

The History of Bacteriologic Concepts of Rheumatic Fever and Rheumatoid Arthritis

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Objectives Review of the development of etiologic and pathogenetic concepts of rheumatic fever (RF) and rheumatoid arthritis (RA) from the beginning of clinical bacteriology to the discovery of antibiotics.

Method Analysis of English and German language publications pertaining to bacteriology and “rheumatism” between the 1870s and 1940s.

Results Early in the 20th century there was a widely held belief that a microbial cause would eventually be found for most diseases. This encouraged pursuit of the intermittent findings of positive blood and synovial fluid cultures in cases of RF and RA. Development of a streptococcal agglutination test supported the erroneous belief that RA is a streptococcal infection, while the simultaneous development of other immunologic tests for streptococci suggested that a hemolytic streptococcus was etiologic in RF. Table 1 provides a chronology of major events supporting and retarding resolutions.

Conclusions Much of the conflicting data and inferences regarding the etiology of RF and RA can be attributed to the absence or inadequacy of controls in observations of clinical cohorts and laboratory experiments.

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At the dawn of bacteriology, in the 1870s, there was uncertainty among physicians whether acute rheumatism (rheumatic fever, RF) and chronic rheumatism (rheumatoid arthritis, RA) were separate diseases or that there was 1 “rheumatism” whose manifestations differed due to influences of age, heredity, and environment. In the decade 1885 to 1895 the possibility of a bacterial etiology of both diseases began to be considered. This article explores the parallel paths, into the 1940s, whereby the bacterial cause of RF was proved and that of RA was disproved. The scene is set with some prebacteriologic opinions.

The Prebacteriologic History

In 1668 the London physician, Thomas Sydenham (1624-1689), attempted to differentiate between gout, febrile, and nonfebrile rheumatism (1). He found that febrile rheumatism chiefly attacks the young and vigorous

and begins with chills and fever. One or 2 days later a migratory polyarthritis begins that persists longer than the fever. This seems to describe RF. However, he also described rheumatism that may make the patient “a cripple to the day of his death and wholly lose the use of his limbs; while the knuckles of his fingers shall become knotty and protuberant.” Unfortunately Sydenham leaves us in doubt whether he believed that RA is a chronic result of RF, or a separate disease. Nevertheless, he was convinced that this “rheumatism” is not a form of gout—a major advance that took 2 centuries to be accepted.

Although the term “rheumatic fever” was introduced in 1806 (2), “acute rheumatism” continued to be the preferred designation, leaving the disease in a spectrum with “chronic rheumatism” meaning RA and/or osteoarthritis. William Balfour, an Edinburgh physician, wrote in 1815: “*Chronic* is often the consequence of *acute* rheumatism (3). Nothing, therefore, can be more evident than that what constitutes the proximate cause of the latter must also form that of the former. For the only difference betwixt the 2 *species* of the disease consists is this, that the *acute* is accompanied with fever, whereas the *chronic* is free, or nearly free, from it”. Balfour conceded that he was speculating that clinical differences are due to a “phlogistic diathesis [predisposition] of the blood” that quantita-

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tively or qualitatively differs in generating fever and affecting the tissues.

Etiologic hypotheses for RF preceded explanations for the cause of RA. Sir James Paget (1814-1899, London) speculated in 1853 that, except for some congenital conditions, all diseases that manifest their symptoms symmetrically, such as “the deformities of chronic rheumatism, must be blood-born” (4). Unfortunately, most “of the morbid conditions of the blood consist in changes from the discovery of which the acutest chemistry seems as yet far distant . . . In the cases of diseases produced by a demonstrable virus [ie, pathogen] we have all the evidence that can be necessary to prove the principle that a general disease of the blood can be the cause of a local inflammation in 1 or more circumscribed portions of a tissue . . . [W]hy for example the skin is the normal seat of inflammation in small-pox, the joints in rheumatism, and so on, I believe we must say that we are on this point . . . ignorant.”

A blood-borne cause for RF was already hypothesized in mid-century, based on either analogy or speculation. Although the relationship between uric acid and gout still was circumstantial, if uric acid causes gout, lactic acid, another metabolic product, might induce acute rheumatism. According to Robert B. Todd (1809-1860, London), the normal concentration of lactic acid in the body results from the balance of its production and excretion (5). “As lactic acid is imperfectly excreted through its natural channel in consequence of the influence of cold checking perspiration, and is too freely developed in the alimentary canal, it should accumulate in the blood exposure . . .” and produce rheumatism. The supporting evidence was that “ill-clad and badly fed children of the poor are the most numerous victims of rheumatism. Hard work, exposure to cold and wet, bad food are strongly contrasted as causes of the rheumatic diathesis, with the ease, comfort and excess which give rise to the analogous one of gout.” Thus, different extrinsic influences on the same predilection result in different diseases.

Austin Flint (1812-1886), the most distinguished American internist of the time, discounted the belief that the skin has a pathogenetic role in RF, and cold exposure probably “acts only as an exciting cause” (6). “The disease involves a rheumatic diathesis which may be congenital and inherited, or it may be acquired.” Evidence for this is “the occurrence of the disease in early life, and by its recurrence more or less frequently in the majority of the persons who are once attacked by it. Statistics establish conclusively the hereditary transmission of the disease. It is a matter of common observation that the disease prevails among different members of certain families.” Flint concluded (1881): “It is quite certain that rheumatoid arthritis has no relation with gout, and it is probable that it differs in its nature from rheumatism . . . The theory that rheumatoid arthritis is of nervous origin is not irrational.” However, Flint neither advocated this hypothesis forcefully nor advanced another.

Armand Trousseau (1801-1867), professor of therapeutics in Paris, pointed out that scarlatinal rheumatism “is an exceedingly common complication of scarlatina” (Table 1) (7). The presence of a rheumatic diathesis in patients who contract scarlatina provides “an explanation of the development of pleurisy and pericarditis: it assists us in understanding why these affections are as frequent as they are, and why it happens that endocarditis occurs.” Trousseau recognized that there is a common factor between the causes of scarlet fever and RF, but writing before the advent of bacteriology, he speculated that this was an inherited susceptibility. Scarlatinal rheumatism as seen in an English “fever hospital” in 1894 was not “exceedingly common,” but was sufficient to impress the investigator: 3.87% of 3066 cases of scarlatina, the association increasing with age (8).

METHODS

The literature that has been reviewed and analyzed in this article was originally published between 1668 and 1944. It has been obtained from 11 books (5 pre-1900), and 14 American, 6 British, 5 German, 1 Italian, and 1 Swedish journals.

RESULTS

The Early Bacteriology of Rheumatic Fever

One of the first observations that was potentially useful for unraveling the pathogenesis of RF was made in 1880 by J.K. Fowler (9). This London physician routinely inquired in cases of acute rheumatism whether tonsillitis or “catarrh of the pharynx” had preceded the attack. He estimated that the association existed in at least 80% of cases of RF, but no cultures were made.

In 1885 Alfred Mantle, as a young house officer in London, confirmed the foregoing observation (10). When he entered a village practice in northern England, he continued to make observations about RF and “the frequency of rheumatic symptoms in scarlatina.” Mantle then wrote a doctoral thesis on the hypothesis “that the throat, joints, and serous membranes become affected during a bacterial invasion” (11). The thesis was accepted, although he later wrote that “my views did not gain acceptance by the examiners, and 1 of them somewhat discouraged my enthusiasm.”

In 1887 Mantle presented a paper on his findings at the meeting of the British Medical Association, an abstract of which was published (12). Although he failed to cite them, Mantle clinically was confirming the observations of Trousseau and of Fowler. Mantle is quoted to have recovered bacteria from 7 synovial fluids, and blood cultures of 26 patients with acute, prodromal, or subacute RF, as well as from unspecified sites in several cases of RA. He consistently found both a Gram-positive diplococcus and a bacillus. He believed that “RA was only a manifestation of the one disease, rheumatism, for a careful history

