ACUTE RHEUMATISM CAUSED BY THE "DIPLO- COCCUS RHEUMATICUS."

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(PLATE XXIII.)

THE clinical features of acute rheumatic fever, and the facts that have accumulated as to its epidemic and infectious nature, have long suggested a bacterial cause. In 1887 Dr. Mantle⁽³⁾, at a meeting of the British Medical Association, put forward this view. In the same year Popoff⁽⁶⁾ obtained cultivations of a micrococcus from the blood of a rheumatic fever patient, and by intravenous injections in rabbits produced arthritis, pericarditis, and endocarditis. These observations received very little attention.

In 1891 Achalme⁽¹⁾ discovered a bacillus resembling anthrax in nine cases of rheumatic fever. From his injections he did not obtain in animals a true picture of rheumatic fever as it occurs in man; but in 1896 Thierloir⁽⁸⁾ isolated a bacillus apparently identical with that of Achalme, and by intravenous injections in rabbits he obtained the entire picture of rheumatic fever. These observations were confirmed by others. Triboulet⁽⁹⁾ in 1898 found a diplococcus in five cases, and in two of these it was associated with Achalme's bacillus. Dana⁽⁴⁾ in 1894 had obtained a diplococcus from a case of chorea following rheumatism. In 1898 Triboulet⁽¹⁰⁾, working with Apert, isolated a diplococcus from eleven cases. In one of these the organism was got from the blood. By intravenous injection in a rabbit they produced thickening of the mitral valve, with hypertrophy and dilatation of the chambers of the heart. They failed, however, to produce arthritis. In 1899 Westphal⁽¹¹⁾, Wassermann, and Malkoff isolated a diplococcus from a case of severe rheumatism and chorea. This organism regularly produced a polyarthritis in a series of eighty rabbits.

Though the evidence seemed strongly to point to a special diplococcus as a causal factor, the matter remained in a very uncertain

state until the valuable work of Drs. Poynton and Paine (⁵) was published in 1900.

It is not necessary to give more than the very briefest outline of their work. From eleven successive cases (since increased to eighteen) of acute rheumatism they isolated a diplococcus—in five cases in pure culture. This diplococcus, inoculated intravenously into rabbits in large doses, produced the clinical characteristics of rheumatic fever—polyarthritis, valvulitis, pericarditis, and chorea. The organism was recovered in pure culture from the joint exudation, heart-blood, urine, and cerebro-spinal fluid of rabbits that had been inoculated with a sufficiently large dose. From their experiments they deduced that “this diplococcus is a cause of rheumatic fever.”

Beaton and Ainley Walker (²) published the results of a similar investigation in January 1903. They obtained a similar diplococcus in fifteen cases, and produced in rabbits typical acute rheumatism.

Recently I have had the opportunity of investigating two cases of acute rheumatism, and my work bears out, in all essential points, the results obtained by Poynton and Paine.

CASE 1.—A woman, æt. 30, was admitted to the Royal Infirmary, Edinburgh, on the 31st March 1903, suffering from pains in the joints, chiefly in the wrists, knees, and ankles. The history was that for a fortnight previous to admission she had been troubled with pain and stiffness in various joints. On admission her temperature was 102°. Both knees were swollen—the right more markedly than the left. The joints of the fingers and of the wrists were swollen and red. There was no evidence of any heart lesion, and the lungs were healthy. On the evening of the 1st April she became delirious. On the 4th April some œdema of the lungs appeared, and a faint systolic murmur was heard at the base of the heart, most marked in the pulmonary area. The next day there was a systolic bruit in the mitral area. Her condition remained practically unchanged, the temperature varying between 103° and 104° until 8th April, when the delirium increased, the pulse became weaker; and the temperature at night rose to 105°·6. The condition of the heart remained as before, except that the first sound in the mitral area assumed a sharp slapping character. From this date onwards the patient went steadily downhill—the mouth became drawn, the face sunken, and the pulse rapid and weak. The joints remained swollen and slightly red.

On the morning of 13th April she died.

Throughout the illness the urine was concentrated—specific gravity, 1037. It contained a trace of albumin, but no blood. The leucocytes were always slightly above or below 25,000, with 80 per cent. of polymorphonuclear cells.

AUTOPSY, April 14, 1903.—The pericardial and pleural sacs were healthy.

Heart.—Weight, 12 oz. All the cavities were dilated. The orifices were normal in diameter. The aortic and pulmonary valves were competent. On the aortic segments, and on the anterior mitral segments, there were a few small recent vegetations. Otherwise the segments were comparatively healthy. The coronary arteries were healthy. The myocardium was pale and very friable, and showed acute myocarditis, with fairly marked fatty degeneration.

The lungs showed no important pathological changes; and the liver, spleen, and kidneys showed only the ordinary changes associated with acute septic absorption. There was very marked congestion of the synovial membranes in both knee-joints. No congestion in the ankle-joints.

