THE BACTERIOLOGY OF ACUTE RHEUMATISM.*

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Since the beginning of modern bacteriology, many observers have believed that acute articular rheumatism belonged to the infectious diseases. Its course, frequently beginning with sore throat and terminating in a relatively short time, its appearance in epidemics and the occasional infection of an attendant, the similarity of the pathologic changes to those occurring in diseases known to be contagious and infectious, stimulated bacteriologists to search for the infectious agent. All types of bacteria were isolated from rheumatic cases, bacilli and cocci, aërobic and anaërobic; each worker had his own specific organism. The diversity of findings led to the conclusion that various organisms might produce identical symptoms and pathologic changes, just as pneumonia might be produced by a variety of bacteria. The occurrence of articular changes, similar to those of rheumatism, in pneumonia, scarlet fever and other infectious diseases made this assumption the more plausible. The view that acute articular rheumatism may be caused by an infection by various organisms—staphylococci, streptococci, pneumococci and others—or by a mixed infection, is still held by a large number of clinicians and bacteriologists.

Of those who believe that rheumatism is produced by a single specific parasite, there are three classes: 1, Achalme and his followers, notably Thiroloix; 2, Triboulet and Apert, Westphal, Wassermann and Malkoff, and their large school in Germany and England—of the latter especially Poynton and Payne; and 3, those who do not believe that the organism has been found.

ACHALME'S ANAEROBIC BACILLUS.

Achalme, in 1891, at the autopsy of a man who had died on the fourth day of an acute articular rheumatism with cerebral manifestations, discovered and grew in pure culture an anaërobic bacillus. It is a large organism, which in human tissues, or when on media prepared from human blood or urine, resembles the bacillus of anthrax; at times it is almost filamentous. It is not motile or very feebly so, stains by Gram's

method and with difficulty may be made to produce spores. In 1897 Achalme reported a second autopsy with similar findings; in the interval he had found the same organism in six living patients, four times in pure culture. Thiroloix had also found the anaërobic bacillus in nine cases of rheumatism, and other French and Italian observers a few times. In both of Achalme's autopsies, the bacillus was present in enormous numbers in the heart's blood and pericardial fluid; in smaller numbers, but also abundantly, in the cerebrospinal fluid, in the myocardium and diseased heart valves.

Inoculation of 1 c.c. of a bouillon culture in guinea-pigs produced death by septicemia in ten hours without local lesions. It resulted in vasodilatation, widespread thromboses, necroses, and the appearance of many mast cells at the site of inoculation. Thiroloix produced lesions in rabbits resembling those of rheumatism: endocarditis, pericarditis and pleurisy.

There is little ground for belief in the specificity of Achalme's bacillus, or at any rate for an assumption that it plays a rôle in many cases of rheumatism. During the last ten years an enormous amount of time has been given to the study of the bacteriology of the disease, and not more than eight or ten observers have found the organism; even those in a very limited number of cases. In the second place, the results of inoculation are most unsatisfactory. The general manifestations in animals have not resembled those of rheumatism in the human being. As a rule, the animals have died within a few hours. Endocarditis, pericarditis and pleurisy have been produced in animals by the inoculation of practically all of the known pathogenic bacteria — streptococcus, staphylococcus, pneumococcus, tubercle bacillus, etc., and their occurrence here does not make the specificity of the bacillus more probable. Recently Achalme has stated that his bacillus is identical with the *Bacillus aërogenes capsulatus* of Welch and Nuttall. He still believes it responsible for some, but not all cases of rheumatism.

THE STREPTOCOCCUS OF TRIBOULET AND APERT.

Triboulet and Apert, in 1898, produced mitral disease in a rabbit by the injection of streptococci obtained from a patient with rheumatism.

In 1899, Westphal, Wassermann and Malkoff isolated a streptococcus from a fatal case of chorea, following rheumatism, which they believed to be specific. The organism was found in pure culture in the heart's blood and the diseased valves. Streptococci had been previously found and described as occurring in ulcerative endocarditis consequent upon rheumatism. Von Leyden, in 1894, and Michaelis and Klemperer, in

