Heart Failure from Unexplained Cardiomyopathy

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In the 10-year period from 1955 to the present time, 12 patients have been studied in the United Bristol Hospitals who developed congestive heart failure and later came to necropsy without a definable cause being apparent for their heart failure. These 12 patients†, who were all seen by one of us, form the basis of this report. Criteria for inclusion have simply been that all the patients presented with heart disease, and that some time before their death they went into congestive heart failure which was shown at necropsy to be due neither to valvular disease, nor to congenital heart disease, nor to hypertension, nor to endocrine disease, nor to ischaemic heart disease. Nor was there any evidence of disease in any other organ that could not be related to heart failure. Thus, the cause of heart failure was considered in each case to be due to a primary disorder of the heart muscle of unknown cause. The majority of these patients were seen before the syndrome of hypertrophic obstructive cardiomyopathy received detailed clinical description (Brock, 1957; Bercu *et al.*, 1958; Morrow and Braunwald, 1959; Goodwin *et al.*, 1960; Teare, 1958). In retrospect, with re-examination of all the hearts, it seems certain that only 1 of these 12 patients could have belonged to this category. In this 10-year period a small number of additional patients have been seen and studied who probably suffered from a similar condition but they are not described because we lacked proof at necropsy of the nature of their heart disease.

CASE REPORTS

Case 1. A man of 33, at the time of admission to hospital, had 12 years earlier come under observation because of a shadow in the right lung base which was regarded as being tuberculous. His heart was of normal size. Sputum examination revealed the presence of

tubercle bacilli and he was given a full course of anti-tuberculous treatment. Nine years later, a chest radiograph showed that there was slight enlargement of the heart. He next presented with a story of breathlessness on exertion and a further chest radiograph showed considerable cardiomegaly (Fig. 1). Clinical examination revealed a forceful apex beat, displaced to the left; a third heart sound, and clear lung bases. The rhythm was regular. The electrocardiogram showed low voltage complexes with intraventricular conduction defect. In view of the past history of pulmonary tuberculosis, it was considered necessary to exclude constrictive pericarditis by full investigation, and this was arranged. By the time of his admission for cardiac catheterization several weeks later, atrial fibrillation had supervened and this persisted until his death. Right heart catheterization revealed a mean wedge pressure of 27 mm. Hg, pulmonary artery pressure of 46/20, and a mean right atrial pressure of 6 mm. Hg. The left ventricle was catheterized retrogradely through the aortic valve. The systolic pressure in the left ventricle was 100 mm. Hg, and the end-diastolic pressure was 11 mm. Hg. A left ventricular angiogram revealed a dilated left ventricular chamber with walls of normal thickness (Fig. 2). There was no pressure gradient across the aortic valve and a diagnosis of myocardial failure of unknown cause was made. An apex cardiogram showed the presence of a prominent rapid filling wave and a sharp third sound point (Fig. 3).

He was discharged from hospital taking digitalis and diuretics and returned to his work. Five months later he was re-admitted with abdominal pain, and acute appendicitis was diagnosed, but at laparotomy no cause for his pain was discovered and nothing was done. Within the next few days he developed signs of a leg vein thrombosis and anticoagulant therapy was begun. His subsequent course included severe bleeding during anticoagulant therapy, further pulmonary embolism, and progressive heart failure.

Family history. His mother died at the age of 53 of heart disease that had been investigated at St. Luke's Hospital at Guildford. At the age of 51 she complained of palpitations due to attacks of paroxysmal atrial tachycardia. She was treated with quinidine, and atrial fibrillation supervened. The principal physical findings were enlargement of the heart with a rise in jugular venous pressure and a systolic murmur over the præ-

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† One further patient, an example of transmission from mother to son, with similarity in their electrocardiograms, is reported in the Addendum.

FIG. 1.—Chest X-rays of Case 1. (A) January 25, 1957. (B) February 24, 1964.

cordium. Atrial fibrillation persisted and she died at home two years later. Her electrocardiogram (Fig. 4B) closely resembled that of her son (Fig. 4A). The family tree is shown in Fig. 11.

