

# Infective endocarditis due to non-toxigenic *Corynebacterium diphtheriae* in a child

## A case report

J. C. MARCUS, I. SPECTOR, W. W. N. CHIN, S. E. LEVIN

### Summary

A case of infective endocarditis (IE) in a 5½-year-old boy in whom blood and bone marrow cultures yielded an unusual organism, a non-toxigenic strain of *Corynebacterium diphtheriae*, is reported. This proved fatal, and at autopsy congenital valvar aortic stenosis was found, but the vegetations occurred on an anatomically normal mitral valve. Organisms such as *C. diphtheriae* should not be ignored when isolated from blood cultures in suspected cases of IE.

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Infective endocarditis (IE) in children may occur as a complication of chronic rheumatic heart disease, or of congenital heart disease, or, more rarely, on an anatomically normal valve. Although  $\alpha$ -haemolytic streptococci are cultured in the vast majority of cases, many different organisms are known to cause IE, including staphylococci, meningococci, *Haemophilus influenzae* and coliform bacteria. We report a case of congenital heart disease (valvar aortic stenosis) with IE, in which the causative organism, *Corynebacterium diphtheriae*, has previously been isolated only on rare occasions. In addition, an unusual finding was that the infection occurred on the anatomically normal mitral valve.

### Case report

A 5½-year-old boy was admitted to hospital with a history of fever for 3 days. There were no other specific symptoms. He had had two previous episodes of epistaxis, but no recent surgical or dental manipulation that might have precipitated an infection. There was no history suggesting past or present cardiac disease other than that he tired rather easily when playing with friends. His immunization schedule could not be obtained. On examination his weight was below and his height just above the 3rd percentile. He did not appear to be ill, nor was he in any distress.

#### Department of Paediatrics, Coronation Hospital, and School of Pathology, University of the Witwatersrand, Johannesburg

J. C. MARCUS, M.B. B.CH., F.C.P. (S.A.), Senior Paediatrician (Present address: 16 Devonshire Lane, Great Neck, NY 11023, USA)

I. SPECTOR, M.D., M.B. CH.B., Pathologist

W. W. N. CHIN, B.Sc., M.B. B.CH., D.C.H. (S.A.), Paediatric Registrar

S. E. LEVIN, M.B. B.CH., D.C.H., F.R.C.P., Principal Paediatrician and Professor

However, his temperature was 39,8°C. There was no pallor, cyanosis, jaundice, clubbing, lymphadenopathy or oedema. The pulse rate was 120/min, regular and of normal character, and all peripheral pulses were present. The blood pressure was 75/40 mmHg. The heart showed mild left ventricular enlargement on palpation. The first and second sounds were soft, and a loud grade 3/6 pansystolic murmur was audible over the whole precordium, being loudest at the apex. No gallop was heard and there were no signs of cardiac failure. The spleen was impalpable and splinter haemorrhages were not seen. The rest of the examination was negative.

### Investigations

Full blood count showed a haemoglobin level of 10,8 g/dl with mild anisochromia of the erythrocytes. The white blood cell count was 14 600/ $\mu$ l, with a differential count of 77% neutrophils, 6% monocytes, 16% lymphocytes and 1% eosinophils. Platelets were normal in number and structure. The prothrombin index was 94%. Since the patient at no time had symptoms referable to the nose or throat, pharyngeal and nasal cultures were not undertaken.

Chest radiography revealed an enlarged heart (cardiothoracic ratio 55%) with left ventricular hypertrophy. The lung fields were clear and the ECG was normal. Echocardiography was not carried out.

Complete urinalysis, cerebrospinal fluid examination, the Paul-Bunnell test, agglutination tests for typhoid, brucella and rickettsiae, tine and streptococcal antibody tests were negative, as was blood film examination for parasites. The streptococcal antihyaluronidase antibody titre was 1:64 and the mucoprotein level was 172 mg/dl (normal 45-125 mg/dl). Initial blood culture yielded a growth of *Staphylococcus albus* after 48 hours' incubation, but blood specimens taken on days 2 and 6 and a bone marrow specimen taken on day 5 yielded a growth of *C. diphtheriae*.