Cultures were made in milk broth from the knee-joints, and a diplococcus

resembling that described by Paine and Poynton was found. It was associated, however, with putrefactive organisms. I was not able to separate the diplococcus, and inoculations into animals were in consequence not made.

CASE 2.—The patient was a girl, *æt.* 16. She had had rheumatic fever at the age of 7, and again at the age of 9, and during the latter attack she developed cardiac disease. At the age of 10 she had pleurisy, and in June 1902 (*æt.* 15) she was again in the Royal Infirmary with rheumatic fever. Her mother had had rheumatic fever twice, with definite cardiac affection. On the morning of the 23rd June 1903 she was perfectly well. She got very wet on her way to work, and in the evening she had pains in both ankles and in both knees. On the 24th she was feverish, and had pains in the shoulders and elbows. The pains continued, and on the 27th she was sent to the Royal Infirmary. On admission both knees were swollen, and contained a considerable amount of fluid. The ankles and elbows were not swollen. All the joints of the fingers were painful on movement. There was a loud presystolic and systolic murmur at the apex of the heart. No pericardial friction. No increase of cardiac dullness.

June 28.—Vomited after taking some milk. Pain entirely gone. No pericardial friction.

June 29.—Urine contained no albumin and no blood. She was breathless; there was a short cough, with frothy, bright, blood-stained sputum. There was friction in the lower axilla and at the base posteriorly on the right side. Cardiac dullness increased both to left and right; no friction. In the evening there was great dyspnoea and cyanosis. The pulse was very rapid and dicrotous. There was a loud presystolic murmur internal to the apex, and numerous medium and fine crepitations all over the right lung, with friction, especially to the right of the sternum and in the right axilla. There was slight dullness at the right base. The hæmoptysis was still present. Later, dyspnoea became more marked, with extremely feeble pulse. Patient collapsed and died suddenly at 2 A.M. on the 30th.

AUTOPSY.—No swelling could be made out in any of the joints. There was a slight amount of turbid fluid in the pericardial sac, and a few fibrous adhesions in both pleural sacs.

Heart.—There were a few petechial hæmorrhages in the posterior groove between auricles and ventricles. Over the right auricle the epicardium was thickened generally, but there were in addition numerous raised nodular thickenings about the size of the head of a small pin. There was a slight amount of very recent lymph on the posterior surface of the left auricle in the region of the great vessels. All the chambers were dilated. In both ventricles there was a considerable amount of pale stringy thrombus. The arterial valves were competent. The tricuspid orifice and cusps were practically healthy. The mitral orifice was dilated. The cusps were long and very much thickened. The chordæ tendinæ were thick and short. There was a small pouch almost $\frac{1}{2}$ in. in length opening on the ventricular aspect of the posterior cusp and projecting upwards towards the auricle. On the edges of the auricular surface of both cusps there were small recent vegetations. The aortic cusps were thickened, but on them there were no recent vegetations. The aorta was healthy, and the coronary arteries were healthy. The muscle of the left ventricle was very friable, without much evidence of fatty change. There were small pinkish areas scattered irregularly through the heart muscle, suggesting an acute myocarditis.

The other organs showed no special changes, except those associated with a chronic heart lesion.

The synovial membranes in both knees were examined, but, with the exception of very slight patchy congestion, nothing abnormal was detected.

EXPERIMENT 1.—Cultures were made from the congested areas in the right knee in milk-bouillon, as recommended by Paine. In twenty-four hours there

was distinct coagulation of the medium, and examination of films revealed a pure growth of a minute micrococcus, occurring in pairs and in short chains. Further examination showed this organism to correspond in cultivation and in staining reaction with that described by Poynton and Paine. Subcultures were made in blood-agar tubes, and on the 21st July, three weeks after cultures were obtained, a rabbit was inoculated. I had considerable difficulty in getting the injection into the vein of the ear, and most of the fluid escaped in the subcutaneous tissues.

No local suppuration or any other result was got from this injection. On the 24th July a second rabbit was injected intravenously with three blood-agar tubes of the culture.

July 27.—There was a slight lameness in one of the hind legs.

July 28.—There was a suspicion of a systolic murmur heard over the heart.

July 29.—The systolic murmur was very distinct, and there was swelling in the left ankle-joint.

August 5.—The rabbit was killed. I found marked endocarditis, with large vegetations on the aortic cusps (Plate XXIII. Fig. 1), and the left ventricle was dilated. There was no evidence of disease on the other valve segments. In the right kidney there was a recent pale infarction. There was fluid, non-purulent, in the right knee and in the left ankle-joint. The synovial membrane in both was thickened, and somewhat gelatinous in appearance. The bladder was distended. Cultures were made from the vegetations, the joint exudations, and the urine, and the diplococcus were recovered in pure growth from them all (Plate XXIII. Fig. 2).

