's syndrome, Reactive arthritis.

INTRODUCTION

There is no consensus about the designation of this entity. In the English literature, it is generally called Reiter's disease, and in North America and in Latin America, it is called Reiter's syndrome. In their book published in 1976, Moll and Wright used the term "Reiter's disease" in accordance with the designation of the Joint Committee on the Nomenclature of Diseases of the Royal College of Physicians of London [1], but in recognition of more recent historical research, we suggest the designation "Syndrome of Stoll, Brodie, Fiessinger and LeRoy, " could justifiably be given to it as these were the first to describe this disease, and not Hans Reiter. It could be simply referring to it as "reactive arthritis, " although this term is generally used in a broader fashion than the classic triad of arthritis, conjuntivitis and urethritis described by Reiter.

HISTORY

Urethritis is an ancient symptom. The Bible alludes to gonorrhea without arthritis or conjunctivitis in Leviticus, chapter 15. In verses 2-4, the injunction is: "Speak unto the children of Israel, and say unto them, when any man hath a running issue out of his flesh, because of his issue he is unclean. And this shall be his uncleanness in his issue: whether his flesh run with his issue, or his flesh be stopped from his issue, it is his uncleanness. Every bed, whereon he lieth that hath the issue, is unclean: and every thing, whereon he sitteth, shall be unclean".

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Hippocrates described young men not suffering from gout until after having had sexual contact, although it is not stated that the arthritis was due to venereal disease. It has been suggested that this constitutes the first description of Reiter's syndrome, although it is difficult to know if this is true or whether the disease was of venereal origin [2, 3]. The majority of descriptions of the initial disease symptoms are associated with enteric infections. D.J. Allison [4], in an interesting letter published in Lancet in 1980 speculated that Christopher Columbus was the first European patient to develop reactive arthritis. There is some evidence that after arriving in the New World, Christopher Columbus became "lame", possibly due to an infection such as shigella flexneri common in the tropics during this time. From his description of his voyages on the high seas between Puerto Rico and Santa Domingo in September of 1494, Columbus presented with a picture of fever, confusion, and severe arthritis of the lower extremities. In 1498, he had a relapse with fevers and acute articular symptoms. Six weeks thereafter, he developed articular inflammation and eye pain: "I have never had such affliction of my eyes with hemorrhage and pain as in this time" [4]. In 1504, Columbus was "paralyzed and bedridden" because of "gout."

The term "gout" was used indiscriminately to refer to inflammatory arthritis in the 16th century [4]. Just as Columbus described this severe form of arthritis, so too did Thomas of Sydenham, who described gout, also describe a form of reactive arthritis [5]. The association between diarrhea and arthritis may also be attributed to Sydenham; it was Francois X. Swediaur who first established the association betreen arthritis and urethritis in 1784 [6].

Christopher Columbus was incapacitated by arthritis and died in 1506. Over four hundred years later, Noer [7]

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described Reiter's syndrome with reactive arthritis occurring on a naval vessel in the Mediterranean in 9 sailors among 602 individuals who suffered from shigella. Solitar and colleagues [8] in 1988 described an epidemic of Reiter's syndrome on the high seas also caused by shigella in Chinese immigrants bound for America on the voyage of the Golden Venture.

Worthy of mention is the description of a patient with arthritis of the knees associated with urethritis in 1507 quoted by John Sharp [9] which appeared in the chapter on Reiter's syndrome in the eighth edition of the textbook *Arthritis and Alike Conditions*. Sharp[9] also cites Culp and Martiniere in relateing a case of secondary arthritis and urethritis from Pierre Van Forest in 1507, and John Hunter's 1786 description of a patient with articular symptoms and episodic urethral discharge. 154 years later, Sir Benjamin Brodie [10] (1783-1863) in his famous book, "Pathological and Surgical Observations on Diseases of the Joints, " describes this syndrome in five patients who had the triad of urethritis, arthritis, and conjunctivitis, a classic description of this syndrome. Table **1** contains a review of some of the important milestones in the description of reactive arthritis.

