ENDOCARDIAL FIBROELASTOSIS

V. CAPTUR
M.D. (MALTA), B.Sc., F.A.C.C.
Cardiology Unit, Pediatric Department
St. Luke's Hospital

J. L. GRECH
M.D. (MALTA), D.C.P. (LOND.), D.M.J., M.C. PATH.
Pathologist, St. Luke's Hospital

J. L. PACE
M.D. (MALTA), B.PHARM., PH.D. (LOND.)
Department of Anatomy,
Royal University of Malta

Read at a meeting of the B.M.A. (Malta Branch) on the 7th March 1967.

Endocardial fibroelastosis still presents a challenge in all its aspects, and much doubt and controversy prevails not only regarding its ætiology and pathology but also its age incidence and geographical distribution. Between 1955 and 1966, 424 post-mortem examinations on children under 2 years of age, including stillborn infants, were carried out in the Department of Pathology, St. Luke's Hospital. In 57 of these cases congenital heart disease was diagnosed or confirmed at autopsy and endocardial fibroelastosis was found at post-mortem in 8 of them. These figures are considered to be representative of the true incidence in the necropsy material as this makes up almost a 100 per cent of the necropsies carried out in Malta during the period under review.

Incidence

Figure 1 shows the incidence and age distribution at death of endocardial fibroelastosis and of congenital heart disease in 424 necropsies carried out on children under 2 years of age. The incidence of congenital heart disease was found to be 13.4%, and that of endocardial fibroelastosis 1.9%. Three of the 8 cases of endocardial fibroelastosis did not show any other associated cardiac anomaly. The sex distribution was equal. The age at death in 7 of the cases was under 1 year, the youngest dying 50 hours after birth and the oldest at 15 months.

Anderson and Kelly (1956) reported that in the majority of the 237 cases of congenital heart disease examined by them, endocardial fibroelastosis was an associated finding; they also distinguished between a "primary" type that was not

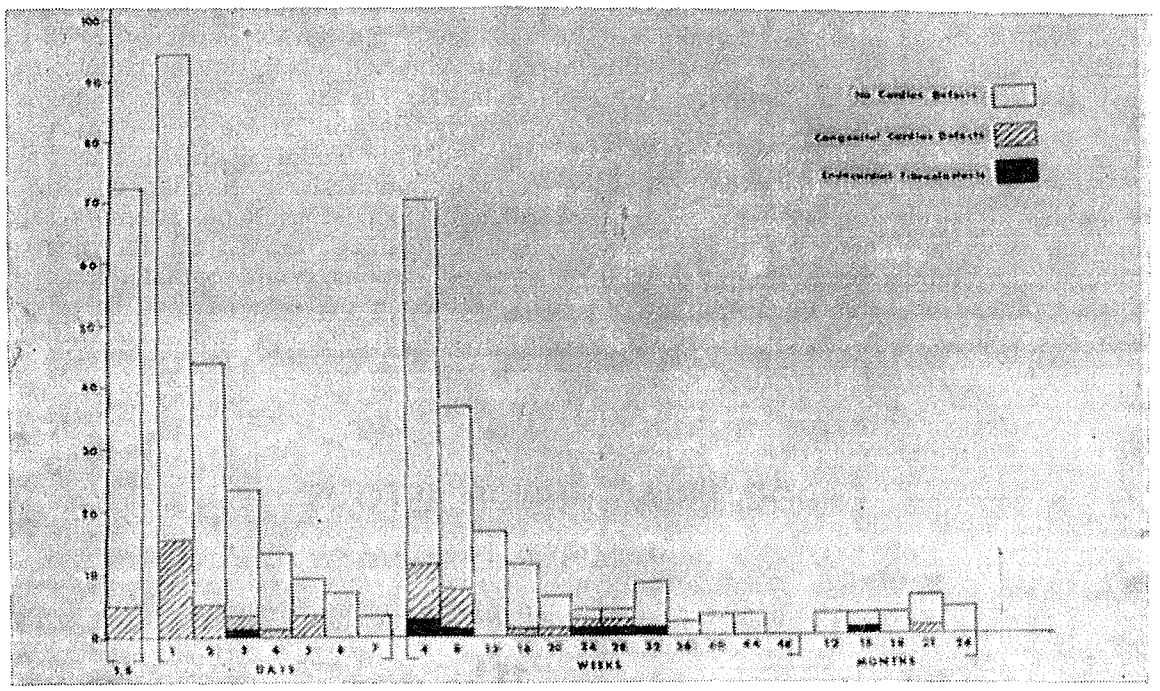

Figure 1: Showing the age distribution of necropsied infants under 2 years without any congenital cardiac anomalies, with congenital cardiac defects, and with endocardial fibroelastosis.

associated with any cardiac defect, and a "secondary" type. Other authors quote various figures (Table I).