Year	First Author	Location	Ref.	Observation
1873	Trousseau	Paris	7	Scarlatina and RF have a cause in common
1883	Petrone	Bologna	28	Gonorrheal arthritis has a specific bacterial cause
1885	Mantle	London	10	RF and RA are one disease, caused by "bacterial invasion"
1893	Schüller	Berlin	30	RA is a specific disease caused by a specific bacillus
1895	Chvostek	Vienna	14	Synovial fluid in RF is sterile and not bactericidal
1896	Bannatyne	Bath	32	RA is caused by a different bacterium than Schüller's
1899–01	Poynton	London	16, 17	RF is caused by a streptococcus
1901	Painter	Boston	34	RA does not have a bacterial cause
1902	Meyer	Berlin	19	Blood and synovial fluid in RF are sterile; streptococci from tonsils resemble streptococci from scarlatina and are the probable cause of RF
1902	Pribram	Prague	35	Rejects evidence for the bacterial etiology of RA
1903	Beaton	London	20	RF is caused by "Micrococcus rheumaticus"
1903	Schottmüller	Hamburg	24	Based on its growth on blood agar discovers <i>Streptococcus viridans</i>
1903	Philipp	Prague	26	Blood and synovial fluid in RF and RA are sterile aerobically and anaerobically
1904	Cole	Baltimore	27	There is no specific <i>S. rheumaticus</i>
1904	Goldthwait	Boston	40	RA is a reaction to infections by various bacteria; coins term "infectious arthritis"
1912–13	Billings	Chicago	45, 47	RA results from bacterial foci located anywhere in the body
1927	Cecil	New York	50	Both <i>S. hemolyticus</i> and <i>S. viridans</i> cause RA
1928	Lancefield	New York	71–73	Identifies serologic types of streptococci
1929	Cecil	New York	58	RF results from allergy to <i>S. viridans</i>
1931	Cecil	New York	52	RA is caused by a specific streptococcus
1931, 1933	Nicholls	New York	53	Streptococcal agglutination test "proves" streptococcal etiology of RA
1932	Lichtman	New York	60	Positive blood cultures in RF and RA statistically indicate contamination
1932	Dawson	New York	64–66	Questions reliability of Cecil's culture techniques; agglutination test does not require a particular strain of streptococcus; RA is usually caused by <i>S. hemolyticus</i>
1932	Todd	New York	78	Discovers antistreptolysins
1932	Coburn	New York	69	Initiation of RF requires exposure to <i>S. hemolyticus</i> , not necessarily with symptoms
1934	Myers	Boston	80	ASO titer is more likely to be elevated in RF than in RA
1934	Archer	New York	61	Streptococci in blood and joint cultures in RF and RA are contaminants
1935	Wilson	New York	83, 84	Doubts role of <i>S. hemolyticus</i> in etiology, of RF; still in 1961
1936	Coburn	New York	81	Identifies asymptomatic interval between infection by <i>S. hemolyticus</i> and onset of symptoms
1936	Dawson	New York	87	Continues to advocate that RF and RA are parts of the same disease spectrum
1939	Coburn	New York	92	Sulfanilamide prevents RF but does not affect established RF
1939	Coggeshall	Boston	94	Sulfanilamide cures gonococcal arthritis but does not affect RA
1944	Boland	Hot Springs, AK	95	Although penicillin cures streptococcal infections, it does not affect RA
1946	Wallis	Philadelphia	89	Particulate agglutination is a nonspecific characteristic of most RA sera

generally disclosed rheumatic pains or fever having been suffered from when young, or an inheritance of rheumatism . . . One thing was certain, that it was not the organisms in that or any other disease which directly caused the symptoms, but the chemical products the results of their action on the tissues." Mantle speculated that the toxic product might be lactic acid, which would relate his bacterial hypothesis to an earlier hypothesis of a lactic acid metabolic pathogenesis (5). Pieter K. Pel (1852-1919), professor of medicine in Amsterdam, was quoted in the same year to have stated: "It [acute rheumatism] only wants the discovery of the specific micro-organic cause of the disease in the inflamed serous membranes to render the present presumption of its specific origin a certainty" (13).

Franz Chvostek, Jr. (1864-1944, Vienna, 1895) criticized the hypothesis that etiologic conclusions could be drawn from urine cultures except in a few diseases, such as tuberculosis (14). Chvostek found synovial fluid in RF always to be sterile. He performed animal experiments in which he demonstrated that joint cultures became positive soon after death, whereby he discredited bacteriologic autopsy findings of cases of RF. He speculated that bacterial toxins make blood vessels more permeable to bacteria and that this effect is related to the virulence of the strain. He found that synovial fluid is not bactericidal, but expressed surprise that he obtained no growth from his patients' joint fluid. Chvostek concluded that bacteria exert no direct effect on joints, but that the arthritis of RF results from bacterial exotoxins and from toxins generated in various tissues from bacterial action. He postulated that the disease may result from more than 1 species of as yet unidentified bacteria.

Alberto Riva (1844-1916, Parma) considered that inability to culture a pathogen from blood or synovial fluid, such as Chvostek had reported, might be attributable to lack of an appropriate culture medium (15). He compared results using a standard liquid medium with a medium to which he added an extract of horse synovium. In all of 8 synovial fluid and 3 blood specimens from cases of acute RF, growth was obtained in the latter medium but in no instance with the former. A large spore-forming bacillus and a small motile bacillus were found in each experiment. Because of the consistency of his findings Riva concluded that he had discovered the pathogen(s) of RF, rather than contaminants.

Most influential of the early bacteriologic investigations of RF was the work of London collaborators Frederick J. Poynton (1869-1943), pediatrician, and Alexander Paine, bacteriologist (16). After their initial investigation was concluded, they became aware of Mantle's paper and gave him credit for having introduced the concept of a bacterial etiology of RF (17). The fundamental etiologic discussion at that time was, whatever the pathogenic microbe(s) might be, is it pathogenic by producing a toxin from a localized site or by directly invading predisposed tissues?

Their investigation, begun in 1899, was based on 8 cases of RF, in 3 of whom blood cultures were positive (18). In 5 autopsies positive cultures of tissues did not correlate with the interval from death to examination. Believed to be most important were the finding of a consistent microbe, considered a streptococcus, and that intravenous injection of this organism into rabbits caused pericardial and heart valve disease, and in some also arthritis. In a second article Poynton and Paine added to their evidence for the etiologic agent of RF by detecting their diplococcus histologically in subcutaneous rheumatic nodules from 2 cases of RF and by culturing this organism from 1 (18). Intravenous infection of a rabbit with this diplococcus resulted in lesions suggestive of RF. Therefore they concluded ". . . that this investigation lends strong support to the contention that this diplococcus is a [not the] cause of rheumatic fever."

Soon after the publications of Poynton and Paine, Fritz Meyer, a junior physician in the University of Berlin clinic, undertook a larger bacteriologic investigation of RF (19). In over 30 cases of acute RF he cultured blood and synovial fluid, all of which remained sterile—an important difference from earlier findings. "It was just these negative findings that led to the theory of toxins and their effects as etiologic." To increase the possibility of obtaining the actual pathogen, he cultured biopsies of tonsils instead of performing throat cultures. Streptococci were usually recovered and he deemed it important that they morphologically resembled the streptococci in throat cultures from cases of scarlatina. He performed numerous experiments injecting rabbits with strains of streptococci from his tonsillar biopsies and from acute diseases, such as erysipelas, as well as control experiments with staphylococci, pneumococci, and diphtheria bacillus. Meyer reached the 3 following prescient conclusions: (1) In RF we are dealing with a particular type of streptococcal infection; (2) There are bacteria with a predilection to cause disease in human organs without being subsequently detectable in these organs by available methods; and (3) Animal experiments have demonstrated that clinical differences between RF and septicemia are due to differences in the virulence of various streptococci.

In 1903 R.M. Beaton and Ainley Walker (London) concurred that the microbe they cultured from cases of RF was the same as had been described by Poynton and Paine, and by Meyer (20). Because of their belief in its specificity, they called this bacterium *Micrococcus rheumaticus*. They performed metabolic studies comparing a strain from a case of acute RF, a case of chorea, and a case of septicemia. Their culture media included "blood serum." According to their second note, ". . . the micrococcus has a hemolytic action on red blood corpuscles greater and more rapid than that of any other streptococcus we have as yet examined—a fact of interest in relation to the very rapid and considerable anemia of rheumatic fever" (21). "We conclude that the bacterial specificity of acute

rheumatism has been satisfactorily established. Its toxic specificity remains to be investigated” (20).

J.M. Beattie (1904, Edinburgh) repeated the study of Beaton and Walker using a strain obtained from synovium and another contributed by Paine, concluding that “this micrococcus rheumaticus is a special organism, and is causal in acute rheumatism” (22). In 1908 Beattie reported further rabbit experiments that appeared to confirm the rheumatogenic specificity of this variety of streptococcus (23). He emphasized, as had previous investigators, that the most important difference between other streptococci and the rheumatogenic strain was that the latter did not cause purulent effusions or lesions.

In 1903 Hugo Schottmüller (1867-1936, Hamburg) reported that streptococci could be meaningfully divided into hemolytic and nonhemolytic types by growth on blood agar (24). Streptococci from cases of scarlatina and erysipelas caused identical hemolysis, while *Streptococcus mitior* never was recovered from severe infections and did not cause blood agar to lose color, but rather induced a greenish hue. Therefore he proposed the alternative name “viridans.” Cultures of blood and effusions of even severe cases of acute rheumatism remained sterile. Schottmüller anticipated that the distinction between more virulent hemolytic strains and less virulent “green” strains would be important for the development of vaccine therapies. His discovery, as shown for example in “The Bacteriology of Acute Rheumatism,” an American review in 1908, was generally ignored (25).

One of the most searching bacteriologic studies of the early period was performed in Prague during 1899 to 1901 (26). Blood cultures were obtained from 27 cases of RF and 4 of RA, as well as synovial fluid cultures from 6 of the former and 2 of the latter. Both aerobic and anaerobic cultures were made and aliquots from 8 RF and 1 RA patient culture were injected into guinea pigs, dogs, or monkeys. No growth was obtained in any experiment. Nevertheless, RF was considered infectious, although no etiologic agent was suggested.

Soon thereafter, Rufus I. Cole (1872-1966, Baltimore) obtained nonhemolytic streptococci from blood, peritoneal fluid, or lymph nodes of 7 patients with various diseases (27). Cultures of these strains, when injected into rabbits, all tended to localize in joints, with severity of the disease being dose related. Since the responses of the rabbits were unrelated to the source of the strains, Cole concluded that the existence of “*Streptococcus rheumaticus*” was disproved. This gave experimental support to the theory, subsequently popularized by Frank Billings (1854-1932, Chicago), that a chronic focal infection could cause a systemic disease (see below).

Bacteriology of Rheumatoid Arthritis

The inconsistent finding of bacteria in rheumatoid synovial fluid was explained mainly by analogy with gonococcal arthritis. Gonococci had been identified morphologi-

cally in inflamed knees of patients who had gonorrhea in 1883 (28). However, the first successful culture of gonococci from synovial fluid was not achieved until 1894 and continued to be difficult (29). The realization that cultures of synovial fluid in a disease with a proven bacterial cause, such as gonorrhea, are frequently negative gave support to the hypothesis that, despite the inconsistent and variable recovery of bacteria from rheumatoid joints, this disease also had a bacterial etiology. The alternative explanation for sterile synovial fluid cultures was that the disease was not caused by direct bacterial invasion but by exotoxins that emanated from 1 or more remote foci.