Table 1. Landmarks in the History of Reactive Arthritis

Hippocrates ca 460 BC	Arthritis following sexual contact
Christopher Columbus 1494	Arthritis, ocular inflammation affecting himself
Pierre van Forest 1507	Arthritis associated with urethritis
Thomas Sydenham ca.1686	Arthritis associated with diarrhea
M Stoll 1776	Arthritis following dysentery
Benjamin Brodie 1818	Classic description of the classic triad of reactive arthritis, conjunctivitis and urethritis
Emile Vidal 1893	Arthritis, keratoderma blenorrhagica following gonococcal infection
Noel Fiessinger, Edgar Leroy 1916	4 patients with conjunctivitis, urethritis and arthritis
Hans Reiter 1916	Arthritis, conjunctivitis and urethritis following dysentery
Ilmari Paronen 1948	344 cases of arthritis following dysentery due to *Shigella* in Finland during World War II.
V.Wright, William Reed 1964	Clearly differentiate reactive arthritis from gonococcal arthritis
P.Ahoven, K. Sievers, K. Aho 1969	Popularize the concept of "reactive arthritis"
Derrick Brewerton *et al.* 1973	Association of reactive arthritis with HLA-B27

On August 21, 1916, a lieutenant of the Prussian Army presented with a clinical picture of body aches and diarrhea [11]. Eight days later, the patient had urethritis and conjunctivitis and the following day, developed polyarthralgias, eventually involving the knees, ankles, elbows, wrists, and interphalangeal joints. The disease followed a waxing and waning but persistent course, with marked debility due to the arthritis and occular symptoms as described by Hans Reiter [11]. This association of arthritis, conjunctivitis, and non-gonococcal urethritis was published by Reiter in the German Medical Weekly who attributed the disease to a spirochete infection [11]. A full translation of Reiter's account performed by one of the present authors, Eric Matteson, accompanies this article.

In the same year, 1916, a pair of French investigators, Noel Fiessinger and Edgar LeRoy [12], described an outbreak affecting four patients with arthritis, urethritis, and conjunctivitis in the bulletin of the Medical Society of Paris. This report appeared eight days prior to the report of Reiter. Fiessinger and LeRoy called it the "conjunctival, urethral, synovial syndrome." The French refer to it as Fiessinger-LeRoy, or Fiessinger-LeRoy-Reiter syndrome. The descriptions of Reiter and of Fiessinger and LeRoy established the relationship between this syndrome and the diarrheal illness. Cooper [13] introduced the concept of a relationship between infection and arthritis, particularly of the joints of the lower extremities in 1824. The description of Cooper [13] virtually passed unnoticed and only began to be explained with the identification of gonococcus by Neiser in 1879 [3]. Twenty years after this discovery, Launois [14] in 1899, distinguished between septic and aseptic arthritis, observing cutaneous lesions on the plantar surface of the feet, which have subsequently been described as keratoderma blenorrhagica. The distinction between septic and aseptic (reactive) arthritis could be further supported after the introduction of antibiotics, which are curative for septic arthritis while unhelpful for reactive arthritis [1, 2].

The first description of reactive arthritis in the United States was not until 1942 by Bauer and Engelman [15]. In 1948, Paronen [16] in Finland published an article on 344 patients with Reiter's syndrome following dysentery occurring during World War II on the Isthmus of Karelia. These soldiers were among 150, 000 patients who suffered from shigella flexneri at that time. Bauer and Engleman [15] in 1942 and Paronen [16] called the association of mono- or polyarthritis and non-gonococcal urethritis "Reiter's disease", believing it to have an infectious cause, although they were unable to demonstrate an infectious agent.

The first description of an association between arthritis, conjunctivitis, and urethritis following a diarrheic illness was likely that of Stoll in 1776 [17], although the authors using the term Reiter's disease were unlikely familiar with Allison's [4] opinion regarding the case of Christopher Columbus. As noted above for many years, it was impossible to distinguish between gonococcal arthritis and Reiter's syndrome until the identification of gonococcus by Albert Neisser in 1879 [6]. In the paper by Benedek and Rodnan [6] on the history of rheumatology, these authors attribute the description of arthritis and urethritis to Francois Bresdiaur, although Pierre and Van Forest and Martiniere had also already described it. Emile Vidal [18] in 1893 reported a patient with arthritis possibly due to gonococcus who also had hyperkeratotic skin lesions. Later, these lesions were termed keratoderma blenorrhagica by Chauffard and Froin. In 1934, they were recognized by Wiedman as one of the classic manifestations of Reiter's syndrome [18], although they were first described by Launois [14].

Harkness, in 1947, emphasized that Reiter's syndrome could follow an intestinal or venereal infection. The syndrome came to be known as "Reiter's syndrome" with the studies of Harkness [19] in 1950, Csonka [20, 21] in

1958 and 1950, Ford [22, 23] in 1953 and 1959, Murray *et al.* [24] in 1958, Oates and Young [25] in 1959, and Hancock [26] in 1960. Previous publications like those of Myers and Gwynn [77] in 1935, Keefer and Spink [28] in 1937, and Lees [29] in 1932 as gonococcal arthritis may also have represented cases of Reiter's syndrome, although this pathogenesis was unclear until Wright and Reed [30] studied 214 patients with arthritis associated with venereal disease and separated gonococcal arthritis from Reiter's disease, thereby defining these two pathogeneses. They also described patients with psoriatic arthritis and for the first time clearly distinguished between seronegative variants of "rheumatoid arthritis." This article went a long way towards recognition of seronegative spondyloarthropathies [30] as distinct diseases.