The figures quoted for the incidence of the "primary" type also vary widely (Table II).

TABLE I
Incidence of Endocardial Fibroelastosis

Investigator	*% of Congenital Heart Disease*
Keith *et al.* 1958	4%
Forfar *et al.* 1964	17%
Present study 1967	14%

TABLE II
Incidence of "Primary" Endocardial Fibroelastosis

Investigator	*% of Cases of E.F.E.*
Halliday 1954	23%
Potter 1961	50%
Fontana and Edwards 1962	5%
Graham 1964	28.5%
Forfar *et al.* 1964	22%
Present study 1967	37.5%

There seems to be general agreement, as shown in Table III, that, in the large

TABLE III
Age at death in Endocardial Fibroelastosis

Investigator	*Age at death*	*Remarks*
Potter 1961	soon after birth	some in latter part of 1st year
Still 1961	3-12 months	50% before 5 months
Fontana & Edwards 1962	4 months	75% before 1st year
Graham 1964	less than 7 months	25% in first week
Forfar *et al.* 1964	4-6 months	50% in first 4 months
		75% in first 6 months
		80% in first year
Present study 1967		88% before 8 months

majority of cases of endocardial fibroelastosis, death occurs before the age of 12 months.

Morbid Anatomy

The pathological diagnosis of endocardial fibroelastosis was made at post-mortem on the macroscopic detection of a whitish-grey, often opaque, mural endocardium that is smooth but abnormally thick.

Table IV shows the details of the necropsied cases of endocardial fibroelastosis.

The following are two representative post-mortem cases of endocardial fibroelastosis, one of the "primary" type and the other with associated cardiac defects.

Case P.M. 30/61 — B.C., a 2 month old male infant, one of twins, was admitted to hospital, 3 weeks before death, with a brief history of pallor, dyspnoea, cough and cyanosis. The heart was radiologically enlarged.

At necropsy, the body was that of a well-nourished infant with no external congenital anomalies; petechial hæmorrhages were present on the visceral pleuræ; the right lung showed incomplete segmentation of the middle lobe and both lungs were œdematous and consolidated.

The heart *(Figure 2)* weighed 45 g. (normal weight 19 g.), was elongated in shape, the left ventricular myocardium was hypertrophied and the ventricle was dilated. The right atrium was also dilated, and was lined by a somewhat thickened and pale-grey endocardium. The tricuspid valve was mal-developed and incompetent with only two cusps, and showed myxomatous verrucæ at the free border; it was held down by short chordæ tendineæ. The left atrium was dilated, the myocardium hypertrophied and the endocardium was considerably thick and greyish white. The mitral valve was atretic, incompetent, and also carried myxomatous verrucæ at the free border. Like the tricuspid valve, it was also bound down by short chordæ tendineæ. There was hypertrophy on the left ventricular myocardium; this was covered by a moderately thick endocardium. The foramen ovale was closed; the

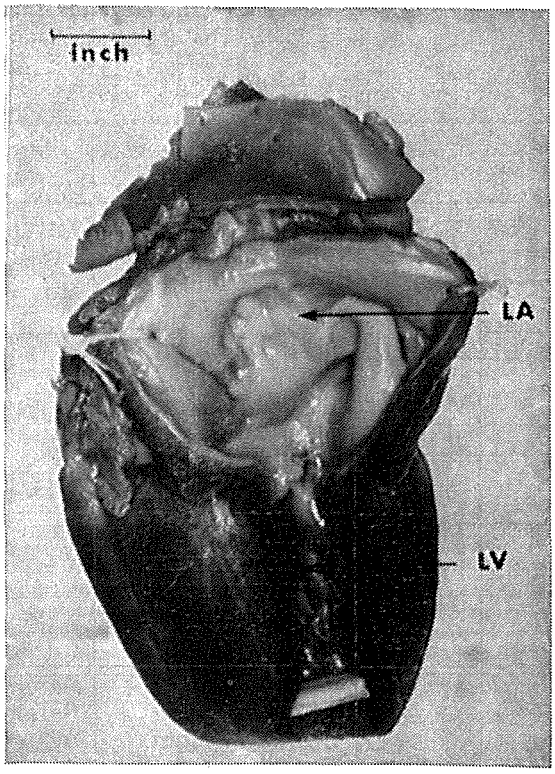

Figure 2. Showing the left side of the heart of Case P.M. 30/61. The thick endocardium of the left atrium is shown.

interventricular septum was complete and bulged to the right. The main vessels and orifices were normal.

