Familial dilated (congestive) cardiomyopathy
Occurrence in two brothers and an overview of the literature

J. Z. PRZYBOJEWSKI, J. J. VAN DER WALT, P. J. VAN EEDE, F. A. C. TIEDT

Summary
Two young White brothers had dilated (congestive) cardiomyopathy. The elder came to autopsy after a chronic course of congestive cardiac failure; the younger underwent repeated cardiac catheterization and transvenous right ventricular endomyocardial biopsy specimens demonstrated histopathological features in keeping with a diagnosis of idiopathic dilated cardiomyopathy. These brothers may have the familial form of the disease, although post-viral myocarditis cardiomyopathy cannot be entirely excluded. The literature relating to familial dilated (congestive) cardiomyopathy is reviewed.

Case presentations
Case 1
This 24-year-old White man was apparently very healthy until July 1981 when he suffered a bad bout of influenza. Some 2 months later he had a pulse rate of 140/min as well as a loud third heart sound on auscultation. He denied having any symptoms but was advised not to exert himself in view of a possible diagnosis of viral myocarditis. An electrocardiogram (ECG) was normal apart from slight left ventricular cardiomegaly and a soft third heart sound. Side-room test results were normal, as were the results of serum chemical and haemarological investigations. The resting 12-lead ECG was unremarkable apart from slight left ventricular cardiomegaly and slight left ventricular hypertrophy. M-mode echocardiography showed features of end-diastolic diameter 55 mm (normal 35-56 mm), end-systolic diameter 47 mm. The right ventricle was not dilated.

REFERENCES
ble normal. Gated blood pool scanning delineated gene­
diffuse, nonspecific ST-T wave changes. Chest radiography
limitations, as were haematological parameters. A resting 12-lead
characteristics on electron micro­
misconceptions. The most conspicuous features were mitochondriosis,
markedly raised end-diastolic pressure.

**Case 2**

This 21-year-old White university student had an early
history of asthma in childhood, recurrent pyelitis in 1974 and a
recent history of spastic colon. He was a moderate cigarette
smoker and drinker. In July 1977 a bout of influenza was
complicated by several episodes of acute bronchitis. In October
1977 he noticed the onset of intermittent abdominal pain
aggravated by walking. Some 2 weeks later he became anorexic
and nauseous and vomited on'several occasions. In addition, he
complained of a sore throat, fever and cough. His general
improvement on the ventricular function as assessed in September
1981.

Cardiac catheterization was undertaken to reassess ventricular
function and obtain endomyocardial biopsy specimens. Tables I
and II reveal a significant deterioration in biventricular failure
despite unchanged cardiac output. Left ventricular cine angi­
ography demonstrated a more severe degree of generalized
hypokinesia with mild mitral insufficiency (Fig. 1). Right
ventricular cine angiography delineated a dilated and poorly
contracting chamber. Multiple right ventricular endomyocardial
specimens showed no specific characteristics on electron micro­
scope; the most conspicuous features were mitochondriosis,
nuclear enlargement, lipofuscin pigment (Fig. 2) and an apparent
loss or degeneration of contractile elements in places (Fig. 3).

These findings, although entirely nonspecific, were in keeping
with a clinical diagnosis of dilated (congestive) cardiomyopathy.

The possibility of cardiac transplantation was discussed but it
was decided that the patient’s haemodynamic status was not
severe enough to justify such a major procedure, particularly
since he had been taking minimal medication. The patient was
given prazosin 1 mg 3 times daily, digoxin 0,25 mg/d and a
moderate dose of a diuretic.