In the 1890s the question whether RF and RA are somewhat different clinical manifestations of the same disease was in dispute, as it was 40 years later. In regard to RA, microbiological research was initiated by Max Schüller (1843-1907, Berlin), a distinguished surgeon who throughout his career was interested in microbiology (30). Schüller’s bacteriologic investigation of RA derived from a study of the histopathology of synovium. He wrote in 1893 (paraphrased): “[It] is most likely from the examinations I have made so far that chronic joint inflammation with villous hyperplasia that up to now has been considered rheumatic, is caused by the bacilli I have demonstrated. If so, then among the first questions to consider is whether it is still justified to include these joint inflammations with acute rheumatic fever. Since bacteriologic examinations in acute rheumatic fever usually have found pus cocci by culture, a genetic relationship [with RA] must be denied . . . In my opinion RA constitutes a special group of joint diseases . . . that are histologically as well as genetically not justified to be associated with RF, or some cases that have erroneously been considered gout. Preceding acute RF only predisposes somewhat to other joint inflammations—as for example that caused by gonorrhea.”

In 1905 Schüller stated: “According to my observations of numerous (several hundred) individual cases, only those joint diseases that manifest hypertrophic synovia and ankylosis that are caused by the dumb-bell shaped bacillus are counted as the polyarthritis chronica villosa I have defined (31). There are some cases having the identical criteria in which, however, by palpation in some, in some roentgenologically, coarser alterations are demonstrated on the cartilaginous margins and surfaces of joints. According to my experience up to now, none of these belong to arthritis deformans (osteoarthritis deformans), but are end stage syphilitic arthropathies on which the villous process (caused by the dumb-bell shaped bacilli) has developed.”

Gilbert A. Bannatyne (1867-1960), a physician at England’s rheumatic diseases center in Bath, and Arthur S. Wohlmann began in 1893 to search for the cause of RA (32). They reported their findings in 1896. “The idea of an organism as a causative factor in any one of the group of “rheumatic” diseases seemed somewhat wild and improbable.” However, the epidemiologic studies of News-

holme (Arthur Newsholme, 1856-1943) (33) “. . . have at least accustomed one to the idea that acute rheumatism may probably prove to be an acute specific disease caused by a definite pathogenic microbe. It was the close analogy of rheumatoid arthritis to tuberculosis that first suggested to our minds the possibility of a micro-organism as the cause of the disease . . . How these micro-organisms gain access to the blood is not at present definitely known, but they probably do so through some chronic catarrh of the gastro-intestinal or genito-urinary systems . . . or tonsils.”

Bannatyne and Wohlmann aspirated fluid from an (unspecified) joint of 25 cases of RA and in 24 the very same microorganism was obtained, usually in enormous numbers. No attempt at blood culturing is mentioned and no synovial tissue was examined. Eighteen specimens were sent to F.R. Blaxall, a bacteriologist in London, for analysis. He found 1 small aerobic microbe with “two bright ends and an intermediate part much less obvious.” It stained best with methylene blue, but was difficult to grow. “The only points of resemblance are the polar staining and the easy discoloration. It therefore appears to be indisputable that the organism of Schüller is not that which was discovered by Bannatyne and Wohlmann.” No further research was published.

Charles F. Painter, a Boston surgeon, soon attempted to confirm Bannatyne’s findings (34). He cultured synovial fluid from 8 cases of RA “following the technique exactly as described by the writers,” but obtained no growth. Subsequently he concluded that his pathologic findings on synovial tissue from cases of RA substantiate that they do not have an infectious cause.

In his 1902 monograph on chronic arthritides, Alfred Pribram (1841-1912, Prague) reviewed the publications of Schüller and Bannatyne (35). “Schüller’s findings as well as those of Bannatyne, Blaxall and Wohlmann in their clarity leave nothing to be desired. We would ascribe the fundamental cause of rheumatoid arthritis to either of them if one would concede the discovery to the other. Unfortunately the experiments that we have conducted on joint contents from several cases of chronic rheumatic arthritis, both with Schüller’s simpler as well as Bannatyne’s more complicated method, have given negative results, so that the question, as near as it appears to its solution, remains unresolved at present.” Schüller (1905) attributed Pribram’s failure to confirm his bacteriologic findings primarily to having cultured synovial fluid rather than biopsies of synovial tissue (31).

In 1905 Roades Fayerweather, a junior orthopedic surgeon at the Johns Hopkins Hospital, reviewed the bacteriologic reports pertaining to RA and added his own experience (36). Synovial fluid cultures were sterile in 3 cases of RA, but growth was obtained from 2 cases of RA, 1 of ankylosing spondylitis (called RA) and 1 of RF. According to the descriptions of the microbes, the organism obtained from 1 of the RA cases differed from the other 3. Intravenous and intraarticular injections of these cultures into rabbits and guinea pigs elicited no symptoms. “Bac-

teriologically there is no evidence to show that there is any essential difference between acute articular rheumatism (RF) and infectious polyarthritis chronica villosa (RA). The difference in the subsequent course of the two conditions is apparently due to differences in the infecting organism and in the degree of disturbance they are capable of provoking.” Fayerweather used Blaxall’s culture techniques and felt that he was confirming Schüller’s findings. However, he did not continue this research. In his last article on this topic (1906) Schüller concluded that Fayerweather’s cases did not fit his diagnostic criteria, and since his own results were now based on 230 cases, Fayerweather was premature in drawing conclusions from 4 (37).

The “opsonic index,” devised in 1902, was the first immunologic procedure for the testing of resistance to a particular disease (38). It consisted of a microscopic comparison of the phagocytosis of bacteria by leukocytes that had been exposed to the patient’s serum and to pooled normal serum. A pathogen was considered to depress opsonic activity, and therefore, serial determinations of this index were believed to indicate whether the infection was improving or not. It was used particularly to monitor vaccine therapy. However, a lack of response could mean either that a vaccine was inadequate against the correctly identified pathogen or that the vaccine was irrelevant to the actual pathogen.

In 1906 Painter became interested in evaluating the opsonic index, at first in relation to the treatment of skeletal tuberculosis with Koch’s tuberculin (39). “In chronic polyarthritis it would be the greatest possible boon if the opsonic test could be employed to discriminate between types of infection . . . In the earlier part of our work there seemed to be considerable to suggest the possibility of a solution of the problems in the diagnosis and treatment of chronic polyarthritis. When, however, one regards the cases through a long perspective, there is not much to give encouragement at the present time.” Even though Painter believed that he had disproved a bacterial etiology of RA several years previously, he now sought to re-investigate the question immunologically.

From cultures that Fayerweather had preserved Painter had a vaccine prepared that he used both diagnostically and therapeutically (39). The opsonic index was “low” with Fayerweather’s bacillus in 5 of the 6 cases of RA for which he gave some details, but also for streptococcus in 4, staphylococcus in 2, and pneumococcus in 1. “All that can be said as a result of practically a year’s experience with the application of the opsonic test for this bacillus is that we have been able to obtain a characteristic serum reaction in the blood of nearly all the patients who were possessed of the clinical signs of this type of polyarthritis. When it has come to treatment I think it is fair to say that there has been no considerable degree of improvement in any case, at least none which is not frequently seen in cases treated by other methods.”

“Discouraging as these cases are, looked at from the

clinical point of view, it must be remembered that we have been applying a new method, the shortcomings of which are not at present wholly understood . . . It may be that cases have been treated with vaccines made from organisms having no possible kinship to the organisms originally present in the patient, though the opsonic findings have pointed that way. Again it may be possible that some of the conditions treated were not originally caused by an infective agent."

In 1904 Joel E. Goldthwait (1866-1961), a Boston orthopedic surgeon, sought to differentiate RA from osteoarthritis, based for the first time on radiologic appearance, with the designations, respectively, of "atrophic" and "hypertrophic" (40). Regrettably, he also introduced "infectious arthritis," an ambiguous term that confused rheumatology for the next half century. "*Infectious arthritis* is by far the most common, and includes most of the cases commonly spoken of as acute or chronic rheumatism and as septic arthritis, as well as many formerly spoken of as arthritis deformans. This type of disease apparently results from the presence within the body of some infectious organism, the symptoms being due either to the presence of the organism itself within the joint, or to some toxin produced by that organism in some other part of the body. It may result from practically any of the infectious or pus-producing organisms, and the type of the lesion or its character will naturally depend on the special organism involved." While Goldthwait did not intend "infectious arthritis" as a synonym for RA, however, that is what it became.

The skepticism Llewellyn Jones (Bath, 1909) expressed regarding the bacteriologic findings in RA resemble Pribram's: "Reviewing the organisms themselves collectively one is struck by the variety they display, and presuming the disease to be infectious in origin, the only inference to be drawn is that not one but many different organisms may produce the disease, and indeed there is nothing unreasonable in the assumption (41)." However, "the infective theory of the origin of rheumatoid arthritis . . . is still wanting in those conclusive bacteriologic data on which alone such a conception of its nature could be established beyond cavil."

Lewellys F. Barker (1867-1943; Baltimore, 1914), was an influential clinician-professor also reluctant to reject infection: "The idea of an infectious origin for many of the chronic arthropathies has gained credence (42). The notion was soon extended to various chronic arthropathies in which, despite the absence of demonstrated bacterial causation, the local processes in the joints and the state of the rest of the body (slight fever, slight leukocytosis, secondary anemia, enlargement of the lymph glands, slight foci of infection elsewhere) make the assumption of a continuous (or occasionally recurring) bacteremia of low grade with joint-deposition seem possible and plausible."