Case P.M. 108/66 — M.C. ,a male infant aged 8 months, was born of a grand-multipara in hospital. The infant was back in hospital soon after discharge because of an upper respiratory tract infection and diarrhoe. Congenital heart disease and mongolism were diagnosed, and his condition improved with antibiotics and digitalisation. After a prolonged stay in hospital he was discharged, He was subsequently re-admitted with bronchitis gastro-enteritis and anæmia, and died two weeks later.

At necropsy, there were moderately well-defined mongoloid features; pallor was marked and the state of nutrition was fair. Both lungs showed bronchopneumonic changes in the upper lobes; both lower lobes were consolidated. Large pulmonary vessels could be followed up to the lung

TABLE IV

Showing the details of the necropsy findings of Endocardial Fibroelastosis

P.M. Cases of Endocardial fibroelastosis in Malta (1955-66)

Total P.M. Cases (under 2 years)	424
Total C.H.D. cases	57
Total E.F.E. cases	8 (10% of C.H.D.)
Total Primary E.F.E.	3 (37·5% of E.F.E.)

PM No.	*Sex & Age*	*P.M. diagnosis*	*Associated cong. cardiac malform.*	*Site of E.F.E.*	*Other cardiac findings*
25/57	F 6/12	C.H.D. E.F.E. Bilat. Pneum. consolidation	Large foramen ovale	R.A. L.A. T. M.	R.V. dilated L.V. hypertrophied T. incompetent M. incompetent
30/61	M 2/12	E.F.E. Pneumonia & pulm. œdema Bilobed R. lung	—	R.A. L.A. L.V. T. & M.	R.A. dilated L.A. dilated R.V. dilated L.V. hypertrophied T. incompetent M. incompetent
20/62	F 3/52	E.F.E. Bronchopneum. Agenesis L. lung	—	R.A. L.A. R.V.+— L.V.	L.V. hypertrophied Bulging septum to right Flat columnæ carnæ.
26/62	M 50hrs	C.H.D. E.F.E. Bronchopneum. Tentorial tear and subdural hœmorrhage	Patent ductus Patent foramen ovale Agenesis pulm. valve Sinus joining left atrium with pulmonary artery	R.V.+ L.V.	R.A. dilated L.A. dilated R.V. hypertrophied L.V. dilated T. incompetent M. incompetent
44/62	M 7/12	E.F.E. Multiple pulm. hœmorrhages Pleurisy	—	L.A.	R.A. dilated L.A. dilated R.V. dilated L.V. dilated
61/66	F 3/52	C.H.D. E.F.E.	Patent foramen ovale. Intervent. septal defect. Over-riding of hypoplastic aorta	L.A. R.A.	R.A. dilated L.A. dilated R.V. hypertrophied L.V. hypertrophied
105/66	F 15/12	C.H.D. E.F.E. Pulm. cong. and œdema	Left atrial hypoplasia. Atrial septal defect. Aorta communicates with both ventricles. Pulm. artery hypoplasia and pulmonary stenosis.	R.A. L.A. R.V.+— L.V.+—	R.A. dilated and hyperthrophied. R.V. hypertrophied L.V. hypertrophied
108/66	M 8/12	C.H.D. E.F.E. Pneumonia	Patent ductus Patent foramen ovale. Hypoplasia left atrium.	R.A. L.A.	R.A. dilated R.V. hypertrophied T. incompetent M. incompetent