In the decade of the 1960s, the presence of a positive rheumatoid factor began to be utilized in classifying disease, particularly early on in Scandinavian studies such as those of Berglof [31] in 1963, Vartiainen and Hurri [32] in 1964, who reported on reactive arthritis in patients suffering from salmonella infections whose joint disease was not septic. Warren [33] developed a concept that arthritis could be the consequence of a sympathetic serosal reaction to an intestinal infection. With this background, Ahvonen *et al.* [39] in 1969 espoused the concept of reactive arthritis in studies of patients suffering from arthritis who underwent arthrocentesis with findings of sterile synovial fluid, although they had previously suffered bacterial intestinal infections. Aho, Ahvonen, Lassus, *et al.* in the book by Dumonde in 1976 [35] popularized the concept of reactive arthritis.

The term "reactive arthritis" has had considerable impact, and many authors use it synonymously with Reiter's syndrome. Reiter's syndrome is considered a reactive arthritis. However, at the same time, not all forms of reactive arthritis should be regarded as Reiter's syndrome, which is more narrowly defined by the triad of arthritis, conjunctivitis, and urethritis [1, 2, 18]. There are numerous bacteria associated with reactive arthritis including shigella flexneri, salmonella minor (thyphinurium, enterocolitica, agona), chlamydia trachomatis, urea plasma urealyticum, yersinia enterocolitica, yersinia pseudotuberculosis, and Campylobacter jejuni [1, 2, 18].

ETIOLOGY AND PATHOGENESIS

In establishing the criteria for reactive arthritis, characterizing patients who present with a picture of peripheral arthritis, urethritis, and conjunctivitis following a gastrointestinal or genitourinary infection [34, 35], an important next step was to establish how vertebral and sacroiliac involvement occurred. Early speculation about this included that of Baston [36] in 1942 who posited that infection of the vertebrae or sacroiliac joints occurred through venous drainage. Grainger [37] in 1959 speculated that sacroiliac and vertebral involvement occurred through venous drainage of the prostate, and Oates and Young hypothesized that this involvement occurred because through drainage of the seminal vesicles and prostate. These theories were abundant in that decade supported by observations of Abel [38] in 1950, Lodge in 1956 of sacroiliitis in paraplegics and by the hypothesis of Mason *et al.* [39] in 1958 [40] who reported on the occurrence of sacroiliitis in patients with chronic prostatitis. To corroborate these theories, Wright *et al.* [41] studied 38 paraplegic patients from a musculoskeletal standpoint and observed changes of osteoporosis due to immobilization without sacroiliitis in 12, now supporting the hypotheses of Baston [36] and Mason [39] and others.

Following these observations, intense efforts were made to isolate a microorganism in the joints of patients with Reiter's syndrome and reactive arthritis. Among early investigators undertaking this effort were Ford and Rasmussen [42] in 1964, Bartholomew [43] in 1965, Ledy *et al.* [44] in 1966, and Decker and Ward [45] in 1966. None of these authors could demonstrate an infectious process at the level of the joint. Finally, the decade of the 1960s and then in the 1970s saw the establishment of a genetic predisposition toward the diseases with the discovery of the presence of HLA-B27 in most patients with Reiter's syndrome by Brewerton *et al.* [46] in 1973, Morris *et al.* [47] in 1974, Brewerton [48] in 1974, and McCluskey [49] and colleagues in 1974.

EXTRAARTICULAR DISEASE IN REITER'S SYNROME

Extraarticular disease is common in Reiter's syndrome, affecting numerous organs in a variety of ways. Some of the important systemic features of Reiters' syndrome are summarized in the following:

Amyloidosis

Amyloidosis was described as a rare complication of Reiter's syndrome by Bleehen [50] in 1966.

Arthritis

The arthritis of reactive arthritis is generally acute and occasionally involves periarticular structures. Synovitis particularly of the knees is well described, for example, by Reiter [10], Weese and McCarty [51] in 1969, Garner and Mowat [52] in 1972, and Moll [1] in 1973. It generally involves the knees and ankles and is almost always assymetric. A spondyloarthropathy mimicking ankylosing spondylitis was described by Ford [22] in 1953.