Case 2. A man of 41 years, who presented with severe breathlessness and attacks of nocturnal dyspnoea, at the age of 27 had been found to have a heart murmur. Three months after the onset of his symptoms he was admitted to hospital and found to be in advanced congestive heart failure with very high venous pressure, a small volume pulse which was diminished by taking a deep breath, considerable cardiac enlargement, and a loud third heart sound at the apex. The electrocardiogram showed regular rhythm with a normal P-R interval; the QRS complexes were of low voltage and there were non-specific T wave changes. The question of pericardial effusion was raised, and a diagnostic aspiration was performed but no fluid obtained. In spite of intensive medical treatment he died two weeks later.

Family history. His father died of heart disease at the age of 52 and his mother also died of heart disease at the age of 45. He had 3 healthy sisters and 2 healthy daughters.

Case 3. A woman of 32 years, who was of English descent but had spent the previous 8 years living in Rhodesia, had, between the ages of 26 and 31 years, 6 pregnancies, 4 of which miscarried. She delivered her second full-term child one month before the symptoms of her last illness. Breathlessness on exertion was her presenting symptom. She was admitted to hospital in Salisbury, Rhodesia, and catheterization of the right

heart revealed that all pressures were normal. The patient returned to England in congestive heart failure four months later. The main findings were a regular heart rhythm with a systolic murmur and a third heart sound, raised venous pressure, and basal râles. Her

FIG. 2.—Left ventricular angiogram (Case 1), showing the dilated cavity with a wall of normal thickness.

FIG. 3.—(Case 1) Tracings from above downwards are: apex phonocardiogram, lead I electrocardiogram, apex cardiogram, and left ventricular pressure curve. Note the third heart sound in the phonocardiogram coinciding with the sharp point in the apex cardiogram.

FIG. 4.—Electrocardiograms of (A) Case 1 and (B) his mother.

chest radiograph showed considerable cardiac enlargement and congestion of the lung bases. She was referred for repeat catheterization but died the night before her investigation was to have been performed. The total duration of her symptoms was 6 months. No family history of heart disease was obtained.

Case 4. A man of 56 years, who for more than 16 years had suffered from attacks of bronchial asthma, had 6 months before his first admission to hospital, begun to notice increasing breathlessness on effort, and 3 months before admission this limited his walking to a short distance. His admission was precipitated by a severe attack of breathlessness, and at first examination his venous pressure was so high that cardiac tamponade was suspected. A paracentesis did not yield pericardial fluid. The rhythm was regular and no third heart sound was recorded. The electrocardiogram merely showed left axis deviation with occasional ventricular ectopic beats. With conservative treatment he was kept free of heart failure for a further 6 months, but by this time the electrocardiogram was showing frequent multifocal ectopic beats, and T waves were flattened over left ventricular leads. On one occasion, pericardial friction was heard and this persisted for 3 days. He was admitted to hospital again 10 months after the commencement of his symptoms with advanced congestive heart failure which failed to respond to treatment.

Case 5. A man of 20 years developed breathlessness on effort while doing National Service, and on this account was invalided from the Forces. A few weeks later he was admitted to Ham Green Hospital with frank congestive heart failure and cardiomegaly. A month later, pericardial friction was heard. At this time the electrocardiogram showed sinus rhythm and non-specific T wave changes over left ventricular leads. One year later he was readmitted with congestive heart failure. The venous pressure was high and a third heart sound was audible. He developed pulmonary infarction and died 16 days later. No relevant family history was obtained.

Case 6. A boy of 15 years complained of central chest discomfort and great tiredness after an influenza-like illness. Six weeks later he was admitted to hospital with breathlessness, and was found to have an irregular pulse, enlargement of the heart, and congestive heart failure. The electrocardiogram showed sinus rhythm, low voltage complexes, and widespread T wave changes (Fig. 5). He developed a loud third heart sound and progressive irregularity from multiple ventricular ectopic beats. Death took place suddenly two months after the onset of his symptoms.

