ACTINOMYCES MURIS ENDOCARDITIS TREATED WITH CHLORAMPHENICOL

BY

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Received June 15, 1950

In 1926 interest in the *Actinomyces muris* was first awakened by its recovery from the blood and synovial fluid of patients in an epidemic of a febrile illness with arthritis and morbilliform rash at Haverhill, Massachusetts (Parker and Hudson, 1926; Place and Sutton, 1934). This organism is also the cause of some cases of rat-bite fever, which can often be distinguished clinically from those due to the *S. minus* by the predominant symptom of arthritis, and has been reported as producing endocarditis on five occasions in Australia, New York, Panama and Chicago (Rowntree and Rohan, 1941; McDermott *et al*., 1945; Wedding, 1947; Priest *et al*., 1947). It has been known to inhabit the nasopharynx of rats in Great Britain since attention was drawn in 1933 to its presence by a sporadic infection in laboratory animals inoculated with blood from bludgeoned rats at Mill Hill (Strangeways, 1933). There are few reports of its appearance in a pathogenic role in men in this country. These are limited to the occasional case of rat-bite fever, and a single fatal case of endocarditis, in which its identity was in doubt (Stuart-Harris *et al*., 1935). A case of subacute bacterial endocarditis has recently been observed in which this organism was twice isolated from the blood. Clinical arrest was achieved with chloramphenicol after treatment with penicillin had failed.

A typist, aged 27, was admitted to University College Hospital under our care on July 4, 1949. In 1937 she was treated in hospital for twelve months for rheumatic fever. Some time later she was told that she had mitral stenosis. In 1939 she had a second attack of rheumatic fever which responded well to salicylates; at this time she was found to have mitral stenosis and a water-hammer pulse.

In January, 1948, she handled a dead rat which her dog had caught. In February, 1948, she sustained a brief febrile illness, and on March 24 became ill with fever, sweating, fatigue, and pains in hands and knees; a severe pain developed in the left upper quadrant of the abdomen. Pain appeared later in the left side of the chest posteriorly and a diagnosis of pleurisy was made, for which she was admitted to the North Middlesex Hospital on April 2. At this time the temperature was 102°F with rapid pulse and respirations and indeterminate signs at the left base. There was tenderness and pain on movement at the metacarpophalangeal and knee joints. There was considerable cardiac enlargement with mitral stenosis and aortic regurgitation. She was treated with salicylates in full doses but the temperature did not settle for two weeks and her joint pains continued. Early in May the temperature rose sharply and continued for three weeks at a level of about 103°F. A single blood culture was sterile. She began a 28-day course of penicillin, 125,000 units 3-hourly on May 25, and the temperature subsided on May 29. During the course of penicillin numbers of rheumatic nodules appeared on the wrists and elbows and were present for two months. Recovery was slow, and joint pains continued despite salicylates. She left hospital on September 24 and by November 25 was back at work. During this illness the spleen was not palpable and there were no emboli into the skin.

247
She remained quite well apart from dyspnoea on unusual exertion, until June, 1949, when she developed recurrent pain in the tips of fingers and toes lasting 48 hours at a time, and accompanied by swelling and tenderness of the pulps and bruising under the nails. She also had painful red swellings on the palms and right shin, and became increasingly tired and short of breath.

Temperature was 99°F, pulse 84 and regular, respirations 28, and blood pressure 150/50. She was a plump, cheerful girl, not acutely ill. No cyanosis. No clubbing. No pyorrhoea or pharyngitis. There was forceful arterial pulsation in the neck, and obvious capillary pulsation in the nail beds. The heart was enlarged 16 cm. to the left in the fifth space. There were signs of mitral stenosis and free aortic regurgitation but not of congestive failure. All peripheral arteries were pulsating. The spleen was palpable 2-5 cm. below left costal margin. All joints were normal. There was a red tender swelling 7-5 cm. in diameter on the right shin.

Blood examination showed Hb 74 per cent and 4,600,000 red cells per cu. mm.; white cells 5,600 per cu. mm., with normal differential. E.S.R. 30 mm. in one hour. Urine contained a faint trace of albumen and one red cell per high-power field. Two blood cultures taken in the first few days after admission yielded Actinomyces maris. During the first week after admission numerous embolic manifestations were seen, including splinter hæmorrhages under the nails, Osler's nodes in the pulps of fingers and toes, and small spots on the palms of the hands. Pending sensitivity tests, penicillin therapy was begun on July 11 with 600,000 units of procaine penicillin twice daily, giving a level immediately before injection of 0-32 units per ml.

