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Reiter's disease

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INTRODUCTION

During the past five years urologists, bacteriologists, and internists have considerably entertained by the increasing incidence of a confusing clinical oddity, the pattern of which does not fit into the every day practice of medicine, and which boasts the reputation of still being little recognized and even less understood. The degree of interest in this condition is evident from the multitude of speculation as to its etiology and even its classical signs and symptoms. Speculations have run the gamut of etiological agents from spirochetosis through the bacterial types of a virus or an allergy. None of these speculations have been substantiated by proof, and they serve no cause other than dignified retreat on the part of the practitioner whose therapy of an acute urethritis, questionably gonorrheal with all its sequellae, results in total failure.

An obscure syndrome, first described by Reiter in 1916, and characterized by acute urethritis, conjunctivitis and arthritis, was called by him "spirochetosis arthritica". This terminology was the result of Reiter's finding a coexistent spirochetal infection of the blood. His conclusion has since been discredited,

but the condition is still known as Reiter's syndrome. The paucity of literature and the general lack of awareness of the existence of such a syndrome suggests that it is rather rare, yet during the past war more cases of this type were reported than in all the combined years since it was first recognized. The principal reasons why this disease has not been more widely recognized are its superficial resemblance to other common diseases, the diversity of the body systems involved, and the general lack of knowledge of its existence.

Since the original description of the triad by Dr. Reiter, other subjective manifestations have been associated with this disease. In a condition which still defies any exposition of its pathogenesis, one is unable to clearly define any of the various manifestations as a part of the disease entity, and it is difficult to consider any manifestations as a complication. This syndrome is so void of tangible laboratory proof and so easily confused with other ill-defined diseases that, lacking the most painstaking studies, most of the reported cases are open to some question.

Despite the confusing picture that this condition presents, the fact remains that there is a disease of

really dramatic proportions characterized by extensive lesions of the joints, the mucous membranes and the skin; a disease of which the etiology is unknown, one exceedingly protracted in course and tending to recur after prolonged periods of remission, and that is utterly refractory to all known treatment.

The usual symptomatology of this condition is that of a spontaneous purulent urethral discharge followed by a mucopurulent conjunctivitis, and in from one to four weeks the triad is completed by the development of an acute arthritis, usually involving one or more of the weight-bearing joints. The arthritis may in some cases initiate the clinical onset. Furthermore, the urethritis and conjunctivitis may be of such short duration and of such benign course that they are frequently overlooked by the patient in stating his clinical history. There are several instances in the literature in which the triad failed to evolve completely; consequently, it is with just hesitation that we accept the diagnosis in those cases. The arthritis is always of longer duration than the conjunctivitis or the urethritis, and the reluctance of the involved joints to subside may prolong the period of active disease into several months. Although perman-

ent joint destruction has not been seen, clinical and roentgenological changes of a rheumatoid nature are usually found. It is indeed extremely difficult, if not impossible, to distinguish radiologically the findings in this disease and those of rheumatoid arthritis. X-ray of the involved joints may show not only demineralization, but also circumscribed areas of subchrondral decalcification, periosteal proliferation and narrowing of the joint spaces. It is further characterized by a tendency to spontaneous remission.

The urethritis is purulent in type and is attended by burning, frequency, meatal itching, and terminal hematuria. The entire urinary tract may become involved, and pyelitis and even hydronephrosis have been reported early in the course of the disease. The urological manifestations extend to superficial papulo-vesicular lesions of the glans penis, which are most resistant to treatment. Another manifestation of the diffuse cutaneous lesions is the identity with keratosis blennorrhagia, but which can be differentiated only by thorough and exhaustive bacteriological studies for gonorrhea. Furthermore, papulo-vesicular lesions appear on the plantar surfaces of both feet and progress even to superficial ulceration.

The conjuctivitis may vary from a mild catarrhal type to extensive iritis and keratitis.

Laboratory findings are not of diagnostic significance. The leukocyte counts vary from 10,000 to 20,000 as in any acute infectious disease. The sedimentation rate is moderately accelerated. Of most significance in laboratory studies, however, are the negative urethral, prostatic, and conjunctival smears and cultures, as well as negative blood agglutinations and cultures, and negative skin tests.

The constitutional symptoms other than those mentioned above are low-grade fever, mild rigors, and generalized malaise, none of which is so marked as those seen in gonorrheal infections.

This disease is primarily one which attacks young male adults only, but one questionable case has been reported in a young woman.

Various explanations have been offered as an etiological basis, among them being an infection with a gonococcus which has undergone morphological changes defying identification, a staphylococcus, an enterococcus, avitaminosis, dysenteric polyarthritis with superimposed toxic features, or a virus or an allergic affair with genito-urinary, ocular, and skeletal systems.

participating. They have been entirely speculative and untenable. Suggested methods of treatment have paralleled the speculations as to etiology. The antibodies have failed completely, artificial hyperpyrexia has resulted in nothing more than exaggeration of the miserable feeling of an already unhappy individual, and salicylates offer unimportant symptomatic relief. Long lists of drugs, some of which have coincided with a spontaneous remission of the disease, have kindled hope in a few enthusiasts who are disappointed when the treatment completely fails in the next patient. Until something of its etiology is known, treatment of Reiter's disease is necessarily limited to symptomatic relief.

HISTORY

Reiter in 1916 reported a case of an officer who had an attack of abdominal pain and diarrhea, and eight days later had a discharge from his urethra, and a severe conjuctivitis. Rheumatic pains and swelling of the joints then followed. The patient presented the complete picture of acute gonorrhea with arthritis and conjunctivitis. The urethral oriface was reddened, abundant pus was discharged, the urine was cloudy and contained shreds, micturation was painful, and there was cystitis. The conjunctivae were reddened and swollen, and discharged much pus; iritis developed. Several joints were swollen and painful, the general health was bad, and the e was continued remittent fever. Reiter cultivated a spirochete from the blood, which he named Spirochaeta forans, and he called the disease Spriochaetosis arthritica. The disease was not to be influenced either by neosalvarsan nor by salicylic acid preparations.

At the same time, Macfie (1917) who was a bacteriologists had the opportunity to investigate quite thoroughly a similar case without diarrhea in West Africa. In his case the urethral discharge contained spirochetes which he believed to be the causal agent.

The spirochetes were most commonly eight to twelve microns in length, and showed four or five spirals; but the range in the 300 parasites measured was from five microns to twenty microns. They appeared to multiply by both longitudinal and transverse division, and by the formation of coccoid bodies. The parasites passed through an intracellular phase which seemed to be as follows: Some of the spirochetes enter the epithelial scales lining the urethra, become quiescent, and break up into coccoid bodies. Those bodies multiply so as to form masses of granules from which young spirochetes develop, grow to about normal size, and eventually escape. Macfie proposed the name Spirochaeta urethrae for the parasite. The treatment given was two intramuscular injections of 1/3 grain perchloride of mercury.

The third report of such a case was from France, where Fiessenger and Leroy (1917) described a similar case associated with dysentery, in which no specific organism could be isolated, and since this, the French have used the term of conjunctivo-urethro-synovial syndrome of the dysentery of Fiessenger and Leroy. They reported four such cases.

Schittenhelm and Schlecht (1918) reported seven

cases under the name of polyarthritis enterica.