Case 7. A man of 45 years, whose first symptoms were breathlessness on effort, orthopnoea, and palpitations. Atrial fibrillation was diagnosed and confirmed by electrocardiography. Treatment with digitalis was instituted. Chest radiograph showed no obvious cardio-

megaly. He came to hospital again one year later with congestive heart failure. There was an apical systolic murmur but no third heart sound was recorded. The electrocardiogram showed progressive changes, but with full medical treatment he recovered and returned home. His final admission to hospital was 5 months later when he was in terminal failure.

Family History. His father died of heart disease at the age of 61. He had two healthy brothers, and two other brothers died suddenly while young of an unknown cause.

Case 8. A man of 52 years was first admitted to hospital in 1959 with an exacerbation of peptic ulceration. At this time a routine electrocardiogram was recorded, and it showed abnormalities of the T wave over left ventricular leads (Fig. 6). A chest radiograph showed no cardiac enlargement. Three years later he began to notice breathlessness on effort and within 6 months he was again admitted to hospital with breathlessness and frank congestive heart failure. A third heart sound was recorded and the radiograph now showed substantial enlargement of the entire heart. Initially, his heart failure responded to conservative measures and he was discharged home. Repeated pulmonary emboli led to his readmission 8 months later when he died of heart failure. All the electrocardiograms showed sinus rhythm.

Family history. There was no family history of heart disease.

Case 9. A man of 37 years first noticed breathlessness when cycling. It increased and 6 months later he was admitted with congestive heart failure. There was a history of several attacks of severe nocturnal breathlessness. No cause for his heart failure could be found. The principal features were regular rhythm, a third heart sound, and an electrocardiogram showing left bundle-branch block. He responded reasonably well to traditional measures and was admitted again on several occasions but died in hospital of congestive heart failure within a year of his first admission.

Family history. There was no family history of heart disease.

Case 10. A man of 63 attended hospital with a history of one month of increasing breathlessness. His heart rhythm was regular. There was a loud third heart sound and a pansystolic murmur at the apex of the heart. Bilateral basal crepitations were present and very high venous pressure. Cardiac catheterization showed a rise in pulmonary artery pressure to 49/27 mm. Hg. Angiocardiography showed a very dilated left ventricular cavity. Within 4 months of his first admission he died of heart failure.

Family history. There was no family history of heart disease.

Case 11. A woman of 31 years attended hospital complaining of sore throat and a cough, and a chest radiograph showed that the heart was enlarged. Three

FIG. 5.—Electrocardiogram of Case 6, showing multifocal ectopic beats.

years later she was admitted to hospital with congestive heart failure. She responded well to digitalis and diuretic therapy and was not readmitted until six years later. At this time the principal features were pleural pain with pulmonary infarction complicated by transient atrial fibrillation (Fig. 7A). The patient was not treated with anticoagulants, and during the same admission she suddenly developed a dense left hemiplegia. The CSF was not blood-stained, and it was assumed that the stroke was due to cerebral embolism. There was a steady return of function on the affected side. At this time she was in sinus rhythm. The principal auscultatory features were a presystolic gallop rhythm; a widely split second heart sound which was attributed to the presence of left bundle-branch block (Fig. 7B), and a fairly loud apical systolic murmur. She recovered sufficiently to

go home to her family, but was readmitted in terminal heart failure of which she died 4 months later.

Family history. Her father and two of her sisters were known to have died suddenly sometime after the discovery that they had enlarged hearts. While she was in hospital recovering from her cerebral embolism the news was brought to her that her 12-year-old son had collapsed and died at home. Her husband gave the history that for some weeks before his death the child had had fainting attacks and the doctor who examined him found a heart murmur. The mode of death was that the child collapsed quite suddenly and was found to be dead. A coroner's necropsy showed the absence of valvular disease or congenital heart disease, and death was attributed to acute heart failure. Three years after this patient's death her eldest daughter, aged 16 years, was

FIG. 6.—Electrocardiogram of Case 8, showing abnormal P wave and the non-specific ST-T changes.

found dead at home. Necropsy showed that death was due to heart failure. There was hypertrophy of all heart chambers with histological evidence of hypertrophy of the muscle fibres with little fibrosis, but no leucocyte infiltration.