In 1917 William Nathan, a New York pathologist, while focusing on RA, theorized a detailed unifying bacterial etiology of most arthritides (43). His supporting

evidence was based largely on histopathologic examinations of experimentally infected dogs. Although Nathan mainly used hemolytic streptococci in his experiments, since similar findings resulted from infection with other bacteria (eg, staphylococci, pneumococci), he concluded that there is no specific arthritogenic bacterium. He believed that attempts to identify bacteria with blood or synovial fluid cultures are usually unsuccessful because the pathogens are rapidly trapped in the epiphyseal or subchondral blood vessels. These become "foci of infection" so that systemic disease results if the pathogen is able to escape from some of these foci. Most morbid changes in joint diseases are attributable to inflammation that is caused by a nonspecific bacterial infection. "The so-called proliferative processes depend on the virulence of the micro-organisms, the resistance of the host, and the mechanical conditions which prevail in each particular case." The mechanical component of chronic joint deterioration results from stretching by large synovial effusions and/or asymmetrical intraarticular postinflammatory changes. "Degenerative conditions, when they follow inflammation, denote the more or less complete inhibition of the reparative process after the active morbid condition has subsided. The mild, repeated joint swellings commonly found in all forms of infections are no doubt analogous to the conditions found in some cases of so-called acute articular rheumatism and a certain percentage of cases of so-called gonorrheal rheumatism." Some symptoms, such as glossy skin, paresthesias, and contractures cannot be attributed to infection; these "are in all probability due to a coincident spondylitis and secondary involvement of the cord or the spinal roots."

The "Focus of Infection" Theory

Nathan's theory apparently failed to arouse much interest and ideas about a bacterial cause of RA lay dormant until the late 1920s. However, research on a bacterial cause of RF persisted. The hypothesis that a bacterial infection of the throat somehow predisposes some people to scarlatina, some to RF, and some to RF after scarlatina gained predominance, while the question whether a specific microbe is pathogenic remained in dispute. An alternative explanation of the inconsistency with which bacteria could be recovered from blood or synovial fluid in cases of either RF or RA was that the pathogen was a relatively noninvasive microbe that was pathogenic by releasing a toxin from hidden, more or less asymptomatic foci. This hypothesis was regressive compared with that of Schüller in that he postulated that his pathogen elicited 1 histopathologically specific disease, while the advocates of focal infection with systemic consequences reverted to pathogens that were causing all sorts of nonpurulent musculoskeletal manifestations. The latter concept originated in 1908 in England based on recognition of an association between chronic gingivitis and rheumatic complaints. K.W. Goadby (London) found that 19% of 263 cases of

uncomplicated infections of the gums “gave a definite history of rheumatic symptoms” (44). A “streptobacillus” was the principal bacterium that was cultured, and injection of these cultures “into and around the knee-joints of rabbits produced symptoms similar to and indistinguishable from arthritis deformans.” However, “My contribution . . . does not seek to establish a specific organism as the etiologic factor in *all* cases of rheumatoid arthritis, infective fibrositis, muscular rheumatism, etc.”

Frank Billings and several collaborators in Chicago began in 1912 to popularize the concept of “focal infection” (45). This concept was derived from analogies, eg, meningitis can result from infection in “the nasal mucous surfaces, gonorrheal arthritis from infection in the genital tract, a local tuberculous focus may cause systemic infection.” Early laboratory support came from his associate, D.J. Davis, who performed experiments similar to those Meyer (19) had performed, except that the latter’s patients had definite RF, while the diagnosis of RA in the patients whom Davis studied was less certain (46). Davis sought evidence of “the specificity of streptococci as causative agents.” Among 42 patients blood cultures in 10 and synovial fluid cultures in 4 were sterile, while hemolytic streptococci were cultured from 90% of tonsillar crypts, mainly at tonsillectomy. When cultures were injected into young rabbits, microorganisms “. . . universally localize in or about joints.” The infection was not rapidly lethal and bacteria were not recoverable by the 3rd day after infection, but the animals gradually became crippled. Davis could not differentiate these streptococci from strains obtained from individuals who did not have an arthropathy. Tonsillectomy commonly resulted in marked improvement or complete relief from arthritis, whether or not the tonsils were inflamed, atrophic, or normal. This was interpreted as evidence that the tonsils are a source of infectious material that is constantly being disseminated.

Billings endorsed the *micrococcus rheumaticus* as the specific pathogen of RA (47). However, he advanced an unique hypothesis to account for the various bacteria to which the etiology had been attributed. Certain bacteria could, influenced by their environment, be converted into the actual pathogen. “The range of transmutation is from a type of streptococcus to the pneumococcus.”

In 1915 Edward C. Rosenow (1875-1966, Chicago) published an elaborate investigation of the question whether a streptococcal infection would preferentially develop in an animal in a site or organ from which it had been obtained in patients (48). No distinction was made between hemolytic and nonhemolytic strains. After having isolated and incubated the organism, he injected a broth culture intravenously into dogs or rabbits. For example, 80% of streptococci that were obtained from cases of cholecystitis were found in the test animals’ gallbladders versus 17% in joints and 10% in endocardium, while 66% of streptococci obtained from cases of RF were found in the animals’ joints, 46% in endocardium, and 3% in the gallbladder. Rosenow concluded: “That the

streptococci are the underlying cause of the diseases from the lesions of which they were isolated is indicated further by the fact that they have selective affinity for the corresponding structures in animals.” However, preferential localization of streptococci also was found for diseases that subsequently were proved to be viral, eg, 73% of streptococci that were isolated from parotid glands in cases of mumps were found in animal parotids. This type of investigation appears not to have been repeated.

In 1922 Billings sought to prove the etiologic significance of “foci of infection” in “chronic arthritis” statistically (49). However, the diagnoses of his 411 cases were imprecise. A focus was found in 94%, being oro-pharyngeal in 75%, among which it was entirely or primarily streptococcal in 93%. About 80% of the streptococcal isolates were *Streptococcus viridans*. Consequently Billings concluded that “. . . primary deforming arthritis is primarily an infectious disease, and that the infectious microorganisms which are the cause are usually strains of non-hemolytic streptococci of relatively low virulence . . .”

In 1927 Russell L. Cecil (1881-1965, New York) with Benjamin H. Archer at Cornell University published a descriptive study of 200 consecutive cases whom they considered to suffer from “chronic infectious arthritis” (50). They stated that “The theory of focal infection has been so widely accepted that many clinicians now consider all arthritis as an infectious disease. As a matter of fact chronic infectious arthritis is a definite clinical entity which can usually be distinguished from other forms of joint disease.” One or more “foci of infection” were found in 182 of their cases, including tonsils in 122 and teeth in another 66. “Cultures from tonsils usually yielded large numbers of hemolytic streptococci, whereas cultures from apical abscesses almost invariably gave pure cultures of *Streptococcus viridans* . . . One is forced to conclude from this that both *S. hemolyticus* and *S. viridans* can act as etiologic agents in infectious arthritis.” These results mimicked those that Billings had reported.

In 1929 Cecil still considered that “The most important contribution to the etiology of chronic arthritis was that made by Billings and his coworkers . . . when they pointed out the relationship that existed between focal infection and chronic infectious arthritis . . . (51). While the relation of focal infection to chronic infectious arthritis is rather generally recognized, there is doubt in the minds of many as to whether the joint manifestations are actually metastatic infections or whether they are merely an expression of some toxic influence on the joint . . . A majority of the investigators look on the streptococcus as the exciting cause . . . There is considerable disagreement as to which type of streptococcus is responsible . . .”

Discrepancies Between Blood Cultures and Immunologic Tests

Cecil, with Edith E. Nicholls and Wendell J. Stainsby, in 1929 made their first report on the immunologic relation-

ship of streptococci with RA (51). A streptococcus was recovered from blood cultures in 62% of 78 cases of RA, while all 54 control specimens were sterile. As of 1931 positive blood cultures had been obtained from 62% of 154 cases of RA and 3.8% of 104 controls (52). Cultures of synovial fluid revealed a streptococcus in 67% of 49 cases and in 44% of 48 cases a streptococcus was recovered from both blood and synovial fluid. The investigators rejected the possibility that the streptococci were contaminants because then “one would expect to find just as high an incidence of positive cultures in the controls as in the arthritic series The observations reported tend strongly to confirm the theory that rheumatoid arthritis is an infectious disease, caused in a high percentage of cases by a specific type of streptococcus”

Forty of the initial 48 blood cultures grew an identical weakly hemolytic strain of streptococcus. This henceforth was called the “typical strain” and was used to immunize rabbits to create the antibody with which serologic testing was performed. In 1933 the concept was extended: “In contrast to the positive results obtained from agglutination tests in rheumatoid arthritis are the negative results in osteoarthritis, gonococcus arthritis, rheumatic fever, and gout (53). A knowledge of this reaction is of practical value in differential diagnosis.”

In 1938 Cecil and D.M. Angevine reviewed another 200 cases of “chronic infectious arthritis (54).” These were Cecil’s private patients with far fewer foci of infection than were found in the earlier cohort of Cornell clinic patients. A bacterial focus was found in 30% of this versus 91% of the earlier cohort. The reason for this study was the beginning of doubt regarding the pathogenetic importance of infected tonsils. In the interval, although childhood tonsillectomies had become very common, Cecil had not found a decrease in the prevalence of RA, as he apparently expected, nor dramatic post-tonsillectomy improvement if RA had been present. A nonarthritic cohort was not examined in either investigation.