Cardiac

Auricular ventricular block was described by Fering [53] in 1945, aortitis by Trier [54] in 1950, and pericarditis by Csonka and Oates [55] in 1957. Csonka *et al.* [56] had expanded on the description of cardiac manifestations in their 1961 article, and carditis and aortic insufficiency were described by Cliff [57] in 1971. Prolongation of the PR interval was reported by Feiring [54] in 1945, Hall and Finegold [58] in 1953, Csonka *et al.* [56] in 1961, Weinberger and colleagues [59] in 1962. Q- and T-wave abnormalities were also described by Feiring [53] in 1945, Hall and Finegold [58] in 1953, and by Weinberger *et al.* [59] in 1962.

Central Nervous System

A clear relationship between Reiter's syndrome and central nervous system involvement has not been definitively established. Csonka [60] in 1958 and Oates and Hancock [61] described central nervous system perturbations which they attributed to Reiter's syndrome including peripheral neuropathy, transitory hemiplegia, meningeal encephalitis, and cognitive impairment.

Eye Involvement

Conjunctivitis is part of the classic triad of Reiter's syndrome. It is characterized by a generally sterile discharge and can accompany diarrhea, as well defined by Popert *et al.* [62] in 1964. In addition, eye involvement can include episcleritis, keratitis, corneal ulceration, and uveitis. Uveitis can present in between 10 and 30 percent of patients according to Ford [22] in patients with chronic reactive arthritis. Ocular hemorrhage and hypopyon were described by Batchelor [63] in 1946, Paronen [16] in 1948, optical neuritis in 1947 by Zewi [64] and by Oates and Hancock [61] in 1959, and retrobulbar neuritis was described by Lindsay-Rea [65] in 1947.

Gastrointestinal Tract

Severe hemorrhage with ulceration as a rare manifestation of Reiter's syndrome was described by Boyle and Buchanan [66] in 1971.

Oral Mucosa

Confluent erythema of the soft palette, uvula, and tonsils with purpuric lesions were described by Montgomery *et al.* [67] in 1959 and Hancock [67] in 1960.

Pulmonary

Pulmonary infiltrates were described by Thiers and Pinet [69] in 1950. Lafon *et al.* [70] also described pulmonary infiltrates associated with reactive arthritis in 1955.

Skin

Cutaneous lesions with the appearance of psoriasis were described by Lever and Crawford [71] in 1944 in relationship to reactive arthritis. Keratoderma blenorrhagica is described above. Purpuric lesions occurring with reactive arthritis were described by Makari [72] and thrombophlebitis by Csonka [73] in 1966.

Urethritis

Urethritis has been well described as a component of Reiter's syndrome associated with mucoid urethral discharge by Reiter in 1916 [11], Colby [74] in 1944, Twiss and Douglas [75] in 1946, and Ford [22] in 1953. As described by Reiter and others, the urethral discharge may occassionally be purulent.

WHY CHANGE THE NAME OF REITER'S SYNDROME?

Reiter's name has been universally accepted as the eponym for the syndrome of reactive arthritis associated with arthritis, urethritis, and conjunctivitis. In 2000, Daniel J. Wallace and Michael Weisman, of Cedar Sinai Medical Center in Los Angeles undertook a review of Hans Reiter's background [76, 77, 78].

During the Nazi era, physicians were responsible for over 200, 000 cases of involuntary sterilization and 170, 000 cases of euthanasia. Millions of prisoners died in the concentration camps under the supervision of physicians, where at least 60 different medical investigations were undertaken. The documents relating to charges against Reiter and their investigation during the Nuremberg Trials between 1945 and 1947 were obtained and published by Drs. Wallace and Weisman. The source material from the National Archives in Washington consists especially of Archives M1019 and M1020. These documents were translated from German and published by Wallace and Weisman in 2004 [76, 77, 78]. Among the charges leveled at Reiter are active participation in experiments related to involuntary sterilization, euthanasia, and experimental vaccination against typhus resulting in hundreds of deaths in the Buchenwald Concentration Camp. They also published other data from these documents regarding Reiter's Nazi Party affiliation and on other criminal investigation charges.

Hans Conrad Julius Reiter was born on February 25, 1881 in Leipzig, the son of a German businessman. Figure **1** is a photograph of Reiter, showing him sporting a Hitleresque moustache. He studied medicine in Leipzig, Breslau, and Tübingen. He passed the state medical examination in Tübingen in 1905 and graduated with a medical degree in 1906. Thereafter, he traveled to Paris, where he stayed for about seven months and worked at the Institute Pasteur. He later traveled to London and worked at St. Mary's Hospital for six weeks under the direction of Professor Almrot Wright. Threafter, he went to Berlin and worked in the Tuberculosis Clinic between 1910 and 1911. Later in Berlin, he worked in a private laboratory and in the Institute for Hygiene of the University of Berlin, and between 1912 and 1914, was an instructor at the University of Königsberg [78].