Rist and Crouzan (1916) reported on the frequency of arthropathies, conjunctivitis, and urethritis following epidemics of bacillary dysentery, in which no bacteriologic diagnosis of bacillary dysentery could be made at the time of the onset of the symptoms.

Other early German authors included Fleischmann (1916), Michael (1917), Sommer (1918), Junghanns (1918), and Stühmer (1922). None of these men could explain the etiology as spirochetes, gonococci, nor other specific organisms could not be isolated, and they believed their cases to fall in the same category as Reiter's cases. Most of these early writers believed that there was a focus of infection causing the syndrome.

The first full report in American literature appeared almost twenty-five years later. Bauer and Engleman (1942) described their case, but offered no explanations as to the etiology, nor specific treatment. Following this, many cases were reported so that by 1946 when Valle reviewed the literature and reported his cases, there was a grand total of 151 cases.

Since the war, however, many reports are in the literature of cases seen in the Armed Forces, so that

the number has now more than doubled.

Since the first case was reported in 1916, in which the three major findings of urethritis, conjunctivitis, and arthritis were grouped together to form a syndrome, many names have been used to describe this syndrome. These many names have included the following:

Sprirochaetosis arthritica

Dysenteric polyarthritis

Dysenteric arthritis

Polyarthritis enterica

Urethral spirochaetosis

Conjunctivo-urethro-synovial syndrome of the dysentery of Fiessenger and Leroy

Reiter's syndrome

Reiter's disease

Infectious uro-arthritis

Polyarthritis urethritica simplex

Reiter and Freund syndrome

Pseudo-gonococcic enteritque

Keratosis blennorrhagica without Gonococci

Many authors in their articles have written up cases that were exactly like the so-called Reiter's syndrome except one of the three major findings was missing. Others had more than three findings, and

also wrote up the case as Reiter's syndrome. This makes the syndrome even more complex and uncertain, and then such things as non-specific arthritis, palindromic rheumatism and others begin to come into the picture.

CLINICAL PICTURE

It is not customary to give the criteria for diagnosis of a disease at this time, but in this particular case it will make more apparent the trouble that has arisen over etiology.

In the original work on this disease, the diagnosis was applied to cases coming to the physician complaining of a purulent discharge from the urethra, a conjunctivitis, and some migratory arthritis. These symptoms look so much like those of a gonococcal affair that the tentative diagnosis is invariably gonorrhea with complications. However, smears are always negative for the intra-cellular diplococci, and if the physician runs a complement-fixation test this is also negative. In checking back on the history, sexual exposure is often denied. As the patient is followed along, Sulfa preparations and Penicillin are tried which would be effective if the tentative diagnosis were correct; however, these drugs offer the patient no relief, and so the physician will carry the patient along with symptomatic treatment for three to four months by which time the symptoms have subsided, leaving no residual.

The above has been enough to apply the diagnosis of Reiter's syndrome to, and with the accumulation of

cases in the literature more findings have been added which cause variation in the pattern.

The age of the patients have varied from sixteen years to over fifty-eight years (Newton, 1947), with an average in the early twenties. There have been only two cases reported in the female sex. (Marshall, 1947).

The urethritis is usually the first sign of the disease. Hollander (1945) found this to be true in 19 of his 25 cases, with four complaining of diarrhea first, and two complaining of the arthritis first. Rosenblum (1945) reported urethritis of a mucoid type, later becoming purulent, to be the first sign of his ten cases. He was convinced that the disease was of venereal origin, as in one of his cases there was a history of sexual contact with the same woman two and one-half years apart, each time followed by the Reiter syndrome in a matter of two to three days. Other authors could not find a history of sexual exposure. (Strochstein, 1945). Hollander (1945), in his earlier ten cases got no history of exposure a month previous to the symptoms and signs, but in a later report (1946) he gave the urethra as the most common portal of entry, but added that the conjuctiva could be the portal,

following his study of 53 cases. Most authors now believe the disease to be of sexual origin, although a few cases are still appearing in which sexual exposure has been denied.

The urethritis is abundant and purulent, accompanied by surprisingly little frequency or pain on micturition. Gross hematuria may occur (Miller and McIntyre, 1945). The urine contains red blood cells in varying numbers, clumps of pus cells, and a little albumin. The discharge presents no evident organisms and is sterile on attempted culture. The urethritis usually clears spontaneously after three to four weeks regardless of treatment, but may recur sporodically (Hollander, 1946).

Renal complications have occurred, including: Prostatis (Hollander, 1945), (Sargent, 1945), (Strachstein, 1945), (Haar, 1945); Prostatic abscess (Colby, 1944), (Strachstein, 1945); Balanitic or perimeatal ulcerations (Hollander, 1945), Strachstein, 1945); Hydronephrosis (Colby, 1944); Chronic pyelonephritis (Colby, 1944); Cystitis (Strachstein, 1945); and Vesiculitis (Strachstein, 1945).

Within ten days of the onset of the urethritis, a mild but purulent bilateral conjunctivitis develops (Hollander, 1945). There is local pain, weeping, and

photophobia, but permanent damage to the eye occurs only rarely. No constant organisms can be found in the conjunctival smears. The condition disappears in five to ten days regardless of treatment. Some of the complications of the conjunctivitis reported in the literature include: Superficial punctate keratitis (Rosenblum, 1945), (Lucas and Weiss, 1945), (Jackson, 1946); Episcleritis (Jackson, 1946); Uveitis (Jackson, 1946), (Lucas and Weiss, 1945), (Haar, 1945); Iridocyclitis; Subconjunctival ecchymosis (Rosenblum, 1945). In 14 of Hollander's original 25 cases (1945) conjunctivitis was absent.

Crops of small vesicles develop chiefly in the central area of the cornea five days after the onset of the conjunctivitis. These break down shortly to form discrete superficial ulcers which show no tendency to coalesce or penetrate, and heal without residual opacifications within the ensuing three weeks. Photophobia is intense during this period, and the iritis follows the keratitis after an interval of five days. (Lucas and Weiss, 1945).

Skyelsgaard (1943) recommended that ophthalmologists keep this condition in mind when dealing with a purulent conjunctivitis of unknown etiology, and in

such cases emphasized the value of a good history.

Cultures from the eye are usually negative, containing only flora normal to the eye such as Staphylococcus aureus and albus, hemolytic and non-hemolytic, toxigenic and non-toxigenic Streptococci, and Diphtheroids. (Rodin, 1945), Gersh, and Reich, 1945).

Within two weeks after the onset of discharge, an acute polyarthritis is noted; without chill, but with temperature elevation to about 101°F., daily for about ten days. The arthritis is uaually migratory in character and involving the weight-bearing joints. Weight loss and muscle atrophy are often marked, and develop fairly rapidly. The joints are red, hot, swollen, and tender, and may appear like rheumatic fever or gonorrheal arthritis.

X-rays of the joints show evidence of soft tissue swelling, and may have narrowing of joint spaces often. X-rays show destruction and are difficult to distinguish from rheumatoid arthritis (Rosenblum, 1945). Usually there is an appearance of osteoporosis of the approximating joint bone ends during the second or third month of the disease. Periosteal proliferation near involved small joints is noted in some cases (Hollander, 1946).

With aspiration of the joints, Jackson (1946) found that the fluid may be purulent but always sterile. Hollander (1945) aspirated eight joints and found 9,000 to 14,000 white blood cells with 65-74 percent neutrophils; smears and cultures both negative.