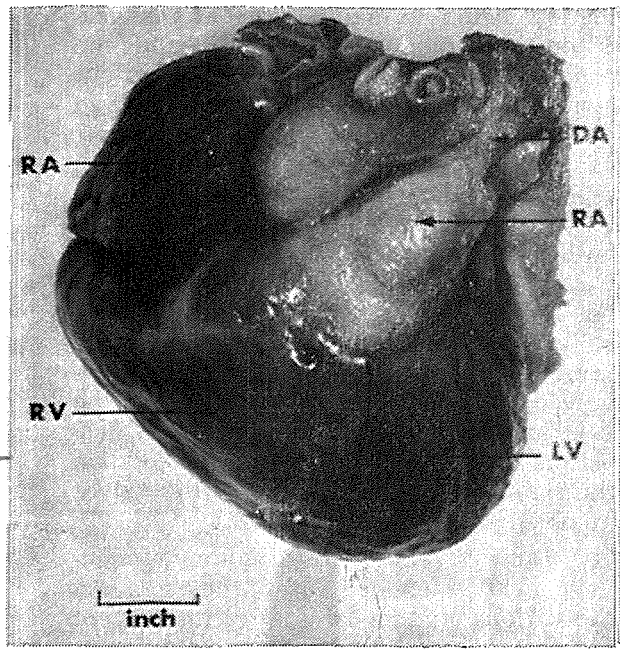

Figure 3. Showing the anterior view of the heart of Case P.M. 108/66.

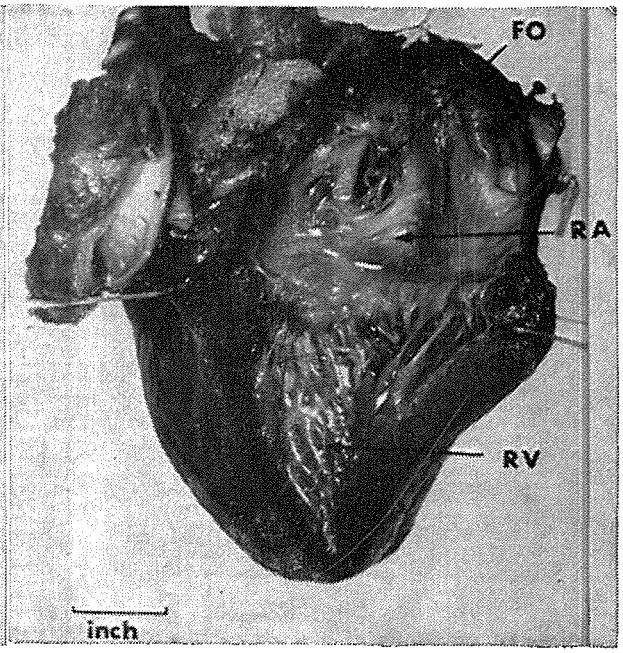

Figure 4. Showing the interior view of the right side of the heart of Case P.M. 108/66.

surfaces. Histologically, the lower lobes showed the alveoli to be filled with hæmosiderin-laden macrophages.

The heart *(Figure 3)* weighed 70 g. (normal 35 g.). The base of the heart was wide with a prominent right atrium and auricle. The left atrium was hypoplastic, and the auricular appendage was vestigial. A patent ductus arteriosus (0.3 cm. in diameter) joined a normal aorta to a dilated pulmonary artery. The right atrial myocardium *(Figure 4)* was hypertrophied in places and deficient in others. There was a patent foramen ovale. The tricuspid valve measured 1.3 cm. in diameter, and was incompetent. The right ventricular myocardium was somewhat hypertrophied and covered with a normal endocardium. The left atrium showed considerable endocardial thickening and the mitral valve was incompetent from a deficient posterior cusp. The left ventricle was slightly hypertrophied, and its endocardium was normal. There were no inter-ventricular septal defects. The aorta and aortic valve were normal. The pulmonary valve was also normal.

Histological examination: The macroscopic features noted in the heart of Case P.M. 108/66 were confirmed by histological sections *(Figure 5a)*. The endocardium is formed of a single layer of endothelial cells and the sub-endocardial layer is much thickened due to an increase in the amount of collagen, which also extends deeper down into the myocardium as irregular septa. Elastic elements are also considerably increased and are intermixed with the collagen, even in between the myocardial bundles which are often found to be hypertrophied. This distribution, therefore, suggests the term "endomyocardial fibroelastosis" as being more appropriate. Furthermore, the elastic elements are irregularly arranged and intertwine; this contrasts with the tendency for the elastic elements to be layered parallel to the surface seen in the normal endocardium *(Figure 5b)*. The hypertrophied myocardial fibres are generally separated by œdema but do not show any degenerative vacuoles and no inflammatory cells are present in the myocardium. Small foci of necrosis and calcification may be present.