Case 12. A girl of 6 years was first seen on account of asthmatic attacks. She was found to have a loud apical systolic murmur and this was attributed to rheumatic heart disease. She was followed routinely as an out patient but kept well for the next 9 years when she was admitted to hospital with congestive heart failure. At this time atrial fibrillation was discovered. The heart

failure was again attributed to rheumatic heart disease with atrial fibrillation and mitral incompetence, and she made a good response to routine measures, so that she kept well and out of hospital for almost 3 years. During this time she was always found to have a harsh systolic murmur at the apex of the heart usually accompanied by a thrill. The electrocardiogram showed left ventricular hypertrophy and left bundle-branch block. These changes were progressive (Fig. 8). There was also progressive radiological enlargement of the heart (Fig. 9). Three years after the onset of her symptoms she was finally admitted with advanced heart failure and died.

FIG. 7.—Electrocardiograms of Case 11. (A) Paroxysmal atrial fibrillation in June 1960. (B) Sinus rhythm with left bundle-branch block pattern in November 1960. (C) Paroxysmal atrial tachycardia with 2:1 block in December 1960.

This patient was studied and died before the clinical features of hypertrophic outflow tract obstruction to the left ventricle were widely known. The report by Teare (1958) of sudden death in patients with asymmetrical hypertrophy of the outflow tract of the left ventricle led to a reconsideration of the necropsy findings. Fig. 12 shows a photograph of her heart and explains why it is probable that this child was an example of hypertrophic obstructive cardiomyopathy. However, her case has been included in this report because she presented as a case of heart failure due to primary muscle disease of an unknown type, and haemodynamic observations are not available to support the idea of obstructive myopathy. Her course was one of steady progression through three years of congestive heart failure.

Family history. There was no family history of heart disease.

DISCUSSION

The Nature of the Disease. These patients have in common simply the fact that they died of heart failure which was judged to be due to a primary myocardial fault. The first question that may be raised is whether they all suffered from the same kind of heart disease. In attempting to answer this question it may be best first of all to review the principal features present in all the patients.

There were 9 men and 3 women, whose ages ranged from 15 to 61 years. In 4 of the patients

there was a history that other members of the family had died of heart disease. This will receive further consideration later.

Symptoms and Signs (Table I). Breathlessness was the major presenting symptom in each case. Six gave a history of paroxysms of breathlessness awaking them from sleep. Six patients complained of palpitations, and in three it was troublesome; all three patients had atrial fibrillation. Central chest pain was complained of by Case 12 and by one other.

On examination objective abnormalities were confined to the cardiovascular system. Raised venous pressure and other signs of congestive failure were present at some stage in all. An apical systolic murmur was recorded in 8 of the 12, and an additional heart sound also in 8. In 3 patients a transient pericardial friction sound was heard. Blood pressures were within normal limits on all occasions in all the patients.

Electrocardiogram. The electrocardiographic features are analysed in Table II. In addition to the 3 patients with persistent atrial fibrillation, 2 others were known to have had paroxysms of atrial fibrillation. Paroxysms of atrial tachycardia were recorded in 3 further patients. Extreme left axis

FIG. 8.—Electrocardiograms of Case 12. The one on the left was taken in December 1964, and shows abnormal P wave; the one in the middle was taken in June 1961, and shows atrial fibrillation; and the one on the right, recorded in November of the same year, shows complete left bundle-branch block.

A

B

C

FIG. 9.—Chest X-rays of Case 12, showing progressive cardiac enlargement.