the following year, had noted similar discoveries, but believed the organism to be one of a number which could give rise to such pathologic changes. Klebs, in 1875, Krause, in 1884, and Mantle, in 1887, had described the finding of streptococci in the joint fluids in rheumatism. Westphal, Wassermann and Malkoff found in addition that their organism, when grown in pure culture, could produce in rabbits changes closely resembling those of rheumatism. In three to ten days following the injection of the organism into the peritoneum, the joints became swollen and tender, the temperature rose several degrees, there was no suppuration, and the disease usually terminated in recovery. They described the organism as a streptodiplococcus, appearing in pairs and in short chains, and as requiring for its growth a high degree of alkalinity and a large amount of peptone in the culture media. This discovery gave a new impetus to the bacteriologic study of the disease. Since 1899 a host of investigators have given their attention to rheumatism. Poynton and Payne, of London, began their study, believing that they might reach the conclusions of Achalme and Thiroloix; in a short time they were followers of the other school. Poynton and Paine, Beattie, Shaw, Beaton and Walker, and many others in England have become convinced of the specificity of the organism. Unfortunately, most of their cultures have been derived from the cadaver. Since the researches of Flexner on terminal infections, it is well known that various organisms proliferate freely in the human body and appear in the circulating blood before death, so that it is possible that the organism found in the heart's blood may have been the ordinary *Streptococcus pyogenes*. The English observers have produced in rabbits practically all the symptoms and complications of rheumatism, as found in the human being; joint involvements, endocarditis, pericarditis, pleurisy and peritonitis. In at least three instances they (Poynton and Paine, Beaton and Walker, and Beattie) assert that they have observed choreiform movements in the head and eyes of the rabbits. Positive results have also been obtained from cultures of the circulating blood and joint fluid. The study of the morphology and cultural characteristics of the streptococcus has given varying results. In general it has been found that the organism does not differ in appearance from the *Streptococcus pyogenes,* except that the chains are usually short, containing not more than ten organisms, and that the chains are divided into pairs. Poynton and Paine maintain that acid media are most favorable to its development, while Beaton and Walker agree with Westphal, Wassermann and Malkoff in preferring alkaline agar and bouillon. The growths correspond rather closely to those of the *S. pyogenes* and to that of the organism of scarlet fever, as

described by Aronsohn and Moser. They are hemolytic, turning blood media to a rusty brown or chocolate color. Cultures on liquid media are not agglutinated by the serum of a rheumatic human being or that of convalescent rabbits.

EXPERIMENTS OF MEYER AND OTHERS.

Contradictory results have been obtained in large numbers. Phillip failed to grow the organism in twenty-one cases in which blood cultures were attempted, and in six inoculations from the knee joint. Meyer was likewise unsuccessful in thirty cases.

The work of Meyer is the most original and interesting of any done on the subject in recent years. He concluded, from his unsuccessful search of the blood, that the disease was either an intoxication from bacteria which remained localized in the throat or that the organisms entered the blood and were there rapidly destroyed. His method of studying the throat bacteria is unique. It is a thankless task to try to isolate the various organisms by agar plates or similar methods. He therefore inoculated bouillon with swabs from the throat, and after twenty-four hours' growth in the incubator, introduced some of this bouillon into the ear vein of rabbits. His results were remarkable. In a few days only one species was found in the joints; their localization he regarded as a sign of special affinity. These organisms, when grown in pure culture and again introduced into rabbits, produced just such results as had been described by Triboulet, Westphal, Wassermann, Poynton and others. They also presented a close resemblance morphologically. The blood and joint fluids were sterile within a few days, but cocci were found in large numbers in the endothelial lining of the joints and of the heart valves affected.

The conclusions as to specificity of the streptococcus reached by Meyer would be very convincing if there were not contradictory evidence. Bezançon and Griffon, in 1899, however, while trying to immunize rabbits against pneumococci, found that attenuated cultures frequently produced joint changes, pericarditis and pleurisy, such as had been described in connection with the streptococcus. Meyer, too, is compelled to assume that in scarlet fever, typhoid fever and other diseases, the transient arthritides are produced by a mixed infection.

Efforts to distinguish morphologically and culturally between this and other streptococci have been unavailing. Beaton and Walker found that it produced formic acid and that it grew on filtered bouillon, in which the *S. pyogenes* has been previously cultivated; to the latter fact (Marmorek's test) has been given special prominence.

Walker, in one of his latest paper on the subject, admits that "the case in favor of the *Micrococcus rheumaticus* is non-proven and appears, in some respects, perhaps less favorable than it did four or five years ago." The morphologic methods of differentiation have suffered especially. He enumerates the differential characteristics as follows:

1. A greenish brown discoloration in blood agar cultures, due to reduction of the hemoglobin. (This was shown by Schottmueller in 1903 to be true of various streptococci).

2. Growth obtained in Marmorek's test, that is, a filtered bouillon, on which other strains of streptococci had been grown. (The value of this test was made doubtful by the work of Meyer and Aronsohn in 1902.)