One case of arthrotomy is on record (Hollander, 1945). It was found that the synovia was congested and presented a reddish-purple appearance. No gross thickening was noted. There were several small circumscribed areas of white fibrinous-like material lying on the surface of the synovium. Portions of synovia from the floor of the suprapatellar pouch just proximal to the articular surface of the condyle and from the congested infrapatellar fat pad were removed for section. The cartilage appeared normal. Microscopic examination showed intense inflammatory reaction which was limited to the superficial synovial layers, and did not involve the supporting collagen, fibrous connecting tissue, nor vessel walls. The synovium was thrown into large club-like projections in which the abundant capillaries were all dilated. Each projection was distended by a heavy lymphatic infiltration, mixed with a smattering of plasma cells and a few neutrophils. No fibrinous exudate was observed. The intima

was approximately six to ten layers deep. Only a few perivascular focal collections of lymphocytes and plasma cells could be found. There were no well defined new capillaries, and the intense hyperemia consisted of dilatation of preexisting capillaries.

Within four to six months under supportive treatment the involved joints appear normal, and the muscles have regained their strength. In only two cases was there actual bony destruction in Hollander's (1945) series of 25 cases.

About one month after onset, superficial ulcerations are noted on the glans penis (balanitis circinate), and in many cases atithis same time keratodermic lesions may be found on the feet and legs of many patients. The keratodermia blennorrhagica usually clears up in two months. The balanitis may be recurrent, independent of the existence of the urethral discharge.

Eight of Hollander's (1945) twenty-five cases had the skin involvement. The dark field examinations are always negative. One case was complicated by subungual abscesses in six fingers. In his later series (1946) of 53 cases, eight had keratodermia blennorrhagica and 26 had balanitic circinate.

Rosenblum (1945) described the skin condition as an erythema multiforme leading to desquamation and denudation of the soles of the feet, glans penis, and oral and pharyngeal mucosa.

Twiss and Douglas (1945) reported generalized lymphadenopathy in one case, and another of hyperkeratotic collections under the finger nails.

Baxter (1946) brought up the differential diagnosis of keratosis blennorrhagica and psoriasis.

One case of endocarditis and lupus erythematosis disseminatus after sulfathiazole treatment was reported by Bauer and Arndal (1946).

Recurrences are not rare. Miller, Dudley and MacIntyre (1945) reported a case of five recurrences - - - 15 years, 11 years, 8 years, and 6 months before the recent attack.

Laboratory findings are not diagnositic. Generally the white blood cell count varies from 10,000 to 20,000. Blood sedimentation rates are rapid. There are urinary findings of pyuria, albuminuria, and hematuria. Prostatic secretions show numerous pus cells. Special tests have been non-conclusive. Agglutination tests for dysentery strains, finding inclusion bodies, blood cultures, smears, complement fixation for gonococcus,

eye tests, and others have been tried by various authors, and will be further discussed under the consideration of etiology.

ETIOLOGY

Many authors have found what they thought was the cause of the syndrome, but there is still no agreement as to a specific organism. Reiter (1916) found a spirochete in the blood of his first case, and called it Spirochaeta forans. Macfie (1917) also found a spirochete in the urethral discharge which he called Spirochaetae urethrae. However, their results were not confirmed by other writers.

A Complication of Bacillary Dysentery

Many writers believe that this syndrome is only a complication of bacillary dysentery; hence the many names to indicate it. Maxwell and Kiep (1918) reported six cases of iritis and cyclitis in dysenteric patients, four of which also had arthritis. In their same article they reported a case of rheumatism of the right ankle which later had iritis. In this case no history of dysentery could be gotten, yet the patient had an agglutination titre of 1:800 for bacillary dysentery; the stools were negative three times. Tice (1920) states that joint affections are not uncommon during epidemics of bacillary dysentery. He states that there is usually an interval of three or

four weeks between the acute attack of dysentery and the appearance of the joint lesions, which is not infrequently preceded by mild conjunctivitis lasting a few days only, and by acute urethritis which is also mild. The joints most commonly affected is the knee, often the ankle, and less frequently the toes. The upper extremities are not often involved, but the elbow and shoulder are sometimes attacked and the wrist and fingers in rare cases. As each new joint is involved there is a moderate rise in temperature.

The heart shows signs of involvement in about one third of the cases, and greatly influences the prognosis.

This group of symptoms is spoken of by the French writers (Fiessenger and Leroy, 1917) as conjunctivo-urethro-synovial syndrome. Since their first case these French authors have attached their names to the syndrome.

Most of the German writers believe this syndrome to be a complication of bacillary dysentery, although many could not make the bacteriological diagnosis of bacillary dysentery. Graham (1937) states that arthritis is a common complication of bacillary dysentery, appearing two to three weeks after the onset of an acute

attack. It is more common in the Shiga infections. The joint becomes painful and swollen from thickening of the periarticular tissues and effusion of the joint. The effusion is rich in fibrin and polymorphonuclear leucocytes. Agglutinins from the dysentery bacilli are present in the joint fluid. The dysentery toxin is the probable cause of the arthritis. Recovery is slow but no disability of the joint remains. Conjunctivitis, iritis, and iridocyclitis are less common complications, and occur most often in cases suffering from arthritis.

Beiglbock (1944) reported on his cases of Reiter's disease and came to the conclusion that it was nothing else than the familiar dysenteric polyarthritis, with some added toxic manifestations which had been previously described. He further states that polyarthritis enterica or dysenteric arthritis is frequently complicated by ocular and urinary manifiestations, especially in mild dysentery, but seldom in the acute Shiga infections, which is not what Graham thought. Beiglbock got positive agglutinations with the Flexner organisms in many of his cases; most of them also ran a mild eosinophilia.

Herson (1946) was in charge of bacillary dysentery

cases of the British Army in the Middle East during the war, and he encountered many cases in which polyarthritis, urethritis, and conjunctivitis were found in patients with acute diarrhea and showing a bacillary exudate on microscopic examination of the stools. He was somewhat confused as to what diagnosis to make: "As severe diarrhea is apparently a feature of Reiter's disease it must be difficult at times to distinguish this from bacillary dysentery complicated by the same triad of symptoms." Marsh (1946) also did not believe in using the term Reiter's disease for such cases, and believed it to be a post-dysenteric syndrome which could occur two to three months after an attack of dysentery. Both men apparently wanted to do away with the term altogether.

Wood (1946) reported twelve cases of Reiter's syndrome in which all gave a history of dysentery, although fleeting, with a latent interval of about ten days; in no instance with the first attack. He succeeded in reproducing the sterile conjunctivitis by instilling a drop of Flexner vaccine into the conjunctival sac in three of the twelve cases; the flare taking place after an interval of five to eight days. It was impossible for him to employ autogenous vaccine because

stool cultures were always negative when his patients were first seen, and it was therefore a matter of chance whether he used the right organism or not. Conjunctivitis did not follow use of vaccine in normal controls, nor in patients with gonococcal polyarthritis, nor with streptococcal polyarthritis (Rheumatic Fever). Vaccine dropped into the urethral oriface in several cases failed to cause urethritis however. Vaccine dropped into the conjunctival sac of cases of dysentery without polyarthritis yielded essentially negative results.

