SUBACUTE BACTERIAL ENDOCARDITIS DUE TO *H. PARA-INFLUENZAE* AND *STR. VIRIDANS*

BY

J. G. GOUDIE, M.B., Ch.B.

AND

C. P. LOWTHER, M.B., Ch.B.

(From the Bacteriology Department, Glasgow University,
and the Medical Department, Western Infirmary, Glasgow)

Streptococcus viridans is the infecting organism in most cases of subacute bacterial endocarditis; haemophilic bacteria occur among the rare causal organisms, and of these *Haemophilus para-influenzae* (Rivers, 1922) is probably the most common (see Miles and Gray, 1938; Craven, Poston, and Orgain, 1940). A case due to this organism was first reported in Britain by Russell and Fildes (1928). Recently this condition has been recognized on a number of occasions and treated beneficially with sulphadiazine (Hunter and Duane, 1946), penicillin and sulphamerazine (Priest *et al.*, 1947), and streptomycin (Briggs and Flinn, 1947; Paul, Bland, and White, 1947; Massel *et al.*, 1948; Olinger, 1948).

Endocarditis due to mixed infection with various organisms has also been described; two cases due to mixed infection with *Str. viridans* and *H. para-influenzae* have been reported (Orgain and Poston, 1942; Olinger, 1948); Olinger's case responded to combined penicillin and streptomycin therapy. A similar case is reported here.

Case Report

An unmarried 27-year-old female bank clerk was admitted to the Western Infirmary, Glasgow, on February 11, 1950, with pyrexia of unknown origin. Over the previous year she had suffered from mild nervousness and occasional anorexia associated with minor emotional upsets, and, when questioned, admitted to having had more dyspnoea on effort than usual. She was otherwise well until the night of December 28, 1949, when she was sleepless from headache and nausea. During the next few days she developed anorexia, some constipation, and pyrexia, with shivering during the day and fever at night; her urine was dark and concentrated, and the output diminished. There was no ankle swelling or palpitation, nor were cardiac murmurs heard during diastole. In the six weeks before admission she was treated with sulphonamides, aspirin, and phenobarbitone without benefit. She gave a history of measles, mumps, whooping-cough, chicken-pox, and tonsillectomy in childhood, but not of rheumatic fever or diphtheria.

On admission she was nervous, with a fine tremor of the hands; her skin was hot and dry; her temperature was 101° F. (38.3° C.), respirations 24, and pulse 116, regular; the blood pressure was 110/50. The heart was slightly enlarged to the left, and a well-marked presystolic murmur and a blowing systolic murmur were audible at the apex. A third heart sound was present. The tongue was coated and there was a small area of tenderness to the right of the umbilicus. The urine contained a few red cells and slightly increased urobilinogen. Blood examination showed: Hb, 75% (Sahli); red cells, 4,600,000 per c.mm.; white cells, 14,000 per c.mm. (polymorphs 79%, lymphocytes 17%, monocytes 4%); slight ring-staining of red cells; E.S.R., 90 mm. in 1 hour (Westergren). The spleen was not palpable and no other abnormalities were detected; salmonella and brucella agglutinations were negative.

Sodium salicylate and sodium bicarbonate, 30 gr. (2 g.) of each, were given three times a day. On February 15, four days after admission, a mid-diastolic murmur was heard at

the left border of the sternum for the first time, and the patient complained of pain in the tips of her fingers, although no lesion was visible. The temperature was remitting between 100 and 103° F. (37.8 and 39.4° C.). Blood was withdrawn for culture, and penicillin therapy, 2,000,000 units daily in three-hourly injections, was begun. By February 19 *Str. viridans* and unidentified Gram-negative filaments were reported in the blood culture. The dosage of penicillin was increased to 5,000,000 units daily. Very slight haematuria was still present, but there were no other embolic phenomena; the cardiac condition remained unchanged. By March 14 the temperature had fallen to 98.8–100° F. (37.1–37.8° C.) and the patient's general condition had improved, although the haemoglobin level had fallen to 55% (Sahli). On March 22 the temperature rose again to 102° F. (38.9° C.) and a hot tender swelling appeared at the site of a penicillin injection; this subsided quickly and then the temperature fell to 99° F. (37.2° C.). On March 30 one pint (570 ml.) of packed cells was given intravenously on account of the anaemia. Penicillin therapy was stopped on April 6, the patient having received 224,000,000 units.