3. Growth in very alkaline media.

4. Production of considerable quantities of acid. (Neither of these characteristics is sufficiently distinctive to differentiate.)

Walker also says that he has "no hesitancy in saying that, as far as its appearance and characteristics went, the organism would undoubtedly be classed as an ordinary streptococcus, if handed without comment to an expert bacteriologist."

Admitting the impossibility of distinguishing the organism described, morphologically and culturally, two more methods remain for its identification as the specific cause of rheumatism: 1, its discovery in all cases of the disease; and 2, the production of the disease in animals by its introduction into their bodies. As mentioned before, the second point has been most emphasized. The work of Beattie and Meyer has been especially important. Beattie compares the results of inoculation in rabbits of the *Streptococcus pyogenes* with those produced by the *Micrococcus rheumaticus*.

STREPTOCOCCUS.

Method of Injection.	No. Subjects.	
Intravenous	34	
Intraperitoneal	7	
Subcutaneous	3	
Subcutaneous and intraperitoneal	4	
	48	

Results.	No. Subjects.	Per cent.
Death in	7	14.5
Arthritis in	9	18.7
Endocarditis in	1	2.

"MICROCOCCUS RHEUMATICUS."

Method of Injection.	No. Subjects.	
Intravenous	13	
Knee joint	1	
Subcutaneous	1	
	15	

Results.	No. Subjects.	Per cent.
Death in	2	13.3
Arthritis in	9	60.
Endocarditis in	5	33.3

In the former the arthritis was definitely purulent and usually involved the wrist joints. The only case of endocarditis was associated with abscesses of the kidney and vertebræ. The arthritis of the latter was non-purulent and usually appeared in the knee joint. Most of the animals that were not killed recovered from the disease.

Meyer's results were similar, although the percentages differed. Of one hundred animals inoculated with the specific organism, twenty-one developed joint disease, while only two of one hundred treated with *Streptococcus pyogenes* exhibited arthritides. Transplantation and animal passage did not increase its tendency to suppuration. Lewis and Longcope inoculated five rabbits with a streptococcus derived from a fatal case of rheumatism twelve hours antemortem; all of the animals showed joint involvement, and one a vegetative endocarditis.

The power of the streptodiplococcus to produce joint disease and its special affinity for the joints is beyond question, but the experiments of Widal, Benzançon and Griffin, and of Cole, have rendered it doubtful whether other organisms may not also act as causative factors in the disease.

Demonstration of the coccus in all cases of the disease has failed most signally. Cole states that for years blood cultures were taken from every case of rheumatism at the Johns Hopkins Hospital, and that these had been invariably sterile; the results of Singer and Phillip were similar. While some of the positive findings of the English observers were obtained in living individuals, the vast majority were derived from the cadaver; the endocardium and synovial membranes appear to be particularly rich in organisms. The blood and synovial fluids were usually sterile at autopsy. The type of rheumatism in England must be much more severe than that seen in this country or on the European continent, as fatal cases of uncomplicated rheumatism are unusual with us; hence the opportunity of studying them bacteriologically at autopsy rarely presents itself. The postmortem study is also associated with dangers. The multiplication of bacteria in the body shortly before death is well known, and their discovery in large numbers may lead to false conclusions. Could similar results be obtained in the living and not moribund, they would be of much greater value in the establishment of the organism as the specific agent. It was with this object that my work was undertaken.

REPORTS.

This work consisted of attempts at cultivating the suspected organism from forty-five cases, all of which were clinically typical of acute articular rheumatism. The cases were taken as the patients entered the Cook County and Presbyterian Hospitals; those which had passed the acute febrile stage were rejected. The large majority had received no medical treatment, or at most a few doses of the salicylates at the time the culture media were inoculated. Relatively few of the patients came under observation during the first week of the illness; almost all during the second week. By this time there were evidences of throat infection only in isolated instances, though the majority gave a history of early involvement of the tonsils.

The media used were at the beginning those recommended for the purpose by Poynton and Paine and their school in England. It was found almost impossible, however, to produce clear alkaline broths and agar; this made the determination of the presence of growths by the naked eye very difficult. All of the liquid media presented precipitates after intervals of twenty-four to seventy-two hours; these probably consisted of minute flakes of fibrin, which adhered to the side and bottoms of the tubes and flasks. When growths were obtained, they were inoculated into all of the special media prepared, as well as on ordinary agar, blood serum, acid bouillon, and litmus milk. It appeared that the growths in acid bouillon were more luxuriant and rapid than those in the original cultures; therefore, in the latter part of the work, acid bouillon was employed for the first inoculations and if growths were present subcultures were made from them. As it was difficult at times to be sure whether or not there would be a positive result, inoculations were made from all of the primary flasks in twenty-four to forty-eight hours after their inoculation. In every case in which any growth was obtained, from 15 to 30 c.c. of a culture in bouillon was introduced into the ear veins of one or two rabbits. In each case the inoculation was repeated if the rabbit lived.