During the first World War, Reiter worked in the field and with Huebner, described the "spirochete forani". In 1918, he received the title of professor. Between 1919 and 1923, he was head of the Institute of Hygiene at the University of Rostock [78]. Between 1923 and 1925, Reiter worked at the Kaiser Wilhelm Institute for Experimental Therapies under the direction of Professor Von Wasserman and continued to work on spirochete infection. Between 1923 and 1933, he was director of the Public Health Department in Mecklenburg [78].

Reiter joined the Nazi Party on August 31, 1931. According to the interrogation occurring on November 22, 1946, his Reich card index is 621,885 of Rabensteinfeld, District of Mecklenburg/Lübeck. He worked as minister of hygiene and the interior, under Dr. Guett until 1939 and then under Dr. Conti after 1939. These physicians were members of Himler's SS. Reiter was director of the Ministry

of Hygiene, which had the support of the National Socialist Workers Party (NSdAP). He was called upon by Hitler to take temporary charge of the Reich Health ministry (Reichgesundheisant) on July 26, 1939. He directed this office and published a book entitled, "The Reich Health Office, 1933 to 1939: Six Years of National Socialist Leadership." He remained in this office until 1941, when he turned 60 years of age [70].

Fig. (1). Hans Reiter (1881-1969).

In 1935 and 1936, he was a member of the Academy of Sciences of Kaiser Leopold in Halle. Reiter wrote more than 140 medical articles and books. One of them had the title, "Vaccination Therapy and Vaccine Diagnosis." [78] Because of his knowledge in the field of bacteriology, worked on a vaccine against typhoid, resulting in the death of hundreds of individuals used in experiments [78]. In 1945, he was captured by the Russians and thereafter, intensely interrogated at Nuremberg. He died in 1969 [78].

In the final years of his life, Reiter faded into obscurity. In particular with the work of Wallace and Weisman, the dark side of this brilliant investigator has come to increased attention. These authors have proposed that Reiter's name should no longer be used to describe the disease now named for him and should only be used in a historical context [78].

CRITERIA FOR REITER'S SYNDROME AND REACTIVE ARTHRITIS

There are at least seven proposals for criteria of Reiter's syndrome and three more for reactive arthritis. The first criteria were proposed by Kellegren, Jeffrey, and Ball [79], in 1963. These have subsequently been expanded on by several authors, including Amor [80] in 1976, Feldman [81] in 1977, Wilkens and colleagues [82] in 1979, Calin [83] in 1979, Good [84] in 1979, and Fan and Yu [85] in 1997.

The comprehensive criteria of Kellegren, Jeffrey and Ball [18, 79] for Reiter's syndrome may summarize the essential components of the condition. These include presence of inflammatory, assymetric arthritis predominantly of lower extremity joints; elevated sedimentation rate and other analogous parameters; presence (usually preceding arthritis) of urethritis and other afflictions of the genitourinary tract (prostatitis, cystitis, etc.) under the exclusion of bacterial infection (in particular, gonococcus); presence of skin lesions (keratoderma) or lesions of the mucosa (balanitis and more rarely stomatitis and glossitis); diarrhea (occurring prior to the arthritis); ocular lesions (conjunctivitis and iritis); and lack of response of the manifestations to treatment with sulfonamides and penicillin. Exclusion criteria include presence of another rheumatic disease or infectious arthritis, well-defined from an etiologic point of view; presence of a chronologic relationship or interdependence between a symptom and other infections; Bouillard's disease; other rheumatic disease such as rheumatoid arthritis, polyarteritis nodosa, ankylosing spondylitis or systemic lupus erythematosus in evolution; positive rheumatoid factor; subcutaneous nodules; gout responsive to colchicine; malignant granulomatosis, melenoma, psoriasis and other skin diseases; other infection such as active tuberculosis.

The first criteria for reactive arthritis were proposed by Amor and Laussadi [86] in 1964, Kingsley and Sieper [87] in 1996 and Pacheco *et al*. [88] in Mexico in 1966. In general, these criteria include the presence of aseptic, assymetric oligoarthritis, low back pain or diffuse back pain, heel pain, and sausage digits, with an accompanying diarrhea preceding the arthritis by at least one month, and usually conjunctivitis accompanying or preceding the arthritis by at least one month of duration, recurrent urethritis or cervicitis or previous urethritis or cervicitis within one month of the onset of arthritis, characteristic mucosal lesions (buccal, ballinitis) or cutaneous psoriaform lesions, and genetic predisposition: HLA-B27, family members with reactive arthritis, ankylosing spondylitis, uveitis or seronegative oligoarthritis or all of these, are also included in the criteria. Absence of septic arthritis due to bacterial infection by appropriate testing (culture or serology), and exclusion of other causes of acute articular rheumatism, infectious arthritis such as gonococcal arthritis, and exclusion of the arthritis of inflammatory bowel disease, Behcet's disease and ankylosing spondylitis are required.