Endocardial fibroelastosis may involve any of the cardiac chambers but

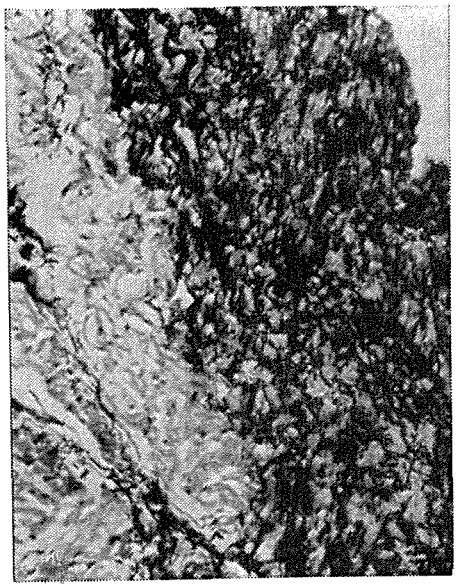

Figure 5a. Showing the histological picture of the atrial endocardium in Case P.M. 108/66. There is increase in the elastic elements and extension of elastic fibres into the myocardium.

Figure 5b. Showing the histological picture of the normal endocardium. The elastic elements are few and parallel to the surface. (Verhoeff and Van Gieson Stain. X120).

those on the left are far more frequently involved than those on the right. The left ventricle is involved in almost all cases, the left atrium in many, the right ventricle is only uncommonly involved, and the condition is distinctly rare in the right atrium. The left atrium is rarely affected in the absence of involvement of the left ventricle, though cases have recently been reported (Shortland-Webb *et al.* 1966) when the involvement was confined to both atria and did not extend to the ventricles. Any of the valves may be involved but those on the left are more frequently affected than those on the right. In the present series, the atria alone were involved in half the cases, but where the ventricles were involved, the left ventricle was always more markedly affected than the right. In only 2 cases were the valves involved.

Table V sets out the frequency of involvement by endocardial fibroelastosis of the various anatomical sites in the present series and in those reported by different investigators.

Aetiology

Much doubt still exists as to the ætiology of endocardial fibroelastosis, and a variety of theories have been put forword.

The earliest to be proposed was that of fœtal endocarditis; however, no inflammatory changes are present in the heart nor is a history of infection in the mother during pregnancy a consistent finding. The condition is believed to be a congenital anomaly arising from a disordered overgrowth of mesenchymal connective tissue (Cosgrove and Kaump 1946; Craig 1949; Gowing 1953); the possibility that it represents a form of collagen disease has also been proposed (Hill and Reilly 1951).

Johnson (1952) suggested hypoxia of the endocardium, resulting from deficient coronary blood supply or permature closure of the foramen ovale during intrauterine life, to be an ætiological factor. Such a theory would account for the preponderance of left-sided involvement as well as for the "primary" type of the condition. It is, however, found to be particularly difficult to render the endocardium anoxic, receiving as it does its main blood supply directly from the ventricle. Even

TABLE V

Site of Cardiac Involvement in Endocardial Fibroelastosis

Cardiac chambers	*Present study 1967* No. of cases	*Forfar et al. 1964* %	*Fontana & Edwards 1962* %	*Dennis et al. 1953* %	*Lambert et al. 1953* %	*Blumberg & Lyon 1952* %
Left side heart	8	89	—	—	—	100
Right side heart	7	38	—	—	—	28
Left side alone	1	63	—	82	—	—
Right side alone	—	11	—	2	—	—
Left ventricle	4	86	100	98	70	96
Left atrium	7	21	89	—	50	24
Right ventricle	3	38	5.5	—	43	88
Right atrium	6	4	—	—	36	12
Cardiac valves						
Valvular lesions	2	36	66	51	34	—
Aortic	—	25	28	38	—	36
Mitral	2	11	28	35	—	24
Pulmonary	—	9	—	—	—	—
Tricuspid	2	4	—	—	—	—

so, no evidence exists that anoxia per se produces endocardial thickening. Moreover, the foramen ovale is found in many cases to be still patent at death. Johnson (1952) described intrauterine functional obstruction of the foramen with anatomical patency.