Many of the patients had mild endocarditis; four had ulcerative endocarditis; of these two recovered. One of these in the course of his illness had a hemiplegia. Of the two fatal cases, the diagnosis in one was confirmed by autopsy. The patient in the other case had a pericarditis in addition to the endocarditis. Another patient had enormous subcutaneous and submucous hemorrhages. Almost the entire body surface was discolored purple or dark red. The slightest traumatism produced hemorrhages, and the introduction of the needle into the median

veins also resulted in enormous effusions. The rheumatic symptoms in this case had also been very pronounced, but had become much less marked when the bacteriologic work was undertaken. The patient died within a week of the time at which blood was taken from his veins, but no autopsy could be made.

Blood was taken from the most prominent vein at the bend of the elbow in each one of the cases. For this purpose a Luer syringe, which had been sterilized in the autoclave, was used and a needle sterilized by dry heat. No joints of any kind were used and no lubricant to make the syringe air-tight. These things were discarded so as to minimize the chances of contamination. It was usually possible to obtain 7 to 10 c.c. of blood in this way. In the earlier part of the work 1 c.c., 3 c.c., and 5 c.c. of blood, respectively, were introduced into three flasks containing 150 c.c. of bouillon; in the latter part two flasks only were used, for one of which 2 to 3 c.c. of blood were used, and 5 c.c. for the other. When possible, fluid was also taken from the joints. In many cases, in spite of the apparently large effusion into the joints, it was impossible to obtain any fluid. The difficulty seemed to be less in the viscidity of the fluid than in the fact that the greater part of the swelling was due to edema of the surrounding tissues. The skin at the point of introduction of the needles was sterilized, as well as possible, by the use of 95 per cent. carbolic acid, followed by alcohol.

Of the forty-five cases thus examined, thirty-four gave no cultures at any stage. In five of these, fluid from the knee also gave no growths. Of the remaining eleven cases, cultures were obtained in ten cases from the blood, in one case from the knee joint.

CASE 1.—Two blood inoculations were made; of these one was negative, 1 c.c. of blood in 100 c.c. of bouillon. One of 3 c.c. of blood in 100 c.c. of bouillon showed an abundant growth in twenty-four hours. The bouillon was very turbid. Microscopically, smears showed numerous cocci not arranged in chains or pairs. Subcultures corresponded to growths of the *Staphylococcus albus*. No further work was done with this culture, as it was assumed to be either a contamination or derived from the skin.

CASE 2.—A luxuriant growth appeared in all the culture flasks in twenty-four hours. Subcultures in glycerin agar appeared as white, pinhead-sized colonies. Milk was not acidified in twenty-four hours. Smears showed staphylococci, which were large, many biscuit-shaped, and sometimes arranged in pairs, never in chains. Inoculation into a rabbit produced no apparent change. This, too, was assumed to be a contamination and the organisms were traced no further.

CASE 3.—This was a case of joint involvement associated with high temperature and cerebral manifestations, resembling those of a meningitis. My cultures during life were negative. At autopsy, minute warty vegetations were found on the mitral valves. The joints were not opened. Cultures taken from the blood and meningeal fluids showed a motile bacillus, which did not produce rheumatic

changes in a rabbit. The organism was a facultative anäerobe, resembling in appearance the typhoid bacillus. It was not identified.

In none of the above cases could any suspicion be entertained that the organism isolated was that believed to be specific for acute articular rheumatism. In all the following a streptodiplococcus was obtained, which morphologically and culturally corresponded to that described by Triboulet and Apert, Wassermann, and Poynton and Paine. All the cases were recent and undoubted acute rheumatics.

Case 1.—Growth appeared in twenty-four hours. Inoculations into ear veins of two rabbits were negative.

Case 2.—Cultures did not become apparent until after six days in the incubator. Inoculations were negative.

Case 3.—Rheumatism with malignant endocarditis and pericarditis. Inoculation into rabbit (10 c.c. of bouillon culture) produced death in twenty-four hours. Heart valves and joints showed no changes.

Case 4.—There was slight turbidity in twenty-four hours. Inoculations were negative.