**TABLE I. INTRACARDIAC PRESSURES**

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<tr>
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<tbody>
<tr>
<td>Right atrium</td>
<td>'a' wave, 9</td>
<td>'a' wave, 13</td>
<td>Slightly elevated</td>
</tr>
<tr>
<td></td>
<td>(mean 3)</td>
<td>(mean 9)</td>
<td>(25 Nov. 82)</td>
</tr>
<tr>
<td>Right ventricle</td>
<td>34/0-5</td>
<td>54/6-10</td>
<td>Raised pressures</td>
</tr>
<tr>
<td></td>
<td>(mean 22)</td>
<td>(mean 40)</td>
<td>(25 Nov. 82)</td>
</tr>
<tr>
<td>Main pulmonary artery</td>
<td>34/16</td>
<td>54/28</td>
<td>Moderate pressures</td>
</tr>
<tr>
<td></td>
<td>(mean 22)</td>
<td>(mean 40)</td>
<td>hypertension</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>(25 Nov. 82)</td>
</tr>
<tr>
<td>Ascending aorta</td>
<td>102/78</td>
<td>120/90</td>
<td>Normal</td>
</tr>
<tr>
<td></td>
<td>(mean 90)</td>
<td>(mean 96)</td>
<td></td>
</tr>
<tr>
<td>Left ventricle</td>
<td>102/9-25</td>
<td>120/9-37</td>
<td>Markedly raised</td>
</tr>
<tr>
<td></td>
<td>(mean 90)</td>
<td>(mean 96)</td>
<td>end-diastolic pressure</td>
</tr>
<tr>
<td>Dp/dt (mm/s)</td>
<td>1829</td>
<td>1778</td>
<td>Normal</td>
</tr>
<tr>
<td>Pulmonary capillary wedge</td>
<td>'a' wave, 25</td>
<td>'a' wave, 46</td>
<td>Very raised</td>
</tr>
<tr>
<td></td>
<td>(mean 15)</td>
<td>(mean 35)</td>
<td>(especially on</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>25 Nov. 82)</td>
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\[Dp/dt = \text{left ventricular stroke work.}\]

**TABLE II. HAEMODYNAMIC DATA**

<table>
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<tr>
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<tr>
<td>Oxygen consumption (ml/min)</td>
<td>200</td>
<td>260</td>
<td></td>
</tr>
<tr>
<td>Arteriovenous (\text{O}_2) difference (mmol/l)</td>
<td>1.60</td>
<td>2.05</td>
<td></td>
</tr>
<tr>
<td>Cardiac output (Fick) (l/min)</td>
<td>5.5</td>
<td>5.6</td>
<td></td>
</tr>
<tr>
<td>Cardiac index (Fick) (l/min/m²)</td>
<td>3.0</td>
<td>3.1</td>
<td></td>
</tr>
<tr>
<td>Pulmonary vascular resistance (U)</td>
<td>1.3</td>
<td>0.9</td>
<td></td>
</tr>
<tr>
<td>Systemic vascular resistance (U)</td>
<td>15.8</td>
<td>15.5</td>
<td></td>
</tr>
<tr>
<td>Pulmonary/systemic resistance ratio (%)</td>
<td>8.0</td>
<td>6.0</td>
<td></td>
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</table>
practitioner diagnosed influenza. Nevertheless, a few days later he noticed swelling of his face, abdomen and ankles, as well as some shortness of breath on exercise and at rest. There was no history of joint pain or swelling, haematuria or oliguria, and he continued to be markedly nauseous.

He was admitted to the local hospital, where a physician examined him on 29 October 1977 and found him to be a very ill, afebrile young man with marked tachycardia accompanied by 'slight paradoxus' and with a blood pressure of 120/100 mmHg. The jugular venous pressure was significantly elevated and there was extensive oedema of the face, sacrum and feet. Cardiomegaly with a marked protodiastolic gallop was noted; the fundi were normal. Further findings were those of extensive bilateral basal crepitations and a grossly enlarged and tender liver but no splenomegaly or jaundice. An ECG was stated to be 'non-contributory', and biventricular cardiac failure probably secondary to 'viral myocarditis' was diagnosed. The erythrocyte sedimentation rate was normal, and antinuclear factor and lupus erythematosus cells were both absent. The patient was confined to bed and given anti-cardiac failure medication and a course of steroid therapy, but he continued to have a tachycardia of 120/min and gallop rhythm, as well as poor peripheral circulation. Since there was no significant improvement he was admitted to the Provincial Hospital, Port Elizabeth, where cardiac catheterization was performed on 13 January 1978, some 6 months after the onset of his illness. This investigation showed normal intracardiac pressures with 'no evidence of left ventricular failure', 'angiography did not show him to have poor myocardial function'. Further comment was that 'the left ventricular muscle appeared perhaps a little bit thickened, possibly due to oedema'. These findings caused the attending clinicians to take a more favourable view regarding prognosis.