The largest studies of the relationship of streptococcal agglutinins to RA after those of Cecil and Dawson (see below) were conducted by J.W. Gray (Newark, NJ) during 1931 to 1935 (55). His conclusions supported Cecil’s, with the refinement that he divided his 200 consecutive cases of RA into “early,” “established,” and “advanced.” A blood culture showed growth in 48% of cases over all: most (65%) in early cases and least (26%) in advanced cases. Streptococci were not recovered from normal or osteoarthritic controls. “A small percentage of staphylococci and diphtheroids also appeared in these cultures, the significance of which cannot be determined without further investigation.” Whether these were found together with streptococci was not stated. Most organisms were *S. viridans*. The strains used in the agglutination tests were not reported. Titers did not closely correlate with the blood cultures: 53 to 59% of the RA cases had a titer of at least 1:640, while only 17% of OA cases had a titer as high as 1:160 to 1:320.

In their first serologic report, in 1931, Nicholls and Stainsby stated that 94% of 110 cases of RA had a streptococcal agglutination titer of at least 1:640, while only 4% of 79 cases of RF had a titer as high as 1:80 (56). “Agglutination reactions with the serums of patients having various other febrile and nonfebrile diseases practically never gave titers above 1:320 with the “typical strain” streptococci.” Later studies gave agglutination results more in keeping with those of other laboratories. A study of 560 cases of RA of at least 6-months duration found only 24% with a titer of 1:640+ and 62% were 1:80 or negative (57). Titers were unrelated to disease duration. In 1946 a 1:160 titer was obtained in 60% of cases in which type A hemolytic streptococci rather than a “typical strain” was used. Calculating from a list of published studies of the agglutination reaction, excluding those from Cecil’s and Dawson’s laboratories, 68% of 902 cases of RA reacted with a significant titer.

Concurrently (1928-1929) with their RA studies, Cecil and colleagues performed blood cultures on 60 patients with acute RF using the same technique (58). Sixty-two percent of the patients were older than 18 years; 57% had had prior attacks of RF; 58% had a positive blood culture and this was unrelated to whether this was a first or a recurrent attack. All but 1 culture grew *S. viridans*, while only 1 of 66 control cases gave a positive culture. The investigators concluded that analogies can be drawn between the findings in RF and the results in gonococcal arthritis and “infectious arthritis.” Their theory of pathogenesis resembled Nathan’s (43). “In both these latter infections a primary focus acts as a nidus for pathogenic bacteria which under certain circumstances break into the bloodstream and become localized in the joints where they set up metastatic infections. In a recent study of the role of the streptococcus in chronic infectious arthritis we have presented evidence which goes far to show that a similar mechanism is at work In both RF and bacterial endocarditis green streptococci are circulating in the bloodstream. In the former disease many joints become infected. In the latter disease, though the bloodstream usually contains more streptococci than are encountered in RF, the joints remain free from infection. It is reasonable to suppose, therefore, that in RF the patient’s tissue is allergic to streptococci, while in infectious endocarditis the tissues are immune to these organisms. A state of allergy toward the streptococcus, however, will probably not in itself induce the lesions or joint manifestations of RF without the concomitant presence of streptococci.”

Concerns About Contaminants

A relatively small study was conducted at Boston City Hospital in 1930 using Cecil’s culture technique (59). Its importance was that these investigators concluded from their findings and the inconsistent results of other published investigations that contaminants rather than pathogens were being analyzed.

Lichtman and Gross (New York, 1932) attempted a different approach to the question of whether the finding of streptococci in blood cultures should be considered pathogenically significant (60). They reviewed blood culture results obtained during 4 1/2 years (1926-1930) at Mt. Sinai Hospital. Nonhemolytic streptococci were obtained in 8% of 188 cases of acute RF, 5% of 126 cases of rheumatic heart disease (RHD), 4% of 48 cases of RA, and 7% of 220 cases of 6 other diseases. Growth was sparse, and inconsistent in cases when multiple cultures were taken. Consequently the authors concluded that such bacteriologic results should not be considered of pathogenic concern, but did not state the organisms to be contaminants.

Archer, Cecil's former collaborator, stated that "... there is ample ground for skepticism regarding the actual presence of streptococci in the blood and joints of patients with chronic nonspecific arthritis (61). The probability of contamination must be kept in mind. . . . [Other authors] found a correlation between the number of positive cultures and the number of bacteria in the air. . . . The streptococci were isolated from the air of the places where cultures were made." Currier McEwen (1902-2003) and associates (New York University) reviewed publications pertaining to the frequency of positive blood cultures in cases of various arthritides to learn whether this might have some differential diagnostic value (62). Their own data showed 19% of cases of RA, 17% of RF, 15% of gonococcal arthritis, and 10% of osteoarthritis were positive. Fifty-eight percent showed growth in 48 hours and *S. viridans* was the most frequently identified organism. These investigators, like Lichtman, did not opt for the explanation that contaminants were being cultured, but only concluded that the frequency of positive cultures and organisms identified were of no diagnostic value.

In 1940 Cecil withdrew the data on blood cultures on which he had relied for more than a decade (63). He speculated that "the pipettes were the most likely source of contamination," the streptococci coming from the technician's mouth. This is unlikely since, unless different technicians consistently handled rheumatoid and control specimens, this explanation could not account for the strikingly different results.

The Conflict Between the Laboratories of Cecil and Dawson

Soon after the publication by Cecil and collaborators of their 1929 paper on "infectious arthritis," Martin H. Dawson (1897-1945) and collaborators (Columbia University) initiated the same research (64). Their results diverged considerably from Cecil's, as did their opinion about the relationship between RA and RF. While Cecil considered RA a distinct disease, Dawson believed it to be in a spectrum with RF. They pointed out the numerous manipulations that were involved in Cecil's culture technique, each of which could result in microbial contami-

nation. They obtained 105 blood cultures from 80 cases of RA, most of which were divided, so that 204 blood samples were studied. These resulted in 58 positive cultures, the majority being either a Gram-positive bacillus or a staphylococcus. Three different microbes were also cultured from 7 of 23 rheumatoid synovial fluids. The same techniques were performed on 31 samples from healthy donors, of which 4 specimens had growth. Consequently they concluded that bacteriologic techniques did not yield etiologically significant results. Nevertheless they partially agreed with Cecil that "Rheumatoid arthritis, in the majority of instances, results from infection with *Streptococcus hemolyticus*. [But] no specific strain of *Streptococcus hemolyticus* can be considered as the sole etiologic agent."

Although interpretations of their bacteriologic findings differed, the results of Cecil's and Dawson's immunologic studies more closely supported each other. The immunogenic potency of the streptococcal strains was determined by immunizing rabbits with intravenous injections of killed streptococci (65). Dilutions of rabbit immune serum were mixed with homologous cultures of streptococci to assay the potency for agglutination. Once the ability to agglutinate bacteria was demonstrated, fresh liquid culture of the live bacteria was mixed with dilutions of RA or control serum. The highest dilution that resulted in agglutination was the titer that was recorded.

Dawson reported more control experiments than Cecil and concluded that Cecil's "typical strain" of streptococcus was not an unique agglutinator (66). Most hemolytic streptococci were agglutinated by rheumatoid serum. Among control bacterial species R-type pneumococci (but not S) shared the agglutinating effect. A titer of at least 1:160 was defined as positive and 70% of RA cases met this criterion, while 38% met Cecil's criterion of 1:640. Among serologically positive controls there were cases of lupus erythematosus, psoriasis, and 1 of 36 cases of RF. The conclusion from these studies was: "There appears to be a relationship between the agglutinins for hemolytic streptococci in rheumatoid arthritis serum and natural agglutinins for many bacteria present in the serum of a wide variety of animal species."

Solution of the Etiology of Rheumatic Fever

In retrospect, Schottmüller had been correct in 1903 when he associated hemolytic streptococci rather than *S. viridans* with RF (24). Nevertheless, investigators who believed that RF is caused by 1 bacterial species accumulated evidence for the next 30 years favoring the etiologic significance of *S. viridans*. This had several mutually reinforcing explanations: (1) In studies of oropharyngeal cultures *S. viridans* was obtained more frequently than a hemolytic streptococcus, although this finding was not correlated either with control subjects or with the phase of the disease; (2) In animal experiments hemolytic streptococci caused purulent, more rapidly fatal infections than

S. viridans, and only the latter was perceived to cause a disease that resembled RF; (3) Most clinical studies were based on blood cultures of patients without adequate controls, so that it was not realized that nonhemolytic streptococci are common contaminants.

In 1925 Homer F. Swift (1881-1953, New York) clearly enunciated facts that for some years continued to be ignored: “. . . (T)he etiologic agent of rheumatic fever has not been demonstrated conclusively; nor has it been possible to reproduce in animals the characteristic clinical or histo-pathological picture of this disease . . . (67). Many consider the disease to be due to the so-called *Streptococcus rheumaticus*, which is really the nonhemolytic streptococcus; but I do not think this opinion can be unqualifiedly accepted. The endocardial vegetations and myocardial lesions so characteristic of the disease known as subacute bacterial endocarditis are also seen in animals properly inoculated with *Streptococcus viridans*. The characteristic lesions of rheumatic fever, namely, Aschoff bodies are not found in the hearts of either these patients or animals. How then are we to regard the occasional recovery of nonhemolytic streptococci from the blood or gross lesions of patients with rheumatic fever?” As was then commonplace, Swift did not consider bacterial contamination for the explanation.