Rosahn (1955) described the condition as a genetically-determined defect, possibly inherited through a recessive gene. Several cases of familial endocardial fibroelastosis have been reported in the literature. Others (Streseman 1955; Kelly and Andersen 1956; Lambert and Vlad 1958) have suggested that a congenital metabolic, or enzymatic, defect in cardiac muscle causes weakening of the myocardium, with consequent dilatation, and fibroelastosis then develops as a secondary phenomenon.

The mechanical causes involved may be of two kinds. According to Black-Schaffer (1957) intracardiac pressure and dilatation leads to an increase in the residual blood volume; this causes tensions in the endocardium which are cyclically accentuated and these in turn lead to a deposition of elastic fibres. The fibroelastic endocardium so formed protects the underlying myocardium from the further stresses of increased diastolic volume. Such a hypothesis would account for the occurrence of fibroelastosis in the chamber proximal to an obstructed valve, though it should be pointed out that not all valvular disease is complicated by endocardial thickening. Alternatively, it is possible that while the increased intracardiac pressure and dilatation per se may not be the cause of the fibroelastosis, stagnation of blood within the chamber is an important factor. Altered blood flow with the formation of abnormal streams of blood, is known to cause localised trauma of the endocardium with the development of fibroelastosis as a protective mechanism, and it has also been found that increased blood flow reduces the likelihood of fibroelastosis whereas diminished blood flow increases it (Forfar *et al.* 1964).

Some investigators (Noren *et al.* 1963; Vosburg *et al.* 1965) have recently shown that children with endocardial fibroelastosis give a significant reaction to mumps antigen. This observation suggests the possibility that subclinical intrauterine infection with mumps virus is the ætiological factor of primary fibroelastosis. In such a case the endocardial thickening need not be provoked by an inflammatory reaction, but may be a response of the heart to the stress caused by the virus infection.

None of the theories so far advanced provide a satisfactory explanation for the morbid anatomical findings, and it is not unlikely that the ætiology is multifactorial.

Clinical Picture

The diagnosis of fibroelastosis is difficult when it occurs as an isolated lesion; when it is associated with defects in the valves or septa the diagnosis is overshadowed by these abnormalities.

When an infant or young child is admitted to hospital in heart failure with clinical evidence of cardiac enlargement and no murmurs are audible, the diagnosis of fibroelastosis is justified until proved otherwise. Electrocardiographic evidence of left ventricular hypertrophy and radiological signs of cardiomegaly confirm the diagnosis.

A history of a recent episode of an upper respiratory tract infection is usually elicited. The infant is in respiratory distress and all the signs of heart failure are evident. There is orthopnea, a raised jugular venous pressure, mild cyanosis and cough. Râles are present over the whole chest.

The cardiac apex is left ventricular, and is palpable in the 5th or 6th left intercostal space. Gallop rhythm may be present. In severe cases the electrocardiogram *(Figure 6)* shows left ventricular hypertrophy with a "strain" pattern. Occasionally there are signs of enlargement of the right atrium and ventricle. The enlargement of the heart observed radiologically *(Figure 7)* involves all the cardiac chambers but is more marked on the left side. Pulmonary plethora is present.

Differential Diagnosis

Fibroelastosis has to be differentiated from other causes producing cardiomegaly in early life.

Acute myocarditis presents the most difficult differential diagnostic problem. The clinical and radiological findings are similar in all respects to those of fibroelastosis. The electrocardiographic findings are, however, somewhat different: the left ventricular hypertrophy is not so marked, sometimes the tracing shows low voltage waves and, occasionally, conduction defects. Laboratory investigations such