The patient continued to display sinus tachycardia but of a milder degree. Towards the end of 1980 he suffered a further attack of influenza and was noted to be in 'flutter-fibrillation' for the first time in October 1980. His physician thought that this arrhythmia was caused by an overdose of digoxin, which was promptly discontinued for 1 week. However, the atrial fibrillation persisted and digoxin therapy was recommenced at a slightly reduced dosage. On 23 January 1981 the patient complained of anorexia, tiredness, swelling of the abdomen and tenderness of
the right hypochondrium; examination demonstrated no oedema, the blood pressure was 110/80 mmHg, and he was still in atrial fibrillation. His lungs were clear, but there was considerable non-tender hepatomegaly associated with possible early jaundice. Investigation failed to establish a possible diagnosis of infective hepatitis. The patient's condition continued to deteriorate with increasing cardiomegaly, and he was admitted to the Provincial Hospital, Port Elizabeth, on 14 March 1981. The atrial fibrillation was converted to rapid sinus rhythm and he was discharged after a week in hospital. During the ensuing few months he continued in biventricular cardiac failure, this necessitating readmission in June 1981. Cardiac transplantation was apparently discussed but the patient died within a few days of admission.

On macroscopic examination the heart showed generalized enlargement and weighed 470 g. Both ventricles were dilated, especially the left one. An antemortem thrombus was present in the left atrium. The heart valves were within normal limits and the coronary arteries were free of atheroma. On histological examination of the heart the myocytes showed obvious signs of hypertrophy, as indicated by the increase in cell size and the presence of bizarre enlarged nuclei. Many myocytes were attenuated and in cross-section appeared atrophic but contained enlarged hyperchromatic nuclei. The latter cells reflect the effect of chronic ventricular dilatation. The interstitium of the heart showed a fine, almost pericellular fibrosis of a very delicate nature (Fig. 4) but no inflammatory cells. The parietal endocardium of the left ventricle showed mild focal thickening due to fibro-elastosis (Fig. 5). Microscopy confirmed the presence of an organizing mural thrombus and the absence of any valvular lesion or significant coronary atherosclerosis. The histological features together with the clinical history and the gross appearance of the heart strongly suggested a diagnosis of idiopathic dilated ventricular cardiomyopathy. The severity of the congestive cardiac failure was reflected by the severe chronic passive congestion seen in the liver, spleen, kidneys and lungs.

**Discussion**

The aetiological factors involved in the pathogenesis of dilated (congestive) cardiomyopathy have occupied the thoughts of many researchers for several decades. Despite numerous publications, no satisfactory answer has emerged. As with many diseases, a hereditofamilial factor has been incriminated in an attempt to solve this most puzzling aspect of an exceptionally common and important disease (especially among Blacks) in Africa. The first report of familial cardiomyopathy, entitled 'Familial cardiomegaly', was that of Evans in 1949, but it is not quite certain whether these cases were of the dilated (congestive) type or the hypertrophic variety. Similarly, authors such as Gaunt and Lecutier, Bishop et al., Kariv et al., and Emanuel et al. were not quite clear in distinguishing between the dilated and hypertrophic forms of familial cardiomyopathy. This distinction is important since it has been well established that hypertrophic obstructive cardiomyopathy can be transmitted genetically. Nevertheless, the picture is somewhat clouded by the suggestion that the hypertrophic type can evolve into the dilated type. Anselmi et al. described identical twin brothers who died suddenly; one had features of dilated cardiomyopathy whereas the other had those of hypertrophic cardiomyopathy. Coelho et al. and Campbell and Turner-Warwick also documented cases of 'familial cardiomyopathy', but again the histopathological features were not entirely clear. Further suggestions of a familial or hereditary pattern in dilated cardiomyopathy were published by Kariv et al., Pare et al., Biörck and Ornisius, Beasley, Walthet et al., Barry and Hall, Garret et al., and Battersby and Glenner. Most of these reports have suggested that the pattern of inheritance is by an autosomal dominant gene, and less frequently a recessive one.

The first report of a familial congestive cardiomyopathy in tropical Africa described twin brothers in Uganda. However, Brink et al. considered these cases probably to be coincidental since dilated (congestive) cardiomyopathy was so common in that part of Africa. These same authors went on to describe the interesting condition of 'hereditary dysrhythmic congestive cardiomyopathy' in a White teenage girl who had repeated episodes of symptomatic ventricular tachycardia and fibrillation. Since the QTc was prolonged a left cervical ganglionectomy was performed, with limited success. Further follow-up revealed a progressively enlarging heart, and the girl died suddenly some 4 years later. Her elder brother had apparently died suddenly after effort but autopsy had not been performed. Ten generations of the family were traced and there was a strong history of sudden death. Furthermore, two young sisters, related through their parental branch to the above girl's family, were said to suffer from 'familial paroxysmal ventricular tachycardia'.