On the next day the temperature began to rise and ran a remitting course between 101 and 102.8° F. (38.3 and 39.3° C.), and some petechiae were seen. In a blood culture taken on April 10 a pure growth of Gram-negative filaments was again found and "aureomycin" therapy was started, 1 g. daily for four days; by that time the organism was identified as a haemophilus sensitive to streptomycin, which was therefore substituted (2 g. daily) for aureomycin, the latter being still scarce. The temperature at once settled and remained normal for a week. By April 24 the mid-diastolic and presystolic murmurs were less intense. On April 28 a small, hot, red swelling appeared over the radial artery of the left wrist; it vanished after a few days and is considered to have been embolic in origin. A subsequent rise in temperature disappeared as soon as the streptomycin was stopped on May 1, and is thought to have been a drug reaction. A total of 26 g. of streptomycin was given.

On May 3 no mid-diastolic murmur was audible. The E.S.R. was 13 mm. in 1 hour (Westergren); the pulse rate returned to normal; the haemoglobin was 80%; blood cultures were sterile; the general condition was excellent; the presystolic murmur had become minimal; and the patient was discharged on June 3.

When examined on July 6 she was found to be remarkably well. Exercise tolerance appeared as good as before her illness. A blowing systolic murmur of moderate intensity was present at the apex, and on reinforcement a typical presystolic murmur could be heard; no enlargement of the heart was detected.

Laboratory Findings

In the first blood cultures* (February 15) *Str. viridans* and a Gram-negative organism grew; the latter was lost before identification. Further cultures on February 15, 17, 21, and March 4 were sterile.

In cultures taken some seven weeks later (April 10, 11, and 13) there appeared, after 96 hours' incubation, fluffy colonies about 1–2 mm. in diameter, lying on the surface of the sedimented cells. The colonies consisted of tangled masses of long thin Gram-negative filaments. Subcultures on 10% horse-blood agar, after 24 hours' incubation, showed minute, non-haemolytic, seemingly smooth, transparent colonies which in 48–72 hours reached 0.5 mm. in diameter and became more opaque and rough with tiny ridges; they were tough and difficult to break up. In meat-extract broth with 10% horse blood, growth was similar to that of the original blood cultures, with small fluffy colonies tending to adhere to the sides of the tubes. Both with solid and with fluid media the organism was highly pleomorphic, ranging in size from cocco-bacillary forms to long thin thread-like filaments, staining fairly evenly but rather faintly with dilute fuchsin, aerobic, non-sporing, non-motile, and non-acid fast.

*Three bottles of media were always inoculated with blood (see Browning and Mackie, 1949).

No growth occurred in ordinary media or media enriched with glucose, starch, human serum, human plasma, or horse plasma, or on Loeffler's inspissated serum.

As growth had been obtained only in the presence of blood, the organism was assigned provisionally to the *Haemophilus* group and the growth requirements were investigated in some detail. On "chocolate blood agar" (heated to 80° C.) growth was slower and weaker than on blood agar; no growth occurred on autoclaved blood agar. On the other hand, the organism grew on ordinary agar around colonies of staphylococci, and in broth to which staphylococcus filtrate was added; abundant growth took place in media containing 10% yeast extract. Thus the organism required the presence of the V or co-enzyme factor, and was independent of the X or haematin factor. It was therefore identified as a non-haemolytic *H. para-influenzae* (Valentine and Rivers, 1927).

Fermentation tests were carried out in peptone water with 10% yeast extract—prepared according to the method of Miles and Gray (1938)—which by itself does not split saccharose or maltose. The organism grew well in this medium and produced acid, without gas, from glucose, saccharose, and maltose, but not from lactose, mannitol, or dulcitol. No change occurred in litmus milk, and indole was not produced.