TABLE I
MAIN CLINICAL FEATURES

	Case Number												
Symptoms and Signs	1	1 (Mother)	2	3	4	5	6	7	8	9	10	11	12
Exertional dyspnoea	+++	+	+	+	+	+	+	+	+	+	+	+	+
Paroxysmal nocturnal dyspnoea	—	—	+	—	+	+	—	+	—	+	+	—	—
Palpitations	+	+++	—	—	—	—	—	+	—	—	+	+	+
Angina	—	—	—	—	—	—	Central chest pain	—	—	—	—	—	Central chest pain
Syncope	—	—	—	—	—	—	—	—	—	—	—	—	—
Progressive cardiac failure	+	+	+	+	+	+	+	+	+	+	+	+	+
Generalized cardiac enlargement	+	+	+	+	+	+	+	+	+	+	+	+	+
Embolic complications	Pul- mon., renal, spleen	—	Pul- mon.	—	Pul- mon., renal, colon	Pul- mon.	—	Pul- mon., renal	Pul- mon.	Renal	—	Pul- mon., cerebral	—
Murmurs	—	—	Apical syst.	Apical syst.	—	Apical syst.	Apical syst.	Apical syst.	—	—	Apical syst.	Apical syst.	Apical syst.
Additional heart sounds	3rd sound	?	3rd sound	3rd sound	—	3rd sound	3rd sound	—	3rd sound	3rd sound	3rd sound	Atrial sound	—
Pericardial friction rub	—	—	?	—	+	+	—	—	—	—	—	—	—

TABLE II
SUMMARY OF MAIN ELECTROCARDIOGRAPHIC FINDINGS

Case No.	Axis deviation	Predominant rhythm	Abnormal P waves	P-R (sec.)	Conduction defects			Abnormal T wave	Arrhythmias			Sv1 + RV5 (mm.)
					Left bundle-branch block	Right bundle-branch block	Intraventricular		Ectopic beats	Paroxysmal atrial tachycardia	Atrial fibrillation	
1	+14	Atrial fibrillation	—	—	—	—	+	+	+	—	P+	18
Mother of Case 1	+15	Atrial fibrillation	—	—	—	—	—	+	+	T+	P+	19
2	+10	Sinus	+	0.16	—	—	—	+	+	—	—	5
3	Normal	Sinus	—	Normal	—	—	—	+	—	—	—	Low voltage
4	-75	Sinus	+	0.20	—	—	T+	+	+	T+	—	17
5	-45	Sinus	+	0.17	—	—	—	+	—	—	—	18
6	+112	Sinus	±	0.16	—	—	—	+	+	—	T+	15
7	-60	Atrial fibrillation	—	—	—	—	—	+	+	—	P+	11
8	-40	Sinus	+	0.18	—	—	±	+	+	—	—	18
9	+18	Sinus	+	0.19	T+ incompl.	T+ incompl.	+	+	+	T+	—	26
10	+30	Sinus	+	0.19	—	—	—	+	+	T+	—	13
11	-55	Sinus	+	0.24	P+C	—	+	+	+	T+	T+	5
12	+18	Atrial fibrillation	+	0.20	P+C	—	+	+	+	T+	P+	45

P, permanent; T, transient; incompl., incomplete; C, complete.

deviation from -40° to -75° was present in 5. Two patients always showed left bundle-branch block, but the principal abnormality of the QRST complex was abnormality of the T wave which was present in all the series. Ectopic beats were a prominent feature of almost all the electrocardiograms. With the possible exception of Case 12, no patient exhibited the high voltage changes of left or right ventricular hypertrophy. In the patients with

sinus rhythm, abnormalities of the P waves suggesting right and/or left atrial hypertrophy were a common feature.

Radiology. X-rays showed dilatation of the heart with pulmonary venous congestion.

Clinical Course. Of the 12 patients, 10 followed a rapidly progressive downhill course to death from