The conceptual reorientation began with an epidemiologic observation by Alvin F. Coburn (1899-1975; New York, 1928) (68,69). He assembled a cohort of 100 children who had had RF, from whose throats he made repeated cultures. He found that recurrences of RF followed throat infections that could be clinically insignificant. They were unrelated to the presence or absence of tonsils, but had in common the presence of hemolytic streptococci. The second phase of his investigations began with the knowledge that scarlet fever and RF were rare in Puerto Rico. He was able to bring a group of New York RF patients to Puerto Rico and observed that hemolytic streptococci spontaneously disappeared from their throats. They remained healthy and free of hemolytic streptococci for the 6 months in Puerto Rico, but soon after their return to New York the same bacteria recurred, and several of these patients had another attack of RF.

W.R. Collis (London), who in 1931 confirmed Coburn's interpretation that hemolytic streptococci are the pathogen of RF, suggested several reasons attention had been diverted from this organism (70): (1) Because of the asymptomatic period between the throat infection and the onset of RF symptoms most cases reached a diagnostician when there was no sign of pharyngitis; (2) The throat culture then recovers no predominant organism; (3) The tonsillitis or pharyngitis may have given minimal symptoms or none; (4) Attention has been focused on blood cultures during the acute phase of RF, that in the minority of positive cases revealed a nonhemolytic streptococcus. Implicit in this list is confusion between subacute bacterial endocarditis that most often is caused by a nonhemolytic streptococcus, and acute RF.

The initial recognition that hemolytic streptococci rather than *S. viridans* have a critical role in the etiology of RF left doubts because, as it turned out, only certain immunologic types of hemolytic streptococci exert this effect. Three immunologic discoveries pertaining to streptococci were made within a few years of each other, 2 of which contributed to the elucidation of the etiology of RF and 1 that misled regarding the etiology of RA.

Beginning in 1928, serologic techniques to differentiate streptococci were developed by Rebecca C. Lancefield (1895-1981) in Swift's laboratory at the Rockefeller Institute (71-73). Initially groups were categorized based on their content of a specific carbohydrate. In 1933 she began to subdivide group A into types using a precipitin reaction. Specific types of group A hemolytic streptococci cause RF.

In the 1930s several immunologic tests for hemolytic streptococci were developed. The first was the “antifibrinolytic” assay. It was found that a culture of hemolytic streptococcus would liquefy a fibrin clot made from blood of a healthy person, but would do this more slowly or not at all with a clot from someone with a hemolytic streptococcal infection, or who was convalescing from such an illness. Walter K. Myers and collaborators (Boston) found that the reaction of normals and patients with RA or gonococcal arthritis was the same, but clearly slower in cases of erysipelas or RF (74). A larger British study confirmed the principal findings. Ninety percent of sera from cases of RA behaved normally (lysis within 51 minutes), while this was true of 40% of cases of active and 68% of convalescent RF (75). Erik Waaler (1937, Oslo) demonstrated that the antifibrinolytic test did not differentiate between hemolytic and nonhemolytic streptococci, and found it to be erratically positive in adult RA patients (76).

Myers's group made a skin test antigen from a scarlatinal strain of streptococcus. This proved to be the least discriminatory (77). Tests elicited erythema in 95% of cases of streptococcal respiratory tract infection, 77% of cases of acute RF, and 70% of RA. Of controls that included cases of erysipelas and RHD, 44% were positive. Skin test results showed little correlation with agglutination reactions.

E.W. Todd, an associate of Lancefield, discovered that 2 antibodies develop to the streptococcal enzyme that ruptures red blood cells (78). He called them “antistreptococcal hemolysin”: antistreptolysins “O” and “S” for short. In 1938 he found that the titer of antistreptolysin O (ASO) reliably indicates that there has been exposure to hemolytic streptococci (79). While it does not indicate that RF has occurred, lack of an increase in the ASO titer is evidence against symptoms being due to RF. It replaced the antifibrinolytic test because it was less time consuming and more easily quantifiable.

Myers and Keefer performed ASO tests in various clinical circumstances (80). They found a considerable overlap between the mean titers of the diagnostic groups and

the maximum normal titer of 200. Highest titers were obtained during convalescence from scarlatina. An average of 6 tests were done in cases of RF. Seventy-eight percent exceeded the mean normal value, similar to 71% of hemolytic streptococcal upper respiratory infections, but clearly more than 33% of cases of gonococcal arthritis and 23% of cases of RA.

Coburn defined 2 criteria as essential for a hemolytic streptococcal infection to elicit RF (81): (1) Contrary to the development of scarlatina, which is evident very soon after the infection has occurred, there is an asymptomatic interval of several days before symptoms of RF appear; (2) The development of an attack of RF is indicated by an increase of the ASO titer.

Coburn's conclusion of the unique pathogenetic role of the hemolytic streptococcus met some resistance. The most influential opponents to Coburn's views were May G. Wilson and her collaborators at Cornell University (82). From pediatric data collected during 1930 to 1932 they concluded that no special etiologic relationship exists between childhood respiratory infections and the occurrence of RF, and they doubted that the presence of hemolytic streptococci in the pharynx was diagnostically significant. Only 11.5% of RF recurrences were preceded by a documented hemolytic streptococcal infection and in 24% of cases of RF there had been no symptoms of respiratory tract infection at all. Although one-half of streptococcal respiratory infections were followed by RF, these were identifiable by increases of the ASO titer. Thus she wrote in 1935: "...while the occurrence of respiratory infections in a rheumatic child may not be a fortuitous event, it would seem to bear no more specific etiological relationship to rheumatic disease than would be attributed to similar episodes occurring in a tuberculous child" (83). As of 1961 Wilson still was of the opinion that "As yet it has not been excluded that the frequent association of streptococcal infection [with RF] may be temporally or concomitantly rather than causally related" (84).

Data that T.D. Jones (1899-1954) and J.R. Mote gathered in Boston in 1935 in part supported Wilson's opinion (85). They performed throat cultures throughout the year on a large number of children. "Infections of the respiratory tract preceded 58% of the first attacks of RF, and 2/3 of these were symptomatic sore throats." The frequency of cultures containing hemolytic streptococci was the same in children who were hospitalized with RF (23%) and healthy children who had frequent upper respiratory infections (25%), while this finding was made in only 13% of "ambulatory rheumatic patients living at home." The investigators did not type the streptococci, but they serologically supported Coburn's view. "Serologic evidence indicates that a hemolytic streptococcal infection was associated with most first attacks of RF, whether or not there were preceding symptoms involving the respiratory tract."

Fritz Klinge (1892-1974, Leipzig) was an influential investigator of the pathology of rheumatic diseases, whose

views were strongly regressive (86). "I am of the opinion that rheumatic manifestations should be conceived of as a unitary, connected whole, of which the individual phases are determined by the relative potency of the pathogenic germ and the immunologic resistance of the body, both of which are variable . . ." "The trigger for the rheumatic process was conceived to be a streptococcal infection that might be localized, as suggested by Billings. Klinge failed to make a distinction between hemolytic and nonhemolytic streptococci. "Today [1933] it is still unknown whether every streptococcus is capable of initiating the rheumatic hypersensitivity reaction, or only a particular strain or group thereof. This question can hardly be answered today because the stability of streptococci and their categorization into distinct types remains open." However, he stated, seemingly paradoxically, "Since the hypothesis of a specific rheumatic virus [pathogen] has not been proven by either bacteriologic or experimental studies, the theory of anaphylactic action . . . has initiated extensive experimental research." RA is age-dependent and requires more chronic immunologic stimulation than RF. "... persons with chronic or recurrent peripheral rheumatism [ie, RA] nearly always have recognizable signs of having experienced . . . manifestations (frequently clinically silent) of visceral rheumatism, especially fibrosis in the heart, vessels, and serous membranes."

In 1936 Dawson and Tyson in essence supported Klinge's views (87). "The two diseases are intimately related and possibly different manifestations of the same process." (1) Both occur within families, although this is more frequent with RF than RA. (2) Both occur mainly in temperate climates and are rare in the tropics. (3) The relationship between upper respiratory infections and RF is acknowledged and "It is our belief that preceding infection of the upper respiratory tract constitutes one of the most important factors in the initiation of RA." (4) The seasonal onset is similar in New York, peaking in March together with the peak of hemolytic streptococcal pharyngitis. (5) While age of occurrence is quite different, cardiac involvement is similar. It is uncommon in RA, but also becomes less common in older cases of RF. (6) There is great histologic similarity in the subcutaneous nodules. (7) Agglutination reactions with hemolytic streptococci occur in the majority of cases of RA, but not RF. "These findings offer suggestive evidence in support of the conception that infection by *Streptococcus hemolyticus* plays a role in the production of the disease . . . In rheumatoid arthritis serums, on the other hand, significant agglutinins are present but the antistreptolysin content is not elevated, except in early and active cases." "It is possible that they may represent different responses to the infection by the same agent . . ." The pathologic evidence, representing a difference in degree rather than in kind, strongly suggests that the two represent different responses to the same, or closely related, etiologic agents."

Chester S. Keefer (1897-1972; 1935, Boston) published an erudite review of the various theories about the

etiology of RA (88). He deemed "One of the strongest arguments in favor of the infective theory of rheumatoid arthritis is the presence of agglutinins and precipitins to hemolytic streptococcus in the blood serum." However, he made the prescient conjecture: "Are these reactions a response to streptococcal infection or, secondly, are they responses to some process which gives rise to changes in the blood serum which are capable of causing the serological reactions observed?"