Willcox, Findlay, Henderson, and Begg (1947) tried the eye test on their three patients diagnosed as Reiter's disease. Flexner bacteria (mixed I - VI) were killed by heat at 55°C., and a suspension of 3,000 million organisms per millileter was prepared. It produced no reaction in three rabbits nor in two human controls. A drop of this material was placed in the right eye of their cases and no reaction was noted. None of these patients sera showed any type agglutination with strains of dysentery bacilli of the Shiga type. They further added that non-specific urethritis, arthritis, and conjunctivitis was not uncommon in the West Africans, among whom Shiga dysentery is exceptionally rare.

Bardhan (1947) states that in India there are thousands of cases of bacillary dysentery and yet there are no authentic records of Reiter's disease. Had the two conditions been etiologically related there would surely have been more cases of Reiter's disease in that country.

Jackson (1946) in answer to Herson (1946) and Marsh (1946) stated that in only a few cases of Reiter's disease does the diarrhea occur, and in no case recorded on this syndrome in Germany or America could he find where dysentery bacillus had been identified. He further stated that in the Bahamas bacillary dysentery was unknown, and that in his three cases he could obtain no history of diarrhea attacks of dysentery type. He concluded by stating, "Naturally because a similar syndrome may occur as a dysenteric sequela it does not follow that such a syndrome always possesses such an etiology. The characteristic signs may in fact be part of a gonococcal infection and it is in the distinction from this that the importance of the recognition of the Reiter's disease syndrome exists."

A Virus Infection

Virus has been considered by many of the recent

authors to be the cause of Reiter's disease. Lindner (1911) was one of the first men to find inclusion bodies in non-specific urethritis, and so concluded that it was a virus disease. Halberstaedter, Prowazek, and Heyman (1910) found inclusion bodies in epithelial cells from the genitourinary tract of mothers with babies suffering from conjunctivitis. Thygeson and Stone, (1941, 1942) writing extensive articles on the epidemiology of conjunctivitis related to genitourinary tract infections, proved the virus theory. They gave the example of the physician who while examining a female got a spurt of blood into his own eye and six days later developed conjunctivitis.

Johnston and McEwin (1945) in their article on non-gonococcal urethritis studied the relationship of urethritis to conjunctivitis and found a great many of their cases due to a virus. F. Wrigley (1946) quoted a German medical officer as saying that Reiter's disease was common on the eastern front and very common on the western front. It was believed by them to be a virus disease. Kersley (1946) believed Reiter's disease to be due to a virus of the Waelsch type, which is probably also responsible for "swimming bath" conjunctivitis and "inclusion cervicitis". (Van Rooyen and

Rhodes, 1940). Harkness found inclusion bodies in the discharge from the urethra and conjunctiva in five cases of Reiter's disease (cited by Jackson, 1946).

Primary herpetic stomatitis of infants and young children is caused by the virus of herpes simplex, and a virus has recently been shown by Buddingh to be responsible for a similar disease associated with diarrhea in children. Strains of the virus are maintained by serial passage from cornea to cornea of rabbits, but unlike primary herpetic stomatitis, no inclusion bodies have been found. In the discussion following Buddingh's paper on this subject, Sabin stated that these inclusions would probably be demonstrated in serial sections. On this occasion, Dodd also reported that she had obtained positive conreal innoculations in rabbits with vaginal swabs taken from the mother of children suffering from the disease. Buddingh had observed similar results with the urethral discharge and oral and conjunctival secretions of a typical case of Reiter's disease (Harkness, 1947).

Pleuropneumonia-like Organisms

Pleuropneumonia-like organisms have been given the credit for many cases of Reiter's disease and non-

specific urethritis. For that reason a brief summary of these organisms and the relation they play in this disease is of interest.

The first member of this group was described by Nocard (1898), when he cultivated but was unable to see the causal agent of bovine pleuropneumonia. In 1910 Bordet stained the organism by Giesa's method and described their pleomorphism, as also did Borrel (1910) who in view of the morphology gave them the name of Asterococcus. That Berkefeld and Chamberland filtrates were infective gave grounds for believing that these organisms could be classified among the filterable viruses.

Bridre and Donatien (1923, 1925) and Celli and De Blasi (1906) derived the second filterable organism of this group from sheep suffering from contagious agalactia.

Following World War I attention was focused on these viruses which be grown on media containing a high concentration of animal protein.

Asterococcuscanis was isolated from dogs with distemper by Shoetensach (1934) in Japan. Positive cultures were obtained from the eyes, nose, lung, liver and pericardial fluid. Shoetensach (1936) and Kliene-

berger (1938-1940) proved that these organisms belonged to the pleuropneumonia-like group, but left doubt as to whether they were more than of secondary importance in canine distemper.

Since the earlier workers mentioned above, many pleuropneumonia-like organisms have been obtained from rats, mice, and guinea pigs.

Dienes and Edsall (1937) were the first to indicate that pleuropneumonia-like organisms might possibly be associated with man when they isolated an organism of this type from the suppurating Bartholin's gland of a woman; she had, however, been working in a laboratory with rats.

Later, in America, Dienes (1940) reported the isolation of five strains from the cervices of women. Dienes and Smith (1942) published reports of the isolation of these organisms from the cervical, vaginal, and urethral secretions of women, and from the urethral and prostatic secretions of man. Organisms were found in 22 percent of 129 unselected cases. Some of the women were suffereing from arthritis, some from gonorrhea, and some from non-specific inflammatory lesions of the genitourinary tract, while all the men were suffering from chronic prostatitis. In Australia, Beveridge (1943), Johnston and McEwin (1945) and Beveridge (1946)

have confirmed these results, since they have found the organisms in both males and females with non-specific urethritis. Fourteen of the patients examined by Beveridge and his collegues yielded positive results. Of eleven women who had had connection with these positive men, only three yielded pleuropneumonia-like organisms. Of 101 normal women, three gave positive results, while 67 healthy male medical students were all negative. Klieneberger-Nobel (1945) working at the London Hospital and the Whitechapel Clinic obtained pleuropneumonia-like organisms from 40 percent of the women attending the venereal disease clinic, and 33 percent of those attending the gynecological department for a vaiety of presumable non-venereal conditions. Only 14 percent of women attending the antenatal clinic were infected. Salaman (1946), in military personnel, found that of gonorrhea patients 34 percent of men and 60 percent of women harbored pleuropneumonia-like organisms. The same organisms were common in women suffering from vaginitis due to Trichomonas and from non-specific cervicitis. The organisms were less common in non-specific urethritis in men, and are uncommon in prostatitis. They were found in the urethra of approximately 17 percent of normal men and 6 percent of normal

women. The frequency with which pleuropneumonia-like organisms are associated with cultures of the gonococcus was orignially noted by Dienes (1940) and later by Brown and Hayes (1942) and Salaman (1946).

The relationship of these human strains to those of rodents has received very little attention. One unequivocal human strain studied by Warren and Sabin (1942) was not pathogenic for mice, and no evidence of toxic production was obtained. Antisera against rat and mouse strains failed to agglutinate the human organisms.

These observations show that pleuropneumonia-like organisms are by no means rare parasites of the genital tracts of both men and women. Although more commonly associated with inflammatory conditions, such as non-specific urethritis and cervicitis, they were also present in apparently healthy individuals. Their isolation from human beings suffering from a particular disease does not, therefore, neceszarily indicate that they are casually related to the disease.