During the first fortnight of penicillin treatment, the temperature partially settled, but embolic phenomena continued and she remained tired and unwell. On July 26 she had a sudden pain in the left upper quadrant of the abdomen and in the left shoulder, and the spleen, which had previously receded, became palpable again and tender. Meanwhile, sensitivity tests had shown that the actinomyces was resistant to penicillin but was of the same order of sensitivity to chloramphenicol as Klebsiella 41. Penicillin was therefore stopped on August 3. Blood cultures on the 5th and 8th of this month were sterile, but continuing embolism showed that the disease was still active. Chloramphenicol 1 g. was given on August 10 and followed by 0-5 g. four-hourly for the next 28 days. By the end of the first week's treatment emboli had ceased and the general health was much improved.

The patient's convalescence was interrupted by a sudden bout of severe precordial pain and tachycardia; there was no fever, but electrocardiographic evidence suggested a small posterior cardiac infarct. At this point there was no other sign of embolism and she felt well as soon as the pain had subsided. She was discharged to a convalescent home on October 25 after a further six weeks' rest, the blood count showing Hb 100 per cent and E.S.R. 8 mm. in one hour.

**Bacteriological Note.** Blood cultures were made in "liquoid" (sodium polyanethol sulphonate) broth and incubated in air, air plus 5-10 per cent CO₂, and anaerobically plus about 5 per cent CO₂ (von Haebler and Miles, 1938). The first sample of blood was taken on the day of admission, the second two days later. All cultures, aerobic and anaerobic, from these two samples yielded an organism having the following characteristics.

**Microscopic appearance.** Very pleomorphic, irregularly staining, but mainly Gram negative streptobacillus. A few branching forms seen in liquid culture, numerous serpentine and some club forms, no moniliform bodies (Fig. 1, 2, and 3).

**Cultural characteristics.** The organism was a facultative aerobe and preferred an anaerobic atmosphere with CO₂ added. All subsequent cultures were incubated under these conditions. Although growth occurred in the original aerobic cultures it was relatively feeble and subcultures from them were sterile unless CO₂ was added to the atmosphere. In spite of a profuse growth of fluffy colonies in the original anaerobic blood liquoid broth, great difficulty was experienced in making successful subcultures and no medium was found which would yield a comparable growth. Subculture on 10 per cent defibrinated human blood agar gave minute non-hæmolytic translucent colonies after 2-4 days, which on further incubation increased to a maximum of about 0-3 mm. diameter. Moderate, slightly granular growth appeared after three days when these colonies were seeded into 30 per cent human serum broth. Cultures in the following media were sterile after five
day's incubation: 10 per cent oxalated horse blood agar (several cultures were made but only one batch of blood was used); 1 per cent glucose nutrient agar; 5 per cent and 15 per cent horse serum broth; Robertson's cooked meat broth; horse blood broth; 1 per cent glucose broth and human blood agar incubated at room temperature.

Sensitivity tests. These were made on human blood agar. For penicillin and streptomycin, filter paper discs impregnated with standard amounts of the antibiotic were used and for chloramphenicol, which was of unknown strength and unsterile, a hole was bored in the medium and sealed with molten agar. The activity of the antibiotics in discs and "cup" was controlled by seeding the unknown strain on one-half of the plate and a control strain of known sensitivity on the other, the antibiotic lying between them. The results are shown in Table I.

### TABLE I

**Results of Sensitivity Tests**

<table>
<thead>
<tr>
<th>Antibiotic</th>
<th>Zone radius</th>
<th>Control zone radius</th>
</tr>
</thead>
<tbody>
<tr>
<td>Penicillin</td>
<td>Nil</td>
<td>15 mm. (Oxford Staph.)</td>
</tr>
<tr>
<td>Streptomycin</td>
<td>Growth irregular, result not readable</td>
<td>12 mm. (Oxford Staph.)</td>
</tr>
<tr>
<td>Chloramphenicol</td>
<td>17 mm.</td>
<td>17 mm. Klebsiella</td>
</tr>
</tbody>
</table>

Since the controls grew more rapidly than the test strain a comparison of the inhibition zones can only give a very rough estimate of the sensitivity. A more precise test in liquid culture could not be made because no liquid medium was found that could be relied on to yield good growth in a series of tubes. As urgent investigations were now complete the culture was freeze dried and put aside for further investigation. Unfortunately, when it was examined a month later it was no longer viable.