Allen D. Wallis (Philadelphia, 1946) proved Keefer's conjecture and thereby disproved that streptococcal agglutinins have etiologic significance for RA (89). He first noticed formation of a precipitate between "many" RA sera and saline, ie, control tubes that contained no streptococcal antigen. Next he found that RA sera with a high titer of streptococcal agglutinins also tended to agglutinate unsensitized collodion particles. The streptococcal and collodion titers were not closely correlated, but were virtually absent in nonrheumatoid sera. Finally he also found RA sera to agglutinate nonencapsulated pneumococci to a higher titer than normal sera. Consequently, Wallis concluded: "The serum of patients with typical rheumatoid arthritis thus appear to have the ability to enhance serologic aggregations." The significance of this observation in the development of the "rheumatoid factor" has unaccountably been neglected (90).

A unique Swedish study of sera collected during 1947 to 1952 showed a higher frequency of "positive" antistaphylolysin (antibody against *S. aureus*) than ASO in cases of RA (63 and 40%) (91). Contrariwise, in RF 85% of ASO but only 14% of antistaphylolysin reactions were positive. These findings devalued the etiologic significance of streptococcal antibodies in RA in another way than Wallis had achieved.

Therapeutic Evidence

While the question of a streptococcal etiology of RA still persisted on bacteriologic and serologic grounds, it was definitively resolved therapeutically. When sulfanilamide was introduced in 1936, it was found to be particularly effective against acute streptococcal infections. Consequently, it was tried to treat acute RF, but found ineffective. However, Coburn and Moore found that pretreatment of rabbits could prevent subsequent infection with streptococci (92). Therefore, beginning in 1938, they began to treat children who had had RF, many of whom had RHD, with sulfanilamide. Seventy-nine of 80 children had no recurrence during the period of observation. Caroline B. Thomas and associates (Baltimore) confirmed the prophylactic effect (93). Their entire cohort had had RF at least 3 years before the investigation and 79% had RHD. The treated cohort received 1.2 g per day of sulfanilamide by mouth, October to June. Four percent of them had hemolytic streptococci recovered in throat cultures compared with 12% of untreated control cases. No treated patients developed an RF recurrence during 79

person treatment seasons, compared with 10% of 150 untreated control seasons.

While these data were being gathered, Coggeshall and Bauer (Boston) evaluated the efficacy of sulfanilamide in gonococcal arthritis and used cases of RA for comparison (94). Much larger doses were administered than in the RF studies. An average of 6 grams per day by intramuscular injection given for 8 to 27 days had no effect in 10 cases of RA, but was curative in 14 cases of gonococcal arthritis. When penicillin became available, it was tried in RA before it was used in RF (95). The justification was: "The blood of the majority of patients who have this disease contain antibodies against hemolytic streptococci, that is, agglutinins, generally in high titer." Ten men with an average duration of 7 months of RA were treated in the US Army Rheumatism Center in 1944 with a total of 1.8 to 3.25 million units over 14 to 20 days without benefit. "Our results offer no support to the idea that hemolytic streptococci may be etiologically related to RA. In view of these negative results with rather large doses (!) of penicillin it does not seem unreasonable to assume that RA is not caused any of the bacteria which are already known to be rapidly affected by penicillin."

DISCUSSION

The development of the understanding of RF was retarded particularly by the lack of recognition of the significance and applicability of the 4 following discoveries:

1. Meyer (19) (1902) concluded from clinical research that causative bacteria need no longer be present when symptoms of RF begin. This was finally appreciated by Coburn in 1936 (81).
2. Schottmüller (24) (1903) discovered that the ability to cause hemolysis differentiates the pathogenicity of some strains of streptococci and associated the hemolytic streptococcus with scarlatina. However, since hemolytic streptococci became associated with acute and purulent infections, the chronicity and nonpurulence of *S. viridans* was considered strong evidence in its favor as the pathogen of RF if, indeed, the disease had a single pathogen.
3. The necessity of adequate controls in both clinical and laboratory research was not recognized. This was demonstrated by the general reluctance of investigators to consider bacteria as potential contaminants in research on both RF and RA. The blood culture results of Cecil (52,53) and Gray and colleagues (55) appeared to provide convincing statistical evidence of a relationship between streptococcal sepsis and RA. Cecil's recovery of streptococci from blood cultures in 62% RA versus 4% controls and Gray's 48% versus 0 remain unexplained. Cecil's eventual explanation of this error of his laboratory was unpersuasive (63).
4. Serologic investigations of streptococcal agglutinins in RA were misinterpreted for 17 years, until Wallis (89) studied bacterial agglutination with adequate controls.

REFERENCES

1. Sydenham T. The Works of Thomas Sydenham, M.D. London, Sydenham Society, 1858. Medical Observations, 1668. Chap. V. 1858;254-5.
2. Dundas D. An account of a peculiar disease of the heart. *Medico-Chirurg Trans* 1809;1:36-46, 39.
3. Balfour W. Observations on the pathology and cure of rheumatism. *Edinburgh Med J* 1815;11:168-187, 174.
4. Paget J. Lectures on Surgical Pathology. Philadelphia, Lindsay & Blakiston, 1854;27.
5. Todd RB. Practical Remarks on Gout, Rheumatic Fever, and Chronic Rheumatism of the Joints. London, J.W. Parker, 1843; 143-4.
6. Flint A. A Treatise on the Principles and Practice of Medicine, 5th ed. Philadelphia, H.C. Lea's Sons, 1881;1094-118.
7. Trousseau A. Clinical Lectures on the Practice of Medicine, 2nd ed. Philadelphia, Blakiston, 1873;2:620-3.
8. Hodges AD: Notes on rheumatism and scarlet fever. *Lancet* 1894; 2:1145-6, 1212-3.
9. Fowler JK. On the association of affections of the throat and acute rheumatism. *Lancet* 1880;2:933-4.
10. Mantle A. Infectious sore-throat, in which rheumatism plays a prominent part. *Br Med J* 1885;2:960-1.
11. Mantle A. A history of the present-day accepted aetiology of acute rheumatism. *Practitioner* (London) 1912;88:185-92.
12. Mantle A. The etiology of rheumatism considered from a bacterial point of view. *Br Med J* 1887;2:1381-4.
13. Anonymous: Professor Pel on acute rheumatism. *Lancet* 1887;2: 496.
14. Chvostek F. Zur Aetiologie des Gelenkrheumatismus. *Wien Klin Wochenschr* 1895;8:469-72.
15. Riva A. Über die Ätiologie des akuten Gelenkrheumatismus. *Ctrbl f inn Med* 1897;32:825-8.
16. Poynton FJ, Paine A. The etiology of rheumatic fever. *Lancet* 1900;2:1306-7.
17. Poynton FJ, Paine A. The etiology of rheumatic fever. *Lancet* 1900;2:861-9, 932-5.
18. Poynton FJ, Paine A. Some further investigations upon rheumatic fever *Lancet* 1901;1260-5, 1261.
19. Meyer F. Zur Bakteriologie des acuten Gelenkrheumatismus. *Z Klin Med* 1902;46:311-38.
20. Beaton RM, Ainley Walker EW. The etiology of acute rheumatism and allied conditions. *Br Med J* 1903;1:237-9.
21. Ainley Walker EW, Ryffel JH. The pathology of acute rheumatism and allied conditions. *Br Med J* 1903;2:659-60.
22. Beattie JM. The "Micrococcus rheumaticus": its cultural and other characteristics. *Br Med J* 1904;2:1510-1.
23. Beattie JM. Acute rheumatism: the evidence in support of its bacterial origin. *Edinburgh Med J* 1908;23:391-8.
24. Schottmüller H. Die Artunterscheidung der für Menschen pathogenen Streptokokken auf Blutagar. *Münch Med Wchnschr* 1903; 50:848-53, 909-12.
25. Loeb LM. The bacteriology of acute rheumatism. *Arch Intern Med* 1908;2:266-76.
26. Philipp C. Zur Aetiologie des acuten Gelenkrheumatismus. *Deut Arch Klin Med* 1903;76:150-73.
27. Cole RI. Experimental Streptococcus arthritis in relation to the etiology of acute articular rheumatism. *J Infect Dis* 1904;1: 714-37.
28. Petrone LM. Sulla natura parasitaria dell' artrite blenorragica. *Riv Clin Bologna* 1883;3:94-113.
29. Neisser A.: Ueber die Züchtung der Gonococcen bei einem Fall von Arthritis gonorrhoeica. *Deut Med Wchnschr* 1894;20:160 (abstract).
30. Schüller II. M. Untersuchungen über die Aetiologie der sogen. chronisch-rheumatischen Gelenkentzündungen. *Berl Klin Wchnschr* 1893;30:865-8, 867. Same material in *Bacteriologic researches into the etiology of the so-called rheumatic joint inflammations. Med Rec* 1893;44:389-91.
31. Schüller M. Ueber den Nachweis der hantelförmigen Bacillen bei der chronischen zottenbildenden Polyarthritis und über Beziehungen der Syphilis zu derselben. *Berl Klin Wchnschr* 1905;42: 1275-78, 1276.
32. Bannatyne GA, Wohlmann AS, Blaxall FR Rheumatoid arthritis: its clinical history, etiology, and pathology. *Lancet* 1896;1: 1120-25.
33. Newsholme A. The Milroy Lectures on the natural history and affinities of rheumatic fever. *Lancet* 1895;589-98, 652-65.
34. Painter CF. Pathological lesions in rheumatoid arthritis. *Boston Med Surg J* 1901;145:593-8.
35. Pribram A. Chronischer Gelenkrheumatismus und Osteoarthritis deformans. Hölder, Wien, 1902;96-9.
36. Fayerweather R. Infectious arthritis: a bacteriological contribution to the differentiation of the "rheumatic" affections. *Am J Med Sci* 1905;130:1051-82.
37. Schüller M. The relations of chronic villous polyarthritis to the dumb-bell shaped bacilli. *Am J Med Sci* 1906;132:231-9.
38. Zinsser H. Infection and Resistance. New York, MacMillan, 1914;330-44.
39. Painter CF. Experiences with opsonins and bacterial vaccines in the treatment of tuberculous and non-tuberculous arthritis. *Boston Med Surg J* 1907;157:621-6.
40. Goldthwait JE. The differential diagnosis and treatment of the so-called rheumatoid diseases. *Boston Med Surg J* 1904;151:529-34, 531-2.
41. Llewellyn Jones R. Arthritis deformans: comprising rheumatoid arthritis, osteo-arthritis, and spondylitis deformans. Bristol, J Wright & Sons, 1909;57-65.
42. Barker JF. Differentiation of the diseases included under chronic arthritis. *Am J Med Sci* 1914;147:1-29, 15.
43. Nathan PW. Arthritis deformans and infectious disease. *J Med Res* 1917;36:187-223, 191-216.
44. Goadby KW. The association of disease of the mouth with rheumatoid arthritis and certain other forms of rheumatism. *Lancet* 1911;1:640-9, 649.
45. Billings F. Chronic focal infections and their etiologic relations to arthritis and nephritis. *Arch Intern Med* 1912;9:484-98.
46. Davis DJ. Chronic Streptococcus arthritis. *JAMA* 1913;61:724-7.
47. Billings F. Chronic focal infection as a causative factor in chronic arthritis. *JAMA* 1913;61:819-22.
48. Rosenow EC. Elective localization of streptococci. *JAMA* 1915; 65:1687-91.
49. Billings F, Coleman GH, Hibbs WG. Chronic infectious arthritis. Statistical report with end-results. *JAMA* 1922;78:1097-105, 1105.
50. Cecil RL, Archer BH. Chronic infectious arthritis. An analysis of 200 cases. *Am J Med Sci* 1927;173:258-70, 258, 265.
51. Cecil RL, Nicholls EE, Stainsby WJ. The bacteriology of the blood and joints in chronic infectious arthritis. *Arch Intern Med* 1929;43:571-605.
52. Cecil RL, Nicholls EE, Stainsby WJ. The etiology of rheumatoid arthritis. *Am J Med Sci* 1931;181:12-25, 24.
53. Nicholls EE., Stainsby WJ. Further studies on the agglutination reaction in chronic arthritis. *J Clin Invest* 1933;12:505-18, 517.
54. Cecil RL, Angevine DM. Clinical and experimental observations on focal infection, with an analysis of 200 cases of rheumatoid arthritis. *Ann Intern Med* 1938;12:577-84.
55. Gray JW, Bernhard WG, Gowen CH. The clinical pathology of rheumatoid arthritis. *Am J Clin Pathol* 1935;5:489-503.
56. Nicholls EE, Stainsby WJ. Streptococcal agglutinins in chronic infectious arthritis. *J Clin Invest* 1931;10:323-35, 335.
57. Cecil RL, DeGara PF. The agglutination reaction for hemolytic streptococci in rheumatoid arthritis; its significance in diagnosis and treatment. *Am J Med Sci* 1946;211:472-9.