In the case of bovine pleuropneumonia, it is well known that in the later stages of the disease inflammatory arthritic changes may occur, while injections into the root of the tail of sucking calves or of raindeer

causes an inflammation of the joints. Intracerebral injection into cows is also said to cause invariably an inflammation of the joints. Meyer (1910) believes that in adult cows the tendency to produce arthritic changes after prophylactic tail innoculations was not due to individual predisposition, but to the particular strain of organism. The power to produce arthritic changes was lost by continued passage either in animals or in artificial media, and no secondary joint affections could be produced subsequently by innoculation of cultures.

In contagious agalactia of sheep, in addition to a mastitis and a conjunctivitis, an arthritis is by no means uncommon. According to Pigoury (1938) arthritis occurs in 10 to 20 percent, coming on usually in goats about a week after the beginning of the disease. One joint alone is usually affected, generally that between the radius and the carpus, more rarely in the tibio-femoral, the tibio-astragaloid or the metacarpals. The symptoms vary from simple stiffness to acute arthritis with complete functional incapacity. Spontaneous cure generally takes place after one or two months, but in some cases anklylosis is complete, with abscess formation involving the articular surfaces. In the chronic

form of the disease there may be remissions and exacerbations of the arthritis without ultimate deformity. Some generalized wasting of the muscles is common. The process in the mammary gland is that of an interstitial mastitis with disappearance of glandular tissue. In the eye there is an interstitial parenchymatous keratitis with infiltration of small cells and vascular proliferation. Histologically the inflammatory lesions of the joints are at first periarticular with and infiltration of polymorphonuclear leucocytes; abscess formation occurs, involving the capsule synovial membrane, and at a later stage the bone and cartilage. A considerable exudate may be found within the joint capsule, while the cartilage is uninvolved. As the disease progresses, cartilage is sooner or later destroyed by a rapid necrotizing process. Osteomyelitis may occur.

In the affected joints there is considerable cellular infiltration and thickening of the periarticular connective tissue, but no involvement of cartilage or synovial membrane. Sometimes, however, there is erosion of the articular cartilage or the formation of polypoid growths of newly formed connective tissue. Endarteritis is described in the joint tissues by Carre (1912).

With the discovery that pleuropneumonia-like organisms are the cause of arthritic conditions in cows, sheep, goats, rats, and mice the question naturally arose whether these same organisms might not be responsible for arthropathies in man. Swift and Brown (1939) in fact, claimed to have isolated pleuropneumonia-like organisms from patients with rheumatic fever. They subsequently agreed, however, that their direct "culture" had been misinterpreted while the strains obtained after passage through mice were biologically and immunologically identical with those normally carried by these animals (Sabin, 1939).

Subsequently, attempts by a number of investigators to cultivate pleuropneumonia-like organisms from joint exudates and from the tissues of patients with rheumatic fever or rheumatoid arthritis have all failed (Sabin, 1939), (Sullivan and Dienes, 1939), (Findlay et al, 1940), (Sabin and Johnson, 1940), and (Preston, 1942). At present the direct relationship of pleuropneumonia-like organisms to rheumatic fever and rheumatoid arthritis must remain unproven. Further investigations might, however, be undertaken to determine whether streptococci isolated from rheumatic joints are ever contaminated with the pleuropneumonia-like organ-

isms. In addition, the effects of infecting streptococci into joints already infected by pleuropneumonia-like organisms appears worthy of study.

Apart from the possible relationship of pleuropneumonia-like organisms to non-specific urethritis, there appear to be two human diseases where further investigation of the role played by pleuropneumonia-like organisms might be worthwhile. These diseases are Haverhill fever and Reiter's syndrome. Haverhill fever is one of the two forms of rat-bite fever, characterized by fever and polyarthritis and usually thought to be due to Streptobacillus moniliformis, which has been cultivated from the blood (Farrell et al, 1939). In view of the frequency with which pleuropneumonia-like organisms are associated with this bacillus, the question arises how far the symptomatology in man is due to an associated pleuropneumonia-like organism and how far to Streptobacillus. All cases of rat-bite fever should, when possible, be investigated for pleuropneumonia-like organisms. Streptobacillus moniliformis, however, is very susceptible to Penicillin, while the evidence at present suggests that pleuropneumonia-like organisms are not.

The second human infection for which there is reason

to think a pleuropneumonia-like organism may be responsible is Reiter's syndrome. Efforts should be made to culture pleuropneumonia-like organisms from the conjunctiva, joints and the urethral discharge of all patients suffering from Reiter's syndrome. Unfortunately, complement fixation tests with cultures of human pleuropneumonia-like organisms have not up to the present proved highly specific. However, there is some evidence that skin sensitivity tests may be of greater value in diagnosing those who are suffering from an active infection due to pleuropneumonia-like organisms.

Beveridge, Campbell and Lind (1946) have concluded that the main objections to the hypothesis that non-specific urethritis is principally or wholly due to infection with pleuropneumonia-like organisms are (a) the failure to obtain growth of the organisms in 80 percent of the cases, and (b) their presence in about 20 percent of normal women. It was not possible, under the circumstances in which the work was done, to make repeated attempts to culture for the same patient. Pleuropmeumonia-like organisms are relatively delicate, and it is easy to imagine circumstances in which they might fail to appear in culture, although they were primarily responsible for the clinical condition.

Such factors might account, at least to some extent, for the rather small proportion of positive results obtained.

The existence of pleuropneumonia-like organisms in the genital tract of a considerable proportion of women showing no clinical evidence of infection cannot be regarded as evidence against the view that this group of organisms is responsible for non-specific urethritis in the male. It would be in line with general concepts of the ecology of bacteria of low potential pathogenicity, for example pneumococci and meningococci in the throat, to find such a state of affairs. Non-specific urethritis in the male is often, perhaps usually, so trivial that it would be likely to escape attention in civil life.

Certainly no conclusion is justified on the present evidence; but, all the facts available are nevertheless consistent with the tentative hypotheses that the disease is in the majority of cases the result of infection by pleuropneumonia-like organisms, according to Beveridge, Campbell, and Lind.

Relationship to Gonorrhea

Since Reiter's disease is misdiagnosed more often as gonorrhea, the relationship of the two is of interest. Since Keratodermia blennorrhagica has already been discussed, this should be a good place to start.

Vidal (1893) was the first to observe and describe this syndrome in a patient suffering from gonococcal polyarthritis. Since then, cases have been published in Europe and America. In 1924, Kein described the histogenesis of the cutaneous lesions from a case under his observation, and distinguished it from pustular psoriasis. Lee and Percival (1931) in a brilliant contribution, and report of eight cases, discussed in detail the histology and clinical considerations which confirmed Kein's observations. Though the association of keratodermia, urethral gonorrhea, and polyarthritis was a constant feature in most of the observed cases, indicating a condition of gonococcal septicemia, the culture of the blood and scrapings of the lesions have invariably yielded negative results. The consensus of opinion now points definitely to the cutaneous eruption as being an allergic expression of a sensitized skin, the sensitization taking place either directly or indirectly through the nervous system (Lee and Percival,

1931). The observation of Scholtz (1927) of the sudden appearance of fresh crops of cutaneous lesions after the administration of gonococcal vaccine - - a sort of Herxheimer reaction - - suggests the gonotoxic nature of the lesions. The occurrence of an endogenous conjunctivitis, a polyarthritis, and a temperature of a septic type certainly points to a profound systemic toxic-allergic disturbance.