Case 5.—Rheumatism with acute endocarditis and hemiplegia. Growths on all media showed typical organisms. Inoculation into one rabbit produced death in a few hours; autopsy showed a thrombus in the right ventricle. Inoculation into other rabbits caused no perceptible change.

Case 6.—The original culture showed no visible growth. A subculture on glycerin agar in one week presented very minute colonies above the water of condensation. Short chains (six to eight cocci) were found in the smears. Inoculations into animals proved negative.

Case 7.—Malignant endocarditis associated with rheumatism. Inoculations into rabbits produced no apparent effect.

Only one positive culture was obtained by the use of joint fluid.

Case 1.—This culture was taken from the right knee. Growths appeared in twenty-four hours. These resembled in all particulars those obtained from the blood in the preceding seven cases. Inoculations into rabbits were negative.

In five cases, joint cultures remained sterile.

Blood cultures were also made from two cases of chorea. Both of these showed growths on all media.

Case 1.—Previous rheumatism; second attack of chorea. Cultures were positive in two days. Smears showed Gram-positive diplococci and staphylococci. The growths appeared as white colonies, pinhead-sized, to a great deal larger. Subcultures were typical of *Staphylococcus pyogenes albus*. Inoculations into a rabbit produced no noticeable symptoms.

Case 2.—Mother of patient had had rheumatism twenty-two years before; one sister had had chorea four times. Blood smears were made on glycerin agar; subcultures in bouillon, which became markedly cloudy after days. Smears showed diplococci longer than broad, with the general characteristics (noted before) of the *Streptococcus pyogenes*. Inoculations into rabbits were negative.

Altogether, then, a streptodiplococcus or streptococcus was isolated from nine cases:

Five were of rheumatism with or without endocarditis of a mild type (four from blood, one from knee).

Three were of rheumatism with malignant endocarditis.

One was a case of Sydenham's chorea.

Other organisms were obtained in four cases, one undoubtedly a contamination; three proved to be the *Staphylococcus albus*. It is more than likely that this organism came from the skin of the patient, in which it is found so frequently that it must be reckoned with as a finding in a fairly large percentage of blood cultures.

On the basis of such findings Sahli and others have contended that rheumatism might be produced by any one of a number of organisms. Nevertheless, the staphylococcus at least is of such frequent occurrence in association with other diseases or cultures from normal blood that its discovery must in most cases be attributed to other sources than the circulating blood.

It is difficult to draw any positive conclusions from my work. I believe it unlikely that the streptococci obtained from the blood in the above cases were identical with those cultivated by Wassermann, Poynton, Paine and others, chiefly because they failed to show the only feature which distinguishes them from other streptococci, their virulence and the production by them of specific pathologic changes in animals. As stated above, cultures and morphologic appearances of the *"Micrococcus rheumaticus"* differ in no essentials from those of other types of streptococci. All the characters supposed to belong particularly to the coccus of rheumatism have been shown to occur with other strains as well. The failure to isolate a virulent streptococcus from the blood does not, however, disprove its existence; there may be truth in the contention of Meyer that the blood is an unfavorable medium, and that the organisms fail to proliferate, and die except when located in the fixed tissues. Animal inoculations with the streptococcus seem to confirm this hypothesis. In many other diseases, too, in which there may be a generalized infection, such as gonorrhea and tuberculosis, the organisms are demonstrated in the blood with great difficulty.

Streptococci have been found in many diseases in which their pathogenicity is far from proved: scarlet fever, smallpox, terminal and other infections. They seem to develop very readily in patients whose general resistance has been lowered. Pathogenic organisms of other types have also been grown from the blood of individuals not suffering from the diseases which these organisms ordinarily produce. Thus Busse has reported the cultivation of typhoid bacilli from the blood of three cases of miliary tuberculosis and one of pneumonia. Krehl (quoted by Busse) reports a similar experience, and the multiplication of blood cultures in clinical work will undoubtedly increase the number. From such evidence

one can judge of the possible source of the organisms obtained by my blood cultures. My results are in accord with those of Singer, Philip, Cole and Meyer, who also failed in their attempts to grow the *Micrococcus rheumaticus* from the blood of patients. It would be folly to deny on such grounds the existence of a specific organism; but it appears that isolation of the coccus from the living body is necessary to fix its position as the specific cause of rheumatism. Postmortem examinations are fraught with too many fallacies, and the organism shares with too many others the faculty of producing rheumatoid lesions, though it may do so with greater frequency. Until the coccus is proved to occur in most of the living patients as well as in the fatal cases of rheumatism, the claims for its specificity will remain on an unstable foundation.

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