58. Cecil RL, Nicholls EE, Stainsby WJ. Bacteriology of the blood and joints in rheumatic fever. *J Exp Med* 1929;50:617-42.
59. Nye RN, Waxelbaum EA. Streptococci in infectious (atrophic) arthritis and rheumatic fever. *J Exp Med* 1930;52:885-94.
60. Lichtman SS, Gross L. Streptococci in the blood in rheumatic fever, rheumatoid arthritis and other diseases. *Arch Intern Med* 1932;49:1078-94.
61. Archer BH. Chronic nonspecific arthritis. *JAMA* 1934;102:1449-54, 1451.
62. McEwen C, Bunim JJ, Alexander RC. Bacteriology and immunology of arthritis. Results of various immunologic tests in different forms of arthritis. *J Lab Clin Med* 1936;21:465-77.
63. Cecil, RL. Proceedings of the American Rheumatism Association, 10 June 1940. *JAMA* 1940;115:2113.
64. Dawson MH, Olmstead M, Boots RH. Bacteriologic investigations on the blood, synovial fluid and subcutaneous nodules in rheumatoid (chronic infectious) arthritis. *Arch Intern Med* 1932;49:173-80.
65. Dawson MH, Olmstead M, Boots RH. II. The nature and significance of agglutination reactions with *Streptococcus hemolyticus*. *J Immunol* 1932;23:205-28.
66. Dawson MH, Olmstead M, Boots RH. Agglutination reactions in rheumatoid arthritis. I. Agglutination reactions with *Streptococcus hemolyticus* *J Immunol* 1932;23:187-204.
67. Swift HF. Rheumatic fever. *Am J Med Sci* 1925;170:631-47, 635.
68. Coburn AF. Commitment Total. A physician's experiences in the battle against rheumatic fever. New York, Walker & Co., 1974; 31-8.
69. Coburn AF, Pauli RH. Studies on the relationship of *Streptococcus hemolyticus* to the rheumatic process. *J Exp Med* 1932;56: 609-32.
70. Collis WR. Acute rheumatism and haemolytic streptococci. *Lancet* 1931;1:1341-5.
71. Lancefield RC. The antigenic complex of streptococcus haemolyticus. I. Demonstration of a type-specific substance in extracts of streptococcus haemolyticus *J Exp Med* 1928;47:91-103.
72. Lancefield RC. The antigenic complex of streptococcus haemolyticus. III. Chemical and immunological properties of the species-specific substance *J Exp Med* 1928;47:481-91.
73. Lancefield RC, Todd EW. Antigenic differences between matt hemolytic streptococci and their glossy variants. *J Exp Med* 1928; 48:769-90.
74. Myers WK, Keefer CS, Holmes WF. The resistance to fibrinolytic activity of the hemolytic streptococcus with special reference to patients with rheumatic fever and rheumatoid (atrophic) arthritis. *J Clin Invest* 1935;14:119-23.
75. Stuart-Harris CH. A study of haemolytic streptococcal fibrinolysis in chronic arthritis, rheumatic fever, and scarlet fever. *Lancet* 1935;2:1456-9.
76. Waaler E. Development of antifibrinolytic properties in blood of patients with rheumatic fever, chronic infective arthritis and bacterial endocarditis. *J Clin Invest* 1937;16:145-53.
77. Myers WK, Keefer CS, Oppel TW. Skin reactions to nucleoprotein of *Streptococcus scarlatinae* in patients with rheumatoid arthritis and rheumatic fever. *J Clin Invest* 1933;12:279-89.
78. Todd EW, Hewitt LF. A new culture medium for the production of antigenic streptococcal haemolysin. *J Pathol Bacteriol* 1932;35: 973-4.
79. Todd EW. The differentiation of two distinct serological varieties of streptolysin, streptolysin O and streptolysin S. *J Pathol Bacteriol* 1938;67:423-45.
80. Myers WK, Keefer CS. Antistreptolysin content of blood serum in rheumatic fever and rheumatoid arthritis. *J Clin Invest* 1934; 13:155-67.
81. Coburn AF. Observations on the mechanism of rheumatic fever. *Lancet* 1936;2:1025-30.
82. Wilson MG, Ingerman E, DuBois RD, Spock BM. The relation of upper respiratory infections to rheumatic fever in children. I. The significance of hemolytic streptococci in the pharyngeal flora during respiratory infections *J Clin Invest* 1935;14:325-32.
83. Wilson MG, Wheeler GW, Leask MM. II. Antistreptolysin titers in respiratory infections and their significance in rheumatic fever in children. *J Clin Invest* 1935;14:333-43.
84. Wilson MG. *Advances in Rheumatic Fever; 1940-1961*. New York, Harper & Rowe, 1962;32.
85. Jones TD, Mote JR. The clinical importance of infection of the respiratory tract in rheumatic fever. *JAMA* 1939;113:898-902.
86. Klinge F. Neuere Untersuchungen über Rheumatismus. *Schweiz Med Wchnschr* 1933;63:681-5.
87. Dawson MH, Tyson TL. The relationship between rheumatic fever and rheumatoid arthritis. *J Lab Clin Med* 1936;21:575-87.
88. Keefer CS. The etiology of chronic arthritis. *N Eng J Med* 1935; 213:644-53, 648.
89. Wallis AD. Rheumatoid arthritis. I-III. *Am J Med Sci* 1946;212: 713-22.
90. Fraser KJ. The Waaler-Rose test: anatomy of the eponym. *Sem Arthritis Rheum* 1988;18:61-71.
91. Westergren A. On serum titres, multiple infections, and complex aetiology in chronic polyarthritis. *Acta Med Scand* 1954;147: 387-98.
92. Coburn AF, Moore LV. The prophylactic use of sulfanilamide in streptococcal respiratory infections, with especial reference to rheumatic fever. *J Clin Invest* 1939;18:147-55.
93. Thomas CB, France R, Reichsman F. The prophylactic use of sulfanilamide in patients susceptible to rheumatic fever. *JAMA* 1941;116:551-60.
94. Coggeshall HC, Bauer W. The treatment of gonorrhoeal and rheumatoid arthritis with sulfanilamide. *N Engl J Med* 1939;220:85-103.
95. Boland EW, Headley NE. The effect of penicillin on rheumatoid arthritis. *JAMA* 1944;126:820-3.