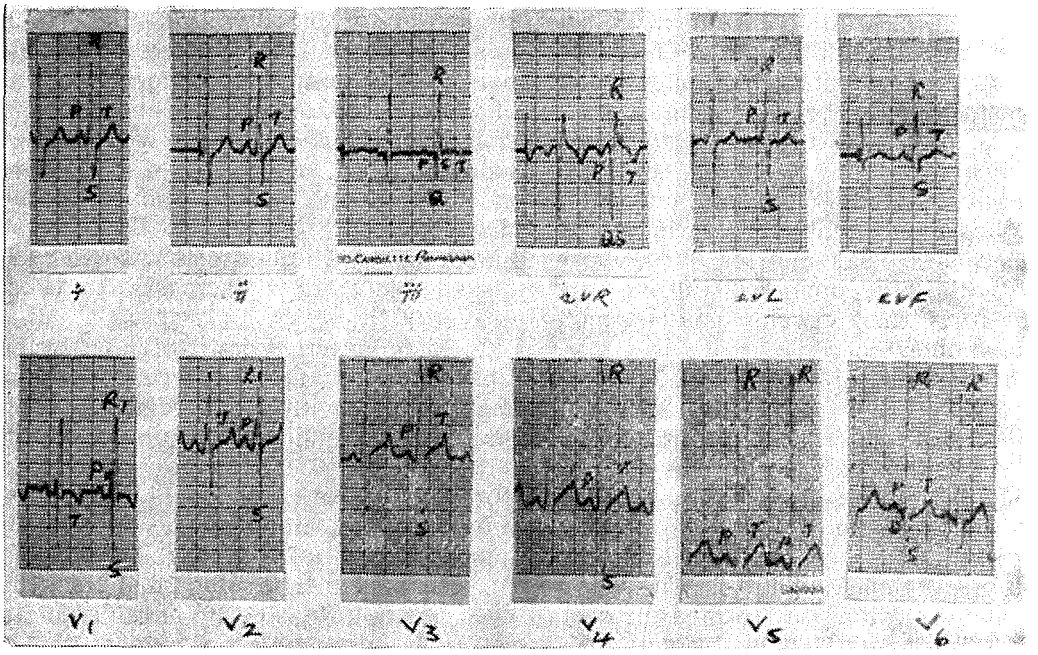

Figure 6. Showing the electrocardiographic pattern in a case of endocardial fibroelastosis.

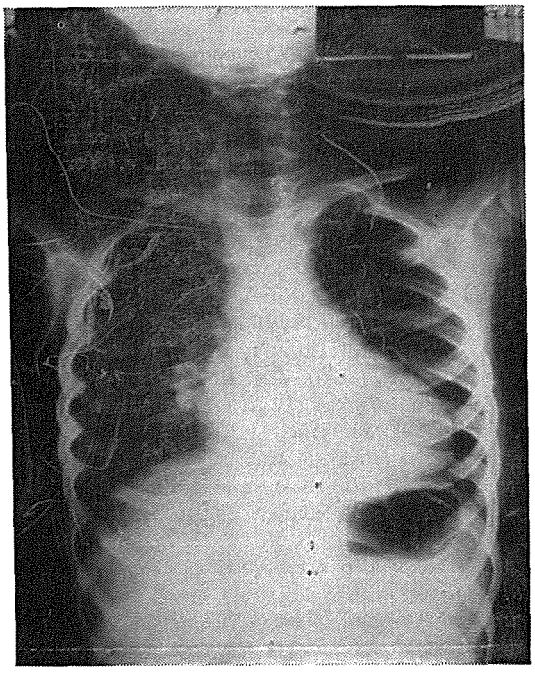

Figure 7. Showing the radiograph of the chest in a case of endocardial fibroelastosis.

as blood cultures, nose and throat washings and fæcal specimens for the isolation of a virus may help.

The cause of acute myocarditis may be viral, bacterial or rickettsial. Occasionally it is "allergic' as in collagen disease and glomerulonephritis, or may be "drug induced". The variety of ætiological agents that may be responsible renders the diagnosis more difficult.

In glycogen storage disease (Cori type II) biopsy of muscle or liver shows a high glycogen content, a finding that renders differential diagnosis easy. Moreover, the disease is commonly a familial one.

A previous history of pain, pallor and perspiration resembling anginal attacks of adults suggest a diagnosis of an aberrant origin of the left coronary artery arising from the pulmonary artery. Moreover, the electrocardiographic findings are similar to the pattern of an antero-lateral infarct. Retrograde aortography is diagnostic.

In aortic stenosis a systolic murmur may be audible over the mid-præcordium and aortic area with extension to the neck vessels. A systolic thrill is usually palpable. A definite diagnosis is made on catheterisation of the left ventricle.

In the postductal type of coarctation of the aorta, absence of the femoral pulses and low blood pressure recordings in the lower extremities point to the aortic lesions, and angiocardiography locates the site of coarctation.

Pericardial effusion presents another difficult differential problem. Clinically the heart sounds are heard with difficulty and are "dampened down". The absence of an apical thrust in the presence of gross cardiomegaly points to a pericardial effusion.