The disease is rare; the incidence of this condition varies from 1 of 5,000 cases (Harrison,1918) to 1 in 7,500 cases (Brown and Hargreaves, 1917) of gonorrhea urethritis. It is most common in men, with a few exceptional cases in women. One case described was that of a girl four years of age.

Lee and Percival report 20,000 cases of gonorrhea treated at the Government General Hospital, Madras, and only one case of keratodermia blennorrhagica. The history of urethritis sixth months previous to the second exacerbation followed full blown. His descriptions of the lesions were typical of keratodermia blennorrhagica.

Treatment with Sulfa was not effective, perhaps due to intolerance to the 4.5 grams daily for three days or history of previous administration of sulfa.

Later six injections of T.A.B. vaccine was used in doses of 25, 50, 100, 200, 400, and 800 million units on alternate days. By the end of the time of these injections the patient could move his legs. During the third week of therapy the skin lesions disappeared. In a month the patient moved about freely, and three months later the patient was putting on weight and has remained well.

Laboratory studies revealed no gonococci on repeated examinations of smears from the lesions. The prostatic secretions showed non-specific organisms. Dark field examination was negative. Serological reaction was positive to syphilis, although no history of syphilis or clinical evidence of the disease was present.

Though the patient gave a definite history of gonorrhea urethritis, repeated examination of smears, urine, and prostatic secretions were negative for Gram-negative diplococci, but only pus cells and normal organisms found.

Epstein (1939) states that absence of gonococci does not hamper diagnosis of keratodermia blennorrhagica. Downing (1934) thought that Vidal considered keratodermia blennorrhagica to be a syphilitic mani-

festation. MacKenna (1937) in his book favored the syphilitic theory as the cause of keratodermia blennorrhagica.

If this condition can be caused by both gonococcus and syphilis there are probably other organisms capable of producing the same allergic reaction (Downing, 1934). Sherman (1939) reported three cases of keratodermia and stated that it must be considered as a microbid. In fact, this condition shows all the characteristics of a toxo-allergic reaction, et cetera. Therefore, the condition represents the combined effect of gonococci and of an allergic body reaction causing a rapid slit of the microbe. He suggested eradication of the primary focus at a therapeautic measure.

Epstein (1939) wrote an article in which he differentiated keratodermia blennorrhagica and psoriasis arthropathies. He cited 75 cases of the former and 33 cases of the latter. He did a very good job of this until the laboratory reports were presented. 27.7 percent of the patients with keratodermia gave a negative complement fixation test for gonorrhea and the gonococci could not be demonstrated by the regular laboratory methods. He did not seem to let this fact make any difference as no explanation was offered.

He suggests that gonorrheal keratosis occurs as the result of sensitization of the skin to a previous gonococcal infection. As far as treatment is concerned, he states there have been no cases of keratodermia blennorrhagica formally reported in which therapy with hyperpyrexia has failed to produce a prompt improvement if the temperature was elevated sufficiently and the elevation maintained for a long enough period. (This gave him much leeway).

These cases in which gonococci could not be found could easily fall into the diagnosis of Reiter's disease, as they likely would if found by anyone familiar with the condition.

The complement fixation test brings up another problem already suggested. Lees (1931) found the test positive in 80 percent of his cases, and stated that a negative test did not exclude the gonococcal infection. He reports 0.6 percent of false positives. Lees was in charge of all cases of gonorrheal arthritis seen in the Royal Infirmary at Edinburgh, and he reported as follows: Of the acute cases he observed four clinico-pathological types:

1. Arthralgia, with no physical signs of disease in the joint.

2. An acute synovitis with an effusion of fluid into the joint. In some of these the capsule and the periarticular structures are thickened and edematous.

3. Acute arthritis involving the synovial membrane and articular cartilage with a serofibrinous exudate into the joint. In these cases the capsule and the periarticular tissue are nearly always attacked.

4. Acute arthritis with purulent exudate involving all the structures. This type is rare.

Of the subacute and chronic cases, there are two clinico-pathological types:

1. The synovial type involving especially the knee joint, and simulating a tuberculous joint.

2. Polyarthritis involving both the synovial membrane and the articular surfaces. This type attacks the small joints more readily; adhesions form easily and deformity results.

Greval and Chowdbury ( ) described the technique and history of the complement fixation test, and gave some reasons why the test has not been applied widely as has the Wassermann reaction in syphilis:

1. A good antigen has been believed to be not easily prepared. Specially selected strains of the bacterium have been considered necessary, and special

preparations, and toxins have been preferred to the simple bacterial suspensions.

2. The reaction is not a strong one.

3. The reaction is not a constantly positive one in gonorrhea as is the Wassermann reaction in syphilis.

Topley (1933) gave the following statistical information concerning the percentage of positive complement fixation tests in various conditions:

Acute gonorrhea	48 %	positive
Subacute and chronic gonorrhea	61 %	"
Epididymitis	82 %	"
Prostatitis	80 %	"
Vesiculitis	88 %	"
Metritis	68 %	"
Salpingitis	77 %	"
Vulvo-vaginitis	50 %	"
Arthritis	82 %	"

Jones (1944) whose report was based on 304 private and 100 clinic cases found the complement fixation test useful in the management of gonorrhea only in cases where slides and cultures were negative, with a suggestive history or clinical findings, and in surgical, social, or family problems. The complement fixation

test remains positive for months after laboratory and clinical findings are negative. It cannot be used as a routine test, as there can possibly be a cross-fixation from other Neisseriae, repeated sub-infections, and innoculations of gonococci which may procrastinate the test.

Scholtz (1927) reported a case of blennorrhagic keratodermia in which there was no clinical evidence of gonorrhea of the genitourinary tract. The pathologist refused to use the complement fixation test as he had no faith in its value. There was a history of gonorrhea eight years before. The treatment used was 0.5 cc. of gonorrheal vaccine injected every three or four days in addition to local hot permanganate solution and mild salicylic ointment to the feet. The patient was fully recovered six months later. Scholtz states that the final diagnosis was held in abeyance because an important link of etiological relationship with gonorrhea could not be found. He considers the steady improvement with the therapy as confirmatory diagnostically; however, he suggests that blennorrhagic keratodermia may merely be a syndrome caused by various types of infections instead of a definite clinical entity.

Benford and Holmes (1945) reported on the influence of diagnostic methods on the gonorrhea rate in the Army Air Forces. They concluded that when positive microscopic findings cannot be obtained in suspected gonorrheal urethritis the diagnosis of non-venereal infection is not justified until three repeated cultures for the gonococcus are negative and three microscopic examinations on successive days are negative. By this method their percentage of gonorrhea cases rose almost 16 percent.

Since these patients are as a whole treated with Penicillin and Sulfa before extensive laboratory work is carried out this may explain a few cases of Reiter's disease. Cohn and Kornblitt (1945) worked on the problem of resistant gonorrheal infection and associated complications in the male following Penicillin and Sulfa treatment. It is interesting to note the discrepancy between the rapid reversal of bacteriologic findings from positive to negative and the much more gradual subsidence of acute symptoms and persistence of clinical signs. One condition responsible for relapses after apparently successful cure is the presence of "inaccessible foci of infection" in the prostate. These walled-off foci of infection may not be reached

by the action of Penicillin. Such foci may conceivably break through subsequently and produce a recurrence.