Before changing to chloramphenicol treatment the blood was again cultured in an attempt to demonstrate continued infection in spite of penicillin. Three blood samples, 5 ml. each, were taken on the same day and delivered as before into "liquoid" broth. All three bottles were
incubated in the most favourable atmosphere (anaerobic plus CO₂); this was repeated three days later. All six bottles were subcultured thrice weekly and all remained sterile after four weeks' incubation.

Although the investigation of the strain could not be completed, it is clear that it resembles Actinomyces muris more closely than any other organism previously isolated from human blood. It is of interest that so delicate an organism flourished in the primary human blood—"liquoid" broth cultures.

**DISCUSSION**

It seems probable that the original infection with Actinomyces muris occurred in 1948, a few weeks after contact with a rat in January. Though blood culture was negative, it is difficult to escape from a diagnosis of subacute bacterial endocarditis at this time in view of the splenic pain and the prompt response to penicillin of the fever which had resisted salicylates. It is also probable, however, that there was some active rheumatism at the same time in view of the rheumatic nodules.

In previous cases of subacute bacterial endocarditis from whom Actinomyces muris has been recovered, the organism has been sensitive to penicillin (McDermott et al., 1945; Priest et al., 1947). The response of the fever in 1948 to penicillin suggests that Actinomyces muris may have been present then in the blood and had become resistant to penicillin by the time it was isolated during the illness of 1949. When dealing with an organism of this sort it is not unusual to encounter difficulties in culture. This is particularly well shown by Rowntree's (1941) case, when the disease ran a fulminant course, but the actinomyces was not recovered till necropsy, and by the two negative cultures in this case at a time when signs of active infection were present.

Occasional cases of subacute bacterial endocarditis from whose blood various strains of actinomyces have been recovered are on record (Curtis et al., 1944; MacNeal et al., 1946; Beamer et al., 1945), but there appear to be only six instances in which Actinomyces muris is involved and these are shown in the accompanying Table II. All the previously recorded cases have been fatal, though one showed temporary improvement with penicillin. One of the interesting features of the case recorded here is the comparatively benign clinical course. The fulminating course of the endocarditis in the case described following a rat-bite (Rowntree, 1941) is comparable in its severity.

<table>
<thead>
<tr>
<th>Case</th>
<th>Course</th>
<th>Blood culture</th>
<th>Mode of infection</th>
<th>Treatment</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stuart-Harris et al., 1935</td>
<td>Subacute</td>
<td>Not known</td>
<td>Not known</td>
<td>Nil</td>
<td>Death</td>
</tr>
<tr>
<td>Rowntree et al., 1941</td>
<td>Acute</td>
<td>Negative but <em>Actinomyces muris</em> recovered from heart valve at autopsy</td>
<td>Bitten by rat</td>
<td>Nil</td>
<td>Death</td>
</tr>
<tr>
<td>McDermott et al., 1945</td>
<td>Subacute</td>
<td>Positive</td>
<td>Contact with rats</td>
<td>Penicillin</td>
<td>Temporary clinical improvement but death in cardiac failure</td>
</tr>
<tr>
<td>Priest et al., 1947</td>
<td>Subacute</td>
<td>Positive Negative but actinomyces recovered from heart valve at autopsy</td>
<td>Not known</td>
<td>Penicillin Sulphonamides</td>
<td>Death</td>
</tr>
<tr>
<td></td>
<td></td>
<td>No blood culture but actinomyces recovered from heart valve at autopsy</td>
<td>Not known</td>
<td>Nil</td>
<td>Death</td>
</tr>
<tr>
<td>Wedding, 1947</td>
<td>Subacute</td>
<td>Positive</td>
<td>Contact with rats</td>
<td>Chloramphenicol</td>
<td>Recovery</td>
</tr>
<tr>
<td>Stokes et al., 1949</td>
<td>Subacute</td>
<td>Not known</td>
<td></td>
<td></td>
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</table>
to rat-bite fever. In contrast, the course run by the subacute cases is more like that of Haverhill fever; in this disease the organism is not injected directly into the blood stream and the route of entry is uncertain.

There were no clinical features that distinguished this case from instances of subacute bacterial endocarditis caused by other organisms. It is noteworthy that 65 g. of chloramphenicol were given over a period of 28 days with no toxic symptoms other than occasional slight headache; weekly white cell counts during this time showed no fall in granulocytes.

SUMMARY

A case of subacute infective endocarditis due to Actinomyces muris is described. There was a satisfactory response to chloramphenicol which controlled the infection after penicillin therapy had failed. No toxic effects resulted from giving 65 g. of chloramphenicol in 28 days.

REFERENCES