There is considerable if not virtually complete overlap in these criteria for Reiter's syndrome and reactive arthritis. Their components greatly expand the classic triad of Reiter's syndrome. With the contemporary understanding of these diseases, and the historical context in which they were described, it seems appropriate to refer to them as "reactive arthrits." From this review, it is clear that a great many observers have contributed to our understanding of these diseases over the past five centuries. Contributions by many more workers can be expected into the future as further advances are made into understanding their pathophysiology and genetic basis.

ON A PREVIOUSLY UNKNOWN SPIROCHETE INFECTION (SPIROCHAETOSIS ARTHRITICA)

By Hans Reiter (Berlin)

On October 14, 1916 Lieutenant N. was admitted to Reserve Army Hospital X. The history of present illness is the following: On August 21 the patient became ill with body aches and diarrhea with a small amount blood (bloody discharge). Since August 29th purulent urethral discharge and purulent conjunctivitis of both eyes. Starting August 29th one stool daily; on August 30th begin of rheumatic complaints. On August 31st the patient was admitted to the field hospital.

The physical examination at admission is as follows: urethral meatus erythematous, purulent discharge, dysuria, marked bilateral conjunctival injection, edematous swelling of the eyelids, abundant purulent secretion, global swelling of the right knee joint, active motion impossible, passive only with great pain.

Spirochaete forans is apparently not a pathogen for guinea pigs; mice succumb rather suddenly with severe diaphoresis on about the eight day after inoculation. To this point, it has not been possible to demonstrate on microscopy the presence of the spirochete in live inoculated guinea pigs and live inoculated mice; as well until now it has not been possible to isolate the spirochetes in the organs of mice succumbing from the inoculation. That it has not been possible to directly demonstrate the spirochete on microscopic examination in the peripheral blood of the patient despite repeated attempts at different time points should in and of itself not be surprising; the situation here is apparently similar to Weil's disease, for which the microscopic demonstration of *Spirochaete nodosa* in the blood of patients has not been possible.

Disease course was the following: September 2nd: Temperature in the evening over 39^0; both knees now swollen and very painful; flexion not possible; lessening of the discharge. September 10th: No gonococci in the urethral discharge. September 11th: the left foot is also swollen; eye findings unchanged; urine clear, without threading. September 15th: The right elbow and left wrists are also affected by the rheumatic process. Conjunctivitis has disappeared except for tiny corneal maculae. September 18th: Must be fed because of the joint symptoms. September 21st: Increased pain and swelling of the left foot; condition otherwise unchanged. September 22nd: Preputial edema. September 24th: Joint swelling somewhat reduced, finger joints of the right hand stiff. September 26th: Ischial decubitus; condition otherwise unchanged. October 1st: Swelling of the foreskin resolving. October 4th. Urethral discharge and eye inflammation have not recurred. The affected joints are somewhat more mobile. October 12th: Because resolution is not expected in the foreseeable future, transfer home. October 14th: Admission to the Reserve Army Hospital. Findings on Admission: elbow joints, metacarpophalangeal joints of the middle and ring fingers of both hands, the proximal interphalangeal joints of the right and left middle fingers, both knee joints, both ankles and the metatarsophalangeal joints of the great toes are swollen and painful, with marked restriction of any joint motion and great pain on passive motion. The spleen is just palpable at the lower costal margin. Liver not enlarged. Preputium has marked edematous swelling. Glans covered with thick pus; urine cloudy, with few coarse flecks, no discharge. Left inguinal region covered with numerous pustules, skin reddened. No gonococci noted in the pus obtained by prostate massage and urethral expression; copious epithelial cells and copious leukocytes in the urine. October 17th: Without aspirin temperature vacillates continuously, ranging between 37 in the morning and 39^0 in the evening. Night sweats regularly. October 20th: Conjunctivae markedly swollen and red, especially on the right. October 21st: Beginning injection of the scleral and ciliary vessels at the nasal pole of the right eye. Swelling of the preputium is diminished. October 23rd: Frank iritis of the right eye. Cystitis is unchanged, as are the joint symptoms; only the joints of the right arm are somewhat improved. Spirochetes detected in pure culture from blood obtained on venipuncture of October 21st. October 26th: Despite poor general condition good appetite and sleep, which is interrupted by nightly diaphoresis. Cystitis and iritis unchanged. October 30th: Right arm can be moved somewhat; finger and elbow joints only barely swollen. Pain in the other joints has diminished somewhat. Evening fever now only to 38^0. Swelling of the preputium and purulent discharge diminished. November 3rd: Condition unchanged, injection with 0.3 Neosalvarsan. November 6th: Repeat injection of 0.3 Neosalvarsan.