The patient continued to run a hectic temperature of up to 40°C, but did not appear very ill. The cardiac findings did not change at any stage and embolic phenomena were not detected. Repeat chest radiographs were identical to those taken on admission. On the 3rd day in hospital the patient's spleen became palpable and thereafter slowly enlarged. Cytological examination of a bone marrow aspirate showed reactive changes indicative of infection, but was otherwise normal. On the 7th day after admission the patient suddenly collapsed on his way to the toilet; resuscitation was unsuccessful. Autopsy was carried out approximately 72 hours after death.

### Bacteriological findings

On three occasions blood and bone marrow culture yielded *C. diphtheriae*. Gram staining showed variably staining, medium-to-long, slender rods, and numerous metachromatic granules were demonstrated with Albert's stain. Growth on blood tellurite agar yielded colonies 2-4 mm in diameter, circular, convex,

dark greyish-black with pale margins and smooth glistening surfaces. Haemolysis was present.

The biochemical reactions were (+ = positive, - = negative): dextrin -, maltose +, sucrose -, catalase +, glucose +, mannitol -, trehalose -, nitrate reduction +, glycogen -, salicin -, xylose -, gelatin liquefaction -, lactose -, starch -, arginine hydrolysis -, urease -.

There was no toxin production on an Elek plate preparation and the organism was identified as non-toxicogenic *C. diphtheriae* var. *mitis*. Confirmation of our diagnosis was obtained from the Public Health Laboratory Service in London.

### Autopsy findings

The left ventricle of the heart was hypertrophic. The aortic valve was tricuspid with a narrowed orifice due to moderately thickened leaflets — evidence of congenital aortic stenosis (Fig. 1). Firm white nodules and blood clots were found on the atrial surface of the anatomically normal mitral valve (Fig. 2). On microscopy this was found to be due to a bulbous mass composed of an acute exudate incorporating numerous bacterial colonies. The valve itself showed no significant pathological changes (Fig. 3). Vegetations were not found on the other valves and the other chambers were of normal size. The lungs were oedematous and there was focal atelectasis and interstitial pneumonia. There was diffuse acute and chronic inflammatory cell infiltration in the enlarged soft spleen. The remainder of the autopsy was unremarkable.

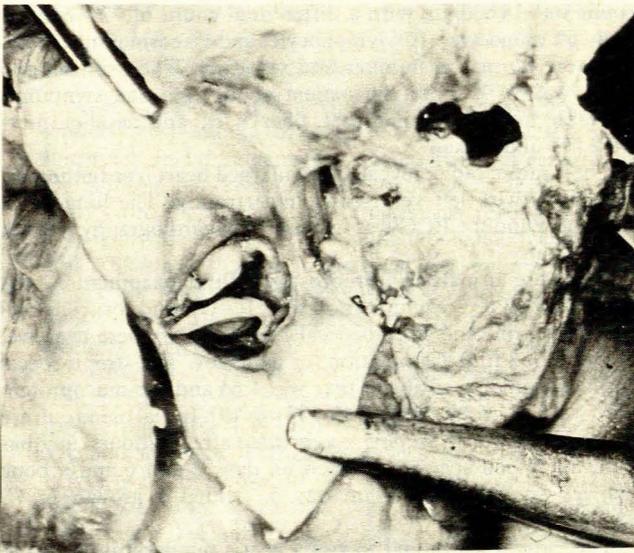


Fig. 1. Thickened tricuspid aortic valve leaflets, with the aorta opened from above.