Coudray (1947) did the same sort of thing while in the Army venereal section for four and one half years, and stated that subacute and chronic residual prostatitis after chemotherapy in acute gonorrhea is of very widespread occurance, and gives rise to physical signs as long as it remains untreated. "If the following are accepted as the criteria of cure in all cases of urethritis then I have found that after chemotherapy in every case of acute gonococcal urethritis return to normal is disappointingly infrequent. The departure from the normality which occurs most often after treatment is the residual prostatitis which fails to respond to further chemotherapy.

1. A persistently clear urine.
2. A persistently dry urethra.
3. A prostate which feels normal on palpation per rectum.
4. A prostatic fluid which is macroscopically clear, and which when fixed and stained shows microscopically no pus cells, and at most only a few (not more than 2 or 3 in any field)."

So much for the gonorrheal link-up with Reiter's disease, and let us concern ourselves with the most likely etiological factor - - - allergy.

Allergy the Etiology of Reiter's Disease

Allergy as the cause of an acute flare-up of Reiter's syndrome has been given much attention. Many of the authors have shown an eosinophilia of around 4-7 percent in cases in which these were looked for (Bardhan, 1947). Some others have shown a response to Benadryl treatment (Henry, 1947). Beiglboch (1944) believed the syndrome due to an allergic reaction to Flexner bacillus. Duke-Elder (1945) agreed that bacterial products liberated from some focus of infection in an immune but allergic patient was the cause. Gersh (1945), Rosenblum (1945), Forbes (1946), Junghans (1918), Fruhwald (1927), and others have considered this allergic response in Reiter's syndrome and other diseases.

The example of erythema nodosum being the result of a variety of infective processes may be mentioned as a possible parallel to the incidence of Reiter's disease following non-specific infections.

Denfield (1946) reported on his experiences of polyarthritis as a complication of a condition called

"basal cystitis", which were observed in southern England in 1943. The main symptoms of this condition were hematuria occuring at the end of micturition, pyrexia, and toxemia. None of the cases seen had been in the Tropics and there was no history of dysentery or venereal infection. The urine contained many pus cells, but was sterile to ordinary methods of culture. Cystoscopy revealed an edematous and hyperemic trigone. The macroscopic terminal hematuria lasted for three to four days, and was followed in 30 - 40 percent of the cases by a polyarthritis and sterile conjunctivitis at about the tenth day of the disease. The joints involved were chiefly the knees, and occasionally the ankles and the elbows. Cultures of the aspirated fluid was sterile. This condition was thought to be due to a virus.

Again, during his stay in northern Nigeria from 1944 to 1946, Denfield very commonly encountered this syndrome of polyarthritis and sterile conjunctivits among the native troops in the acute stages of gonococcal urethritis. In no instance did it appear during the first attack of gonorrhea and invariably a history of four or five previous attacks was obtained. Its appearance coincided with the onset of the ureth-

ritis, which was shown to be gonococcal in origin. Sometimes one would see a sterile conjunctivitis without polyarthritis in the acute stage. Further attacks of gonorrhea in the patients who had previously exhibited this syndrome resulted in an even more intense associated polyarthritis and conjunctivitis during the acute stage of the urethritis. In view of the appearance of this syndrome after many known attacks of gonorrhea, and the increase in the severity during subsequent attacks, it was considered to be an allergic manifestation of the gonococcal organism. Obviously thenmany conditions can give rise to this combination of sterile conjunctivitis and polyarthritis. It occurs as a complication of bacillary dysentery, non-specific urethritis, "basal cystitis", and gonococcal urethritis. (In the last three conditions there is an infection of the lower urinary tract.)

Some authors still state that food allergy may be an important factor in the rheumatic state. Pottenger (1938) concluded from a study of 150 consecutive patients with arthritis that 94 percent had gastrointestinal symptoms that were considered due to food allergy. Trout and Vrtiak (1939) studied 359 patients with rheumatic heart disease, atrophic or hypertrophic

arthritis, and 100 non-rheumatic patients and concluded that the rhematic group showed from two to three times more allergy as the controls.

A small group of allergic patients with intermittent attacks resembling subacute rheumatoid arthritis have demonstrated specific food excitants. The evolution of the attacks resembled those of intermittent hydrarthrosis, but multiple small joints were involved. Often just one hand or foot was affected. Sometimes the reaction occured in more than one extremity, and at times one or two large joints became inflamed either simultaneously or independently. The local picture was of swelling, redness, pain, and tenderness. The attacks would last from two days to a week, rarely longer. In some, the joints were objectively normal between attacks; in others there were low-grade arthritic changes. Vaughn (1942) in his study of 1,000 consecutive adults with allergic conditions (asthma, hay fever, urticaria, angioneurotic edema, migraine, gastrointestinal allergy, and allergic dermatitis) established how 2.7 percent of his patients had rheumatic flare-ups from certain foods, even though they were not able to definitely designate the causative food. The rheumatic flare-ups were relieved with

improvement of the allergic state.

Solis-Cohen (1914) reported 27 cases resembling the above condition, to which he gave the term "angio-neural arthrosis". However, his cases varied in only minor details: 40 percent of his cases were febrile, and many were effected by general erythemas and one by vesicles and bullae. Many of his cases lasted for over three weeks. 70 percent of his cases had poly-articular attacks.

Kahlmeter (1939) reported 54 patients with similar symptoms and findings of his 5,000 rheumatic patients, in which he believed allergy to be the causative factor. He used the term "allergic rheumatism". He further noted occassional fleeting fever with the attacks and often noted erysipeloid rashes.

Hench and Rosenberg (1941) described 34 patients with recurring joint disease without articular residue which they termed "palindromic or recurrent rheumatism". Their cases represent a collection seen in the Mayo Clinic since 1928. Their cases did not have fever, nor were any skin rashes noted. The majority of their cases were monarticular. They discussed in their paper the hypothesis of allergy as the etiological factor. Points in favor of this theory include:

1. Food allergy was suspected as the cause of the disease by 16 of their patients.

2. The suggestive nature of the attacks, their sudden onset, short duration, and rapid disappearance without residues.

3. The presence of allergic reactions in 17 relatives of 10 patients.

4. The presence of allergic reactions of the orthodox type in 18 (53 percent) of the patients; however in only two of these 18 cases did the allergic reaction ever coincide with the arthritis and then only occasionally.

5. The presence in four cases of positive skin reaction to certain foods, these usually not the foods which the patient suspected as being the cause of the disease.

Points against the allergic hypothesis include:

1. Absence of familial allergy in 70 percent of their cases.

2. Absence of any orthodox allergic reactions in 47 percent of the cases.

3. The presence of essentially negative skin reactions in 80 percent of the cases tested.

4. Inability to provoke attacks by giving, or to

prevent attacks by withholding the foods incriminated either by the patient or by skin tests.