PURE CULTURE OF *SPIROCHAETE FORANS*, 4 DAYS OLD. (From Reiter's Original Article)

Characteristic for the disease, which I propose be termed *Spirochaetosis arthritica*, is initially the course of fever, which without influence of aspirin usually is 37^0 in the forenoon, 39^0 in the evening and is fairly regularly accompanied by night sweats. In the foreground of the

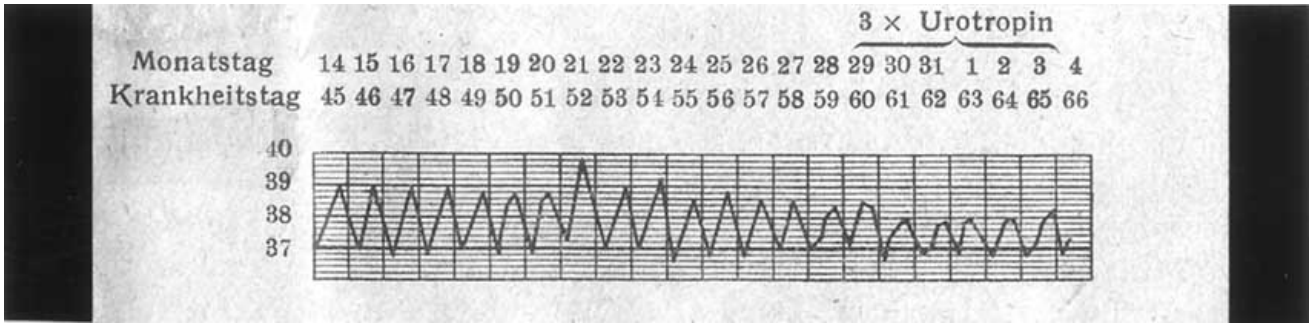

Fig. (2). Fever cure from Reiter's original article**.** Monatstag = date; Krankheitstag = day of disease course.

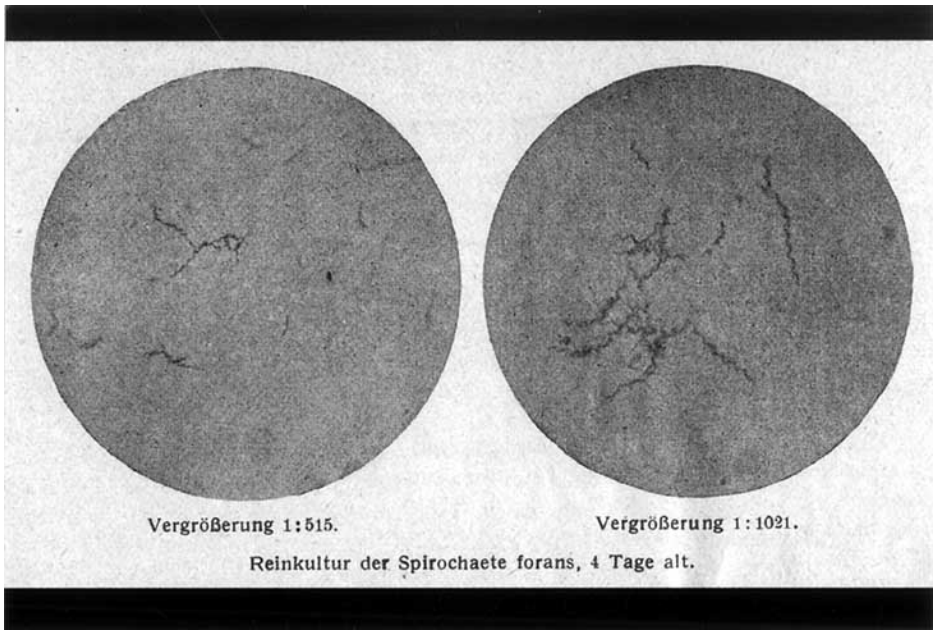

Fig. (3). Magnification 1:515 Magnification 1:1021.

clinical picture are very severe joint involvement, cystitis and conjunctivitis. The virtually unchanged disease course of 13 weeks is severe in the extreme. The patient is firmly bed bound, suffers marked decline, decubitus and complete helplessness, so that he must at times be fed. Other features are the pale skin color and the 60-70% drop in blood hemoglobin. Salvarsan has no influence on the disease course.