Pericardiocentesis is generally diagnostic.

Treatment

Since no specific therapy is available, treatment should be directed to heart failure. Because the condition is not necessarily fatal, treatment should be bold and persistent.

The infant should be propped up in bed with elevation of the head and upper part of the body. The administration of oxygen in concentration of not more than 30% should be instituted immediately.

Digitalis and diuretics are indicated, at first parenterally and later orally, in a dosage calculated on the body weight. Sedatives are given as required.

As oral feeding is not tolerated during the acute stage, 0.21% NaCl solution in 5% glucose is given by intravenous infusion. A regular check on the level of the electrolytes in the plasma should be kept.

Appropriate antibiotic therapy is given to combat any respiratory infection that may so often be present.

Once the acute stage has been overcome the patient may have to be maintained on digitalis therapy for many years. In our series two of three children have been having digitalis for four years, the other for two and a half years. All are symptom-free and two show definite

radiological improvement and return to normal of the cardiac shadow.

Summary

During the 11-year period 1955-66 eight cases of endocardial fibroelastosis were diagnosed or confirmed at autopsy. This represents an incidence of 1.9% in the 424 necropsies carried out on children under 2 years of age. The frequency of congenital heart diseases was found in the same series to be 13.4%. In almost 1.2% of the cases endocardial fibroelastosis was associated with cardiac anomalies.

The literature on the subject is reviewed, and the findings of the present study are compared with those of previous reports.

Acknowledgement

Our thanks are due to Professor G. P. Xuereb for the use of the post-mortem records in the Department of Pathology at St. Luke's Hospital.

References

ANDERSON, D.H. and KELLY, J. (1956). Pediatrics. *8*, 513.

BLACK-SCHAFER, B. (1957). A.M.A. Arch. Path. *63*, 281.

BLUMBERG, R.W. and LYONS, R.A. (1952). Amer. J. Dis. Child. *84*, 291.

COSGROVE, G.E. JR. and KAUMP, D.H. (1946). Amer. J. Clin. Path. *16*, 322.

CRAIG, J.M. (1949). Bull. Internat. A.M. Museums. *30*, 15.

DENNIS, J.L., HANSEN, A.E. and CORPENING, T.N. (1953). Pediatrics *12*, 130.

FONTANA, R.S. and EDWARDS, J.E. (1962). Congenital Cardiac Disease: a review of 357 cases studied pathologically. (W.B. Saunders, Philadelphia, London).

FORFAR, J.O., MILLER, R.A., BAIN, A.D. and MACLEOD, W. (1964). Brit. med. J. *2*, 7.

GOWING, N.F.C. (1953). J. Path. & Bact. *65*, 13.

GRAHAM, G.R. (1964). Fibroelastosis (p. 353) in: Cardiomyopathies (Ciba Foundation Symposium) J. & A. Churchill Ltd., London.

HALLIDAY, W.R. (1954). Dis. Chest *26*, 27.

HILL, W.T. and REILLY, W.A. (1951). A.M.A. Amer. J. Dis. Child. *82*, 579.

JOHNSON, F.R. (1952). A.M.A. Arch. Path. *54*, 237.

KEITH J.D., ROWE, R.D. and VLAD, P. (1958). Heart Disease in Infancy and Childhood. MacMillan, New York.

KELLY, J. and ANDERSEN, D.H. (1956). Pediatrics *18*, 539.

LAMBERT, E.C., SHUMWAY, C.N. and TERPLAN, K. (1955). Pediatrics *11*, 255.

NOREN, G.R., ADAMS, P. and ANDERSEN, R.C. (1963). J. Pediatrics *62*, 604.

POTTER, E.L. (1961). Pathology of the Fœtus and the Infant 2nd Ed. Y.B.M.P., Chicago.

ROSAHN, P.D. (1955). Bull. N.Y. Acad. Med. *13*, 453.

SHORTLAND-WEBB, W.R., TOZER, R.A. and CAMERON, A.H. (1966). J. Clin. Path.. *19*, 549.

STILL, W.J.S. (1961). Amer. Heart. J. *61* (5), 579.

STRESEMAN, N.E. (1955). Arch. f. Kreislaufforsch. *23*, 77.

VOSBURGH, J.B., DIEHL, A.M., CHIEN, L., LAUER, R.M. and FABIYI, A. (1965). Amer. J. Dis. Child. *109*. 69.