This organism died out on agar plates in 48–72 hours but survived for 11 weeks in blood-culture bottles which, after five days' incubation at 37° C., were left at room temperature. It survived heating to 56° C. for five minutes, but not for 10 minutes.

The organism was completely resistant to penicillin (10 units per ml.), was highly sensitive to streptomycin in the "ditch test," and in fluid media growth was inhibited by 1.6 µg. of streptomycin per ml. of medium.

On May 22 the patient's serum was tested for antibodies. Miles and Gray (1938) reported agglutination of *H. para-influenzae* by their patient's serum to a titre of 1 in 90, but stressed the difficulty of preparing a stable suspension of the organism. The same difficulty, due to roughness of the colonies, was experienced with our strain. Unsuccessful attempts were made to emulsify colonies in saline by raising the pH to 8.2. Fine suspensions of organisms or fragmented organisms were obtained by grinding colonies in a mortar and slowly adding saline or ox bile; gentle centrifugation was necessary to remove unbroken clumps of organisms. Such suspensions were agglutinated markedly at 56° C. by the patient's serum to a titre of 1 in 100, but slight sedimentation also occurred in higher dilutions of the serum and in control tubes. The most satisfactory results were obtained by the method for suspending tubercle bacilli used in the Pasteur Institute. The colonies were ground in olive oil, and 0.85% NaCl was slowly added to make an emulsion. Left for three hours, the emulsion separated, and between the oil and the sediment of unbroken remnants of colonies there was a fine suspension of organisms completely stable at 56° C.; this was agglutinated by the serum overnight at 56° C. to a titre of 1 in 250, and to the same titre but rather more slowly at 37° C.

Discussion

Proof that a case of endocarditis is due to a particular organism is not easily obtained during the patient's life; repeated positive blood cultures are usually taken as significant. It seems reasonable to assume that the unidentified bacterium in the first blood culture was the *H. para-influenzae* grown later on three separate occasions. The repeated presence of this organism in the blood stream, its disappearance after antibiotic therapy, to which it was sensitive, accompanied by the disappearance of the pyrexia and marked clinical improvement of the patient, all point to the organism being a causal agent of the disease. *Str. viridans* was grown only from the first blood culture, but thereafter intensive penicillin therapy probably precluded the possibility of its sub-

sequent isolation. However, definite clinical improvement and lowering of the pyrexia during the penicillin therapy (to which the haemophilus was completely resistant in *in vitro* tests) led us to believe that the streptococcus was also a causal agent.

Summary

The clinical and laboratory findings are given of a case of subacute bacterial endocarditis apparently due to a mixed infection with *H. para-influenzae* and *Str. viridans*: the successful treatment of the case is described.

The unusually long (11 weeks) survival of *H. para-influenzae in vitro* and the method of preparing a stable suspension are thought to be interesting laboratory findings.

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LEG-LENGTHENING*

BY

F. G. ALLAN, M.B., B.S., F.R.C.S.

Orthopaedic Surgeon, United Birmingham Hospitals;
 Surgeon, Royal Orthopaedic Hospital, Birmingham; Senior
 Visiting Surgeon, Robert Jones and Agnes Hunt
 Orthopaedic Hospital, Oswestry

Since shortening of the lower limb is a common complication of many conditions, attempts have naturally been made from time to time to correct this deformity by operative means. Little success, however, attended these efforts until the principles of skeletal traction were well established. Putti (1921) published his paper on operative lengthening of the femur; then in 1927 Abbott described his method of tibial elongation, and all subsequent methods have been based on his work. His operative technique was complicated, and involved a good deal of soft-tissue division, and the distraction apparatus used had no provision for preventing secondary deformities.

The present paper is based on 101 personal cases.

Indications and Contraindications

The indication for leg-lengthening is a shortening exceeding 1½ to 2 in. (3.75 to 5 cm.) with a mobile pelvis, or exceeding 1 in. (2.5 cm.) if no compensation is possible by pelvic tilting.

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