5. The failure of epinephrine to produce a therapeutic effect (one possible exception).

6. The absence of provocative effect of large doses of histamine given intravenously.

7. Negative results with cold allergy tests.

8. Unimpressive therapeutic effects of histamine desensitization or histaminase (oral).

9. Absence of eosinophilia in blood or tissue during the attacks.

10. The pparent dissimalarity in the pathologic reactions in these cases and those of orthodox allergy.

Vaughan (1942) differed in some of these points. "The absence of familial allergy in 70 percent of the cases is not conclusive, because anamnesis is often fallacious, minor allergy in other members of the family is often overlooked, the inheritance may skip generations, and allergists are not yet generally agreed concerning the inheritance of the disease. The therapeutic failure of epinephrine, histamine, and histaminase can be paralleled in the more classical allergic diseases. The absence of eosinophilia in blood or locally is not conclusive. The apparent dissimilarity in the pathol-

ogic reactions observed from those of orthodox allergy can be countered by the recollection of the large and small joint changes observed in serum disease. Absence of orthodox allergic skin reactions in 47 percent, presence of essentially negative skin reactions in 80 percent, and inability to provoke attacks by giving or to prevent attacks by withholding foods incriminated is first of the inaccuracy and fallibility of skin reactions to foods and second of the crazy pattern of the allergic responses, particularly in that proved allergins may often be eaten at times with impunity. The degree of sensitization to a given food may vary from time to time, and the manner of the clinical response to a single food may change almost over-night, sometimes appearing as migraine, at other times as a gastrointestinal manifestation or urticaria." He presented a case to illustrate his point.

As can be seen by the above discussion, there is much work to be done in the field of allergy and its relation to arthritic conditions. Further, observation will be required to show whether or not "palindromic rheumatism", "angioneural arthrosis", and allergic rheumatism are identical or distinct, and the relation that Reiter's syndrome plays in the field of allergy.

Since the similarity of Reiter's disease and "palindromic rheumatism" have been mentioned, it may be well to mention the treatments tried in the cases of "palindromic rheumatism". Hench and Rosenberg (1941) stated that prior to admission at the Mayo Clinic most of their patients had had foci of infection removed, and had received vaccines, bee venom, and various medicines without relief, in addition to heat and analgesics for symptomatic relief. Treatments which they tried, most of which were ineffective were: administration of epinephrine, ephedrine, benzedrine, ergotamine tartrate, histaminase, typhoid vaccine, and autogenous vaccines made from infected foci, removal of foci, low purine diets, diets free of suspected foods, and histamine desensitization. One physician claimed to have stopped his attacks by taking 100 grains of calcium gluconate daily. Another patient adopted a baby, quit worrying about herself, and was "cured".

Kahlmeter (1939) claimed to have cured a few patients by repeated injections of detopine soufie (sodium keratinate) the action of which is similar to that of a foreign protein.

Hench and Rosenberg performed biopsies on only two

joints during arthritis, one tendon during para-arthritis, one knee and one nodule between attacks. During attacks an acute or subacute inflammation was found to occur in the synovial membrane and capsule, or in tendon sheaths. Many leukocytes, including many neutrophils, appear in the interstitial tissue, and about small blood vessels. There is a fibrinopurulent exudate in joint tissues and cavity. As an attack subsides there are fewer neutrophils, more lymphocytes, plasma cells and proliferating fibroblasts. The gross and histologic examination of one knee between attacks revealed no abnormality whatever, although it had been involved in at least 15 attacks. This observation, amply supported by much clinical data, seems to indicate that between attacks the articular tissues recover completely. Direct examination of three joints coupled with clinical and roentgenographic studies indicates that there is no formation of pannus, destruction of cartilage or persisting inflammation. In the sections of affected tissue studied there were no large follicle-like collections of lymphocytes (supposedly "characteristic" of rheumatoid arthritis), no urates, and no eosinophiles.

Solis-Cohen (1914) and Kahlmeter (1939) did not

report pathologic data on their cases. The former suspected the presence of angioneurotic edema of joints and assumed that there was present a transudate which was from an autonomic ataxia or angioneurosis, "not a true inflammation, not an arthritis, but an arthrosis". Kahlmeter assumed that there was present a serous effusion from an allergic reaction.

Before leaving the subject of etiology, the possibility of a new organism not yet written up as pathogenic in man must be considered, since new organisms are continually being isolated. Barnes, Cherry, and Myers (1945) isolated a Salmonella of Avian variety from a rectal swab specimen taken from an asymptomatic food handler who denied having any previous gastrointestinal illness. Yet this organism was the causitive organism for a mild epidemic of diarrhea.

Small colony forms are also coming of interest in clinical material. Morton and Shoemaker (1945) studied the bacterial variations and detection of atypical Neisseria gonorrhea. Youmans, Williston, and Simon (1945) produced small colon variants of Staphylococcus aureus by action of Penicillin, as did also Schnitzer, Caurogni, and Buch in 1943.

The hormonal production of arthritis of the type found in Reiter's disease has been produced experimentally by Selye, Sylvester, Hall, and Lebland (1944). They gave desoxycorticosterone acetate in overdosage to rats causing a polyarthritis which histologically resembled that seen in acute rheumatic fever. On the basis of the similarity, they indicated that the adrenal cortex may play an important role in the pathogenesis of arthritic conditions. Their work, however, has not interested many in this field.

TREATMENT

Many substances have been used in the treatment of Reiter's disease, but the results from all are rather discouraging.

Reiter (1916) used aspirin and neoarsphenamine. Macfie (1917) used bichloride of mercury injections. Sulfathiazole, sulfadiazine, intramuscular Penicillin, sodium salicylate, Colchicine (Rosenblum, 1945) have all been tried. Fever seems to give the most relief. Levine's (1945) patient had a reaction to Sulfadiazine and the fever of this reaction caused the symptoms to subside. Strachstein (1945) had fair results with intragluteal injections of 10 cc of milk boiled for ten minutes. This produced a chill within four and a half hours, followed by a temperature usually of 105°F. The temperature will usually remain at about 101° through the night. This was enough to clear up the arthritis in his patients but six days later a shoulder become involved, and another 6 cc. of milk was used. No re-currances were reported then in eight months.

Newton (1947) recommends diathermy and Spa treatment. Findlay, Henderson, Willcox and others used gold salts with fair results. Beiglbach (1944) cured his

case with Arthigon, 0.1 to 0.2 cc. and increased dosage.

The most dramatic was the case of Henry (1947) who gave his patient 50 mgm. of Benadryl four times each day, and within twenty-four hours after the first dose the patient's temperature returned to normal and did not recur during his stay in the hospital. He felt much improved and did not experience any pain on passive motion of affected joints. Within 72 hours the papular rash had disappeared from the glans penis and the soles of the feet. The patient tried walking and experienced only moderate discomfort in the affected joints in doing so. His condition steadily improved and he was discharged at the end of ten days. The author admitted that since spontaneous remissions occur in three or four months that treatment may have been coincidental, since there was a three months elapse of time. The same can apply to most of the other cases where good results have been obtained.

CONCLUSION

It is at least possible that Reiter's disease may occur without one of the three "essential" inflammatory symptoms, but until the causal agent is discovered this is likely to remain a speculation. One might, indeed, go further and suggest that perhaps a single symptom may at times represent an incomplete form of the disease, thus bringing up the possible relationship between Reiter's disease, "non-specific urethritis", keratoconjunctivitis of unknown etiology, "palindromic rheumatism", and others.

The main importance of an awareness of the syndrome lies in its distinction from chronic gonorrhea, thereby altering the prognosis and avoiding hectic treatment and the stigma of a venereal disease. It is possible that Reiter's disease occurs much more commonly than is recognized. It is considered that the symptom-complex herein described is pathognomonic, and usually should be unmistakable.

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