By venipuncture, defibrinization and culture in blood-ascites-meat broth agar it was possible to isolate a spirochete in pure culture, the micro-photographic images of which are presented. The spirochete was relatively easy to stain (Giemsa, Löffler) and superficially resembles *Spirochete pallida*. Relapsing fever must of course be considered, however speaking against this is the form of the spirochete, its properties in culture, and the clinical course of the disease. On dark field examination the spirochete moves by a rotational motion and demonstrated almost no flexion motion, for which reason I suggest calling the microorganism *Spirochaete forans*. Longer, mature spirochetes with about 7 to 10 angulations move slowly across the field of view, while small ones with one to 3 angulations move with great speed across the field of view. In four day old cultures the spirochetes demonstrate regular angulations in the midsections, with slightly tapered, short, straight components at their ends. In culture the spirochetes prefer to aggregate; also attempt, forming a more or less acute angle, to separate so that one has the impression of branching. This is especially the case there, where the spirochetes that touch each other have various lengths. In the six day old pure culture one sees, in addition to the spirochetes which have grown rather long, others which demonstrate nodular thickening in their course. Smaller spirochetes preferentially stretch out sideways from these points; a direct connection is not recognizable with certainty, and in addition one sees scattered nodules, which are larger than cocci clusters and demonstrate some distinguishing characteristics on high power magnification. In eight day old cultures the spirochetes already give the impression of degeneration; their angulations are noticeable flatter, and the staining is no longer uniform. The cultures die after eight to nine days. Subcultures have thus far not succeeded.

With regard to the manner of transmission of the disease, one can only raise preliminary speculations. Mass outbreaks have not occurred. The patient apparently never suffered from lice, flees or bed bugs, however there were great numbers of mosquitoes and flies in his immediate surroundings. Because the patient did not regularly make use of the mosquito net, and because lay persons are unfamiliar with the distinction between the common housefly and the biting housefly, *Stomoxys calcitrans*, an infection transmitted by biting flies or mosquitoes cannot be excluded.

It can be assumed that any number of similar afflictions have occurred and are now to some extent scattered about the country, but are not recognized as a distinct disease. On the other hand it cannot be ruled out that this particular case had a particularly severe course and that as a rule less severe cases may come to attention with the clinical picture of milder joint rheumatism. It will be the charge of further epidemiologic research to determine how the disease is transmitted and with what means it can be prevented.

Addendum at proofing: The patient received another 0.6 Neosalvarsan on both November 14th and 21st. The evening temperature on the 16th and 17th was only 37.5 and 37.6 respectively; no diaphoresis (Salvarsan effect?). On November 18th the evening temperature again about 38.5. Otherwise no significant improvement in the condition of the patient. Joints still swollen and painful, albeit somewhat less. Iritis on November 14th somewhat better (Salvarsan effect?). Ciliary injection resolving, cystitis virtually unchanged. Appetite good, mood better. The dosing of Neosalvarsans was deliberately very careful; it cannot be excluded that a more significant effect would result from higher doses.

TRANSLATION OF REITER'S ORIGINAL ARTICLE INTO ENGLISH

Notes on the Translation by E. L. Matteson

The translation of the account by Hans Reiter of reactive arthritis is the first published translation into English of which we are aware. This work was originally published under the title "Über eine bisher unerkannte Spirochäteninfektion (Spirochaetosis arthritica), " in the German medical weekly, Deutsche Medizinische Wochenschrift, volume 42, pages 1535-1536. The account itself is remarkable for its brevity yet relative completeness, including a description of unsuccessful attempts to culture the pathogen, which the author believed to be a spirochete. Whether the patient had more than one infection, or whether this spirochete found was a contaminant is uncertain; clearly Reiter believed it was not. He considers differential diagnostic possibilities including relapsing fever, and discards these on clinical grounds, a conclusion the modern reader must agree with.

In keeping with the original style, I have retained Reiter's word usage and punctuation, except where they would be too confusing in English. Urotropin is referred to in the text and in the first figure, which shows the fever curve of the patient from day 45 to day 66 of his illness (in degrees Celcius). Urotropin (hexamethyllentetramine) is a urinary tract antiseptic in use for many years before and after World War I. Treatment attempts were made with Salvarsan, which it seems were in the hope, but without real expectation, of improvement. The German physician Paul Ehrlich discovered Salvarsan and Neosalvarsan, the world's first chemotherapeutic agents used for systemic treatment of a microorganism infection in 1906.

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