### Discussion

Almost any bacterium is capable of producing IE, although streptococci and staphylococci account for the great majority of cases (90 - 95%) in which an infecting organism can be identified. Fungi, especially candida and aspergillus species, can cause mycotic endocarditis, and a rickettsia (*Coxiella burnetii*) has been implicated as a cause of infective endocarditis.<sup>1</sup>

Although there are numerous reported cases of corynebacterial ('diphtheroid') endocarditis, cases due to *C. diphtheriae* have rarely been recorded. According to Pike,<sup>2</sup> the isolation of *C. diphtheriae* from the bloodstream of patients with clinical diphtheria during life was first reported by von Nieson in 1902, although Loeffler had already cultured the organisms

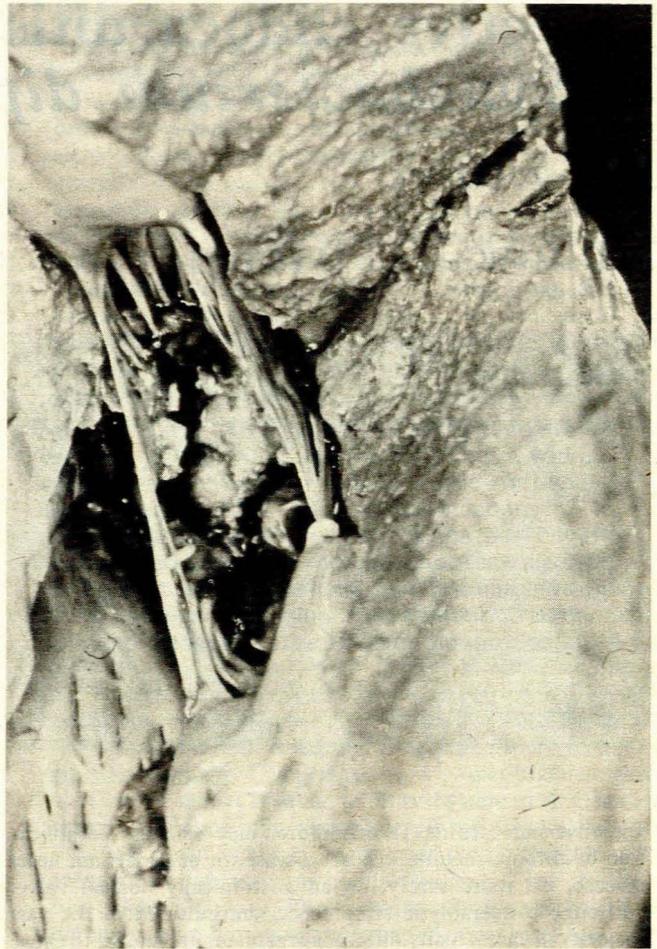
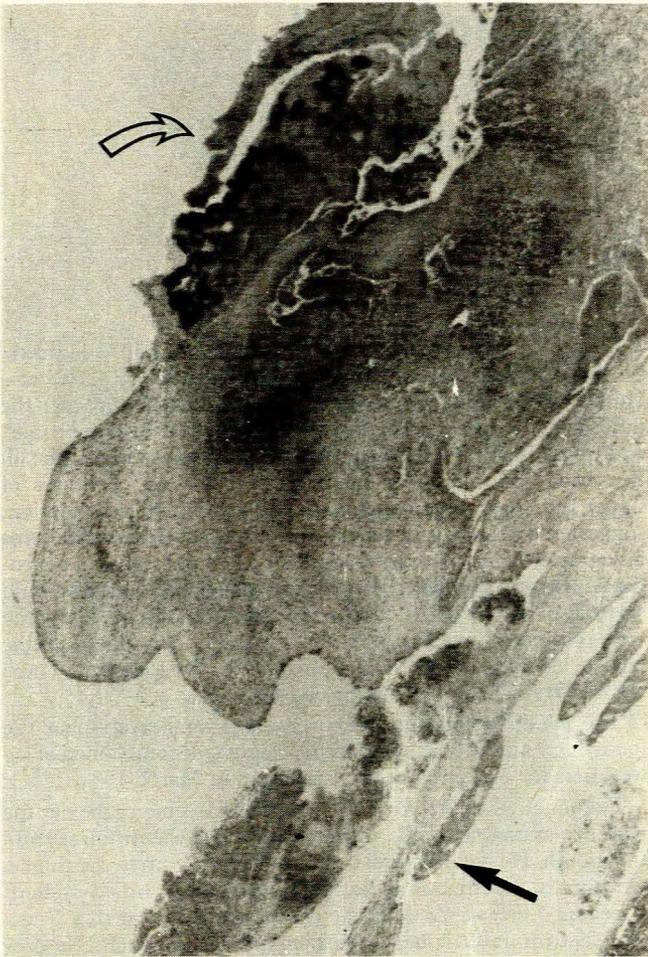