Microscopic examination was made of the vegetations and of the infarction. The vegetations contained great masses of the diplococcus (Plate XXIII. Fig. 3). No organisms were found in the infarction, though the cell changes pointed definitely to its being of not more than a few days' duration.

EXPERIMENT 2.—On 11th August two rabbits received an intravenous injection of a small dose—one agar tube. This produced absolutely no result, except a rise of temperature for a couple of days. On the same day a third rabbit was injected with one agar tube of culture, the injection being made into the right knee-joint.

August 12.—No rise of temperature. The right knee was much swollen and tender. The swelling gradually subsided, and the animal appeared to be quite well. It was killed on the 26th August. There was no fluid in the right knee-joint, but the synovial membrane was thickened. The other joints were healthy. No other naked-eye lesion was found, except a very minute vegetation on the mitral valve.

Cultures from this vegetation gave a pure growth of the diplococcus.

A point of special interest in this experiment is the fact that the organism may remain latent in the joints for some time, and later cause an endocarditis. Since I read this paper before the Pathological Club of Edinburgh, Shaw (7) has published the results of several similar experiments, with like results.

EXPERIMENT 3.—On 19th August another rabbit was inoculated intravenously with the contents of four blood-agar tubes—subcultures from the original cultivation.

August 21.—There was very definite chorea, with twitching of the head and eyes to the right side.

When the animal attempted to walk it fell to the right side, and the twitching became much more marked.

August 23.—The chorea was much less marked.

August 24.—The twitchings had now practically ceased.

August 26.—The rabbit was killed.

At the autopsy nothing abnormal to the naked eye was detected. Cultivations were made from the heart blood and from the urine. A pure culture of the diplococcus was got from the urine (Plate XXIII. Fig. 4), but no growth was obtained from the blood. Through an unfortunate oversight cultivations were not made from the spinal cord.

Microscopic examination of the cord showed an exudation of polymorpho-nuclear leucocytes on the surface, at irregular intervals. In these areas I have not found any organisms.

In the light of all the work which has been done on this subject it seems impossible to resist the conclusion that acute rheumatism and its associated disease chorea is a bacterial disease. The only question, then, that need be discussed is, "Is the diplococcus a specific organism?" The fact that in cases of definitely rheumatic endocarditis we do not find the organism is only what one would expect. As Poynton has emphasised, rheumatic fever is rarely fatal when the lesions are in their early or very acute stages. The diplococcus is very minute, and may easily escape observation. Further, it seems to be easily destroyed in the tissues. In my cases, both fairly acute, though the organism was got in culture, even after most careful search I have been able to find only two or three very minute groups of organisms in the heart in Case 2, none in any of the other organs, and none even in the recent vegetations.

The finding of streptococci, pneumococci, and other organisms in the vegetations proves nothing. These are liable to be deposited on any damaged area; and until it can be shown experimentally that these organisms reproduce the disease, we must treat them as accidental invasions.

Up to the present time only two organisms have been shown experimentally to produce typical acute rheumatism—the bacillus of Achalme and the diplococcus described by several observers. It is highly improbable that all the recent workers on acute rheumatism could have overlooked an anthrax-like bacillus, even though it needed to be cultivated anærobically. Moreover, Paine commenced his work with the object of confirming Achalme's observations, and in not a single case did he find the bacillus.

On the other hand, it is quite possible that in the earlier work by Achalme and others the diplococcus was overlooked. Achalme's failure to produce acute rheumatism in rabbits, and Dana's observations, where, in two of his first five cases, he found a diplococcus associated with Achalme's bacillus, at least suggest that there may have been a fallacy in Thiroloix's results.

FIG. 1.

FIG. 2.

FIG. 3.

FIG. 4.

Whether this be the case or not, the weight of evidence is at present in favour of the organism, which Walker has called the "Diplococcus rheumaticus," being, if not the principal, at any rate a causal agent of acute rheumatism.

In conclusion, I have to thank Dr. R. A. Fleming and Professor Greenfield, under whose care the patients were, for clinical notes of the cases, and for permission to publish them; and Mr. Richard Muir for the drawing and micro-photographs.

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DESCRIPTION OF PLATE XXIII.

FIG. 1.—Heart of a rabbit, inoculated with a micrococcus from the synovial membrane of a case of acute rheumatism, showing the mass of vegetations on the aortic valve.

FIG. 2.—Twenty-four hours' culture in milk-broth, from the vegetations. ($\times 1000$.)

FIG. 3.—Vegetations on the aortic valve, showing masses of the micrococcus. ($\times 40$.)

FIG. 4.—Twenty-four hours' culture in milk-broth from urine of a rabbit which developed chorea. ($\times 1000$.)