Ross et al. reported on what appears to be a similar (and unusual) disease to that documented by Brink et al. They encountered the condition of 'idiopathic familial myocardopathy' in families of three generations in which the inheritance pattern approached that of autosomal dominance. Some of the hearts displayed histological features resembling both idiopathic dilated myocardioapathy in adults and the idiopathid endocardial fibro-elastosis seen in children. Unusually extensive myocardial fibrosis was also encountered in some cases documented by Ross et al., a feature unusual in dilated cardiomyopathy and more commonly associated with severe coronary artery disease.
An unusual type of familial dilated (congestive) cardiomyopathy associated with hypogonadism and a unique collagenoma was described by Sacks et al. in a 48-year-old White man, the proband, in whom severe tricuspid insufficiency was associated with significant right heart involvement and far less left heart involvement, a feature described in adults with 'right ventricular dysplasia'.

The possibility of antecedent viral infection, particularly coxsackie B virus, in the two brothers described by us cannot be excluded with certainty. Viral myocarditis leading to dilated (congestive) cardiomyopathy has been strongly suggested by some workers. Cambridge et al. demonstrated a high level of antibodies against coxsackie B virus in the serum of patients whose illness commenced with a fever and lasted less than a year. In a large series of patients with idiopathic dilated cardiomyopathy Fuster et al. found that about 20% had suffered a viral-type illness before presenting with cardiomyopathy. The onset of atrial fibrillation in both our patients caused haemodynamic deterioration and is usually a poor prognostic sign, occurring in some 15 - 20% of patients with this disease. Immunological studies have also been carried out in cases of cardiomyopathy but no correlation between circulating antihist antibodies and the type of cardiomyopathy was demonstrated.

Recently, Factor and Sonnenblick presented a challenging hypothesis incriminating a diffuse hyperactive myocardial microcirculation (microvascular spasm) in the pathophysiology of congestive cardiomyopathy. This, they say, rather than a primary disorder of heart muscle cells, is of prime importance and dictates the possible beneficial effects of treatment with calcium-antagonist drugs such as verapamil. Further work by Bristow et al. and Willerson demonstrated that p-receptor density is diminished in congestive cardiac failure secondary to idiopathic dilated cardiomyopathy and `ischaeic cardiomyopathy' (following previous myocardial infarction). This decrease, they claim, gives rise to decreased p-adrenergic pathway sensitivity with subsequent diminished p-agonist-stimulated myocardial contraction. Further research into dilated cardiomyopathy involved the use of thallium-201 scans after exercise. Some authors have claimed that perfusion defects occur with ischaemic heart disease but not with idiopathic dilated cardiomyopathy. However, Dunn et al. recently showed that this differentiation was unreliable.

Further management of the surviving brother described by us was made more difficult by the death of his older sibling. The parents have been exceptionally keen for him to undergo cardiac transplantation because they fear that he may also die. Nevertheless, he remains exceptionally well despite the obvious haemodynamic deterioration over a 1-year period (demonstrated by repeat cardiac catheterization). We do not believe that his present condition justifies the drastic intervention of heterotopic cardiac transplantation, and we will continue to follow him up closely on medical therapy in conjunction with his private specialist physician.

The authors wish to thank sincerely Miss H. Weyman of the Cardiology Unit, Tygerberg Hospital, for preparing the manuscript and some of the illustrations. Thanks are also due to Mr Chris Wilberforce, Head of the Department of Clinical Photography, for his painstaking preparation of the photographs. Dr R. M. Lawson, Consultant Pathologist to the South African Institute for Medical Research, Port Elizabeth, is thanked for supplying the slides relating to the postmortem material in case 2. Finally, due appreciation is shown towards Dr J. P. van der Westhuysen, Acting Chief Medical Superintendent of Tygerberg Hospital, for permission to publish.

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25. Cambridge GM, MacArthur CGC, Waterson AP. Coxsackie B virus in the two brothers described by us cannot be excluded with certainty. Viral myocarditis leading to dilated (congestive) cardiomyopathy has been strongly suggested by some workers. Cambridge et al. demonstrated a high level of antibodies against coxsackie B virus in the serum of patients whose illness commenced with a fever and lasted less than a year. In a large series of patients with idiopathic dilated cardiomyopathy Fuster et al. found that about 20% had suffered a viral-type illness before presenting with cardiomyopathy. The onset of atrial fibrillation in both our patients caused haemodynamic deterioration and is usually a poor prognostic sign, occurring in some 15 - 20% of patients with this disease. Immunological studies have also been carried out in cases of cardiomyopathy but no correlation between circulating antihist antibodies and the type of cardiomyopathy was demonstrated.

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