Fig. 2. View of mitral valve from within the left ventricle, with large vegetations on the leaflets.

from the blood and organs in fatal cases of diphtheria in 1884.

Cases of endocarditis due to *C. diphtheriae* in which the patient did not manifest clinical diphtheria have been documented; in the majority of these the organism was not toxigenic.<sup>3-5</sup> A few cases are on record as being due to a toxigenic strain.<sup>2,6</sup> More recently Van der Horst *et al.*<sup>7</sup> described a case of fulminant mitral valve endocarditis due to a non-toxicogenic strain of *C. diphtheriae* isolated from the valvar vegetation; they were not able to isolate the organism from the single blood specimen taken. A congenital cardiac lesion was not present in their case.

Although nearly every type of cardiovascular malformation is susceptible to IE, the propensity of the bicuspid aortic valve (with or without aortic stenosis) to endocarditis is well recognized, and the incidence is reportedly 10 - 15%.<sup>8</sup> In a series of 555 congenitally abnormal hearts an incidence of 17.6% was reported by Abbott.<sup>9</sup> Whether in acquired or congenital heart disease, the bacteraemia of IE is relatively constant.<sup>10</sup> As in the present case, if one blood culture is positive, all tend to be positive. In our patient mitral vegetations were present; none occurred on the abnormally thickened tricuspid aortic valve. It has been suggested that vegetations generally develop at the site of greater turbulence with endocardial damage or jet lesion, and 'down-stream' from the site of the lesion.<sup>11</sup> In this regard Kumar *et al.*<sup>12</sup> report no episode of IE in 55 patients with Ebstein's anomaly followed up for a total of 300 patient-years, which they attribute to the relatively low velocity of blood in hearts with this malformation. In our case, however, the endocardial lesion was 'upstream', occurring on an anatomically normal valve with no spread to the abnormal aortic leaflets. The reason for this ten-



**Fig. 3.** Exuberant vegetation on the atrial surface of the mitral valve (high-power view) (H and E). Note the cellular infiltrate at the base of the vegetation with dense aggregates of bacilli at the free edge of the vegetation (white curved arrow), and the thin, normal mitral valve leaflet (black arrow).

gency of vegetations to be located on the atrial surface of mitral valve leaflets is not readily apparent.<sup>13</sup>

We were unable to obtain a history of immunizations in our patient. In the case reported by Van der Horst *et al.*<sup>7</sup> the diphtheritic organism found its way to the mitral valve, despite immunization against diphtheria. This is not entirely surprising as immunization is directed against the toxin produced by the organism and would therefore not affect colonization or invasion. Treatment was withheld in our patient while awaiting confirmation of the blood culture result. Our case further underlines the fact that organisms such as *C. diphtheriae* should not be ignored when isolated from blood cultures in a suspected case of IE. This dictum may also apply to other organisms thought to be either innocuous or contaminants.

## Addendum

Since submission of the article there has been a further report of *C. diphtheriae* endocarditis in an adult, successfully treated with intravenous penicillin.<sup>14</sup>

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