TABLE III
SUMMARY OF THE NATURAL HISTORY OF THE DISEASE

Case No.	Age (yr.)	Sex	Family history of heart disease	First objective evidence of cardiac involvement	Onset of symptoms of cardiac decompensation	Congestive heart failure	Progressive myocardial failure	Date of death	Mode of death	Total duration of symptomatic state until death
1	33	M	+	Probable cardiac enlargement (Nov. 1960) Increased CTR on X-ray, atrial fibrillation (Sept. 1963)	Mar. 1963	Dec. 1963	+	Aug. 1964	Gradual	17 mth.
Mother of Case 1	53	F	+	Paroxysmal atrial tachycardia, congestive heart failure, atrial fibrillation (Dec. 1959)	Oct. 1959	Dec. 1959	+	July 1961	Gradual	20 mth.
2	41	M	+	Murmur (1941)	June 1955	Sept. 1955	+	Sept. 1955	Gradual	4 mth.
3	32	F	—	Dyspnoea, murmur (Jan. 1956)	Jan. 1956	May 1956	+	June 1956	Sudden	6 mth.
4	56	M	—	Congestive heart failure (May 1960)	Jan. 1960	May 1960	+	Nov. 1960	Gradual	11 mth.
5	21	M	—	Congestive heart failure (June 1956)	May 1956	June 1956	+	July 1957	Gradual	14 mth.
6	15	M	—	Congestive heart failure (Jan. 1961)	Dec. 1960	Jan. 1961	+	Feb. 1961	Sudden	2 mth.
7	47	M	+	Atrial fibrillation (June 1958)	June 1958	Sept. 1959	+	Feb. 1960	Gradual	20 mth.
8	53	M	—	Electrocardiographic changes (Mar. 1959)	Jan. 1962	June 1962	+	March 1963	Gradual	18 mth.
9	38	M	—	Congestive heart failure (Jan. 1962)	June 1961	Jan. 1962	+	Jan. 1963	Gradual	18 mth.
10	61	M	—	Congestive heart failure (July 1962)	June 1962	July 1962	+	Oct. 1962	Gradual	4 mth.
11	40	F	+	Increased CTR on X-ray (June 1951)	? 1945	Feb. 1954	+	Dec. 1960	Gradual	? 10–15 yr.
12	18	F	—	Apical systolic murmur (1949)	Oct. 1958	Oct. 1958	+	Dec. 1961	Gradual	38 mth.

congestive heart failure (Table III). From the onset of symptoms 3 died within 6 months, and the other 7 within 20 months. Case 11 ran a much more slowly progressive course. Her heart was found to be enlarged when she presented with upper respiratory symptoms and complained of a "funny feeling" in the chest. Congestive heart failure was first apparent 3 years later but she survived for a further 6 years. Similarly, Case 12 survived for over 3 years after congestive heart failure appeared.

Necropsy Findings. These are analysed in Table IV. All showed variable degrees of left and right ventricular hypertrophy and dilatation with enlargement of both atria. The valves were normal except for some increase in the circumference of the mitral and tricuspid valves in most cases (Fig. 10). Coronary vessels were patent. Microscopical examination of the heart revealed varying degrees of hypertrophy of myocardial fibres, interstitial fibrosis, and some focal myocardial lysis. There was some correlation between mural thrombosis and the total

duration of the symptomatic state; the average duration in those with mural thrombi was 33 months, and in those without it was 12 months.

Classification of Primary Myocardial Diseases. Brigden (1957) described 50 patients with non-coronary cardiomyopathy on an aetiological basis. His main groups were (1) alcoholic, (2) infective, (3) familial, (4) amyloid, (5) pregnancy, (6) hypersensitivity with collagen disease.

Goodwin *et al.* (1961) gave an account of 66 patients divided on clinical grounds as follows. *Type 1*, congestive heart failure with atrio-ventricular valvular incompetence: these were further described as simulating ischaemic heart disease or heart failure of uncertain aetiology; *type 2*, obstructive simulating stenotic valvular disease—principally aortic; *type 3*, constrictive simulating constrictive pericarditis.

Under Brigden's aetiological grouping, 4 of our 12 patients would be included in those with familial heart disease and one possibly infective heart

TABLE IV
SUMMARY OF HISTOPATHOLOGICAL FINDINGS

Case No.	Heart weight (g.)	Chambers enlarged				Valve cusps	Coronary atheroma	Coronary occlusion	Thickness of wall		Mural thrombosis	Embolic complications	Histology						Systemic changes	
		LV	RV	LA	RA				LV (cm.)	RV (cm.)			Hypertrophy of myocardial fibres	Focal myocardial lysis	Leucocyte infiltration		Fibrosis			
															M	P	E	M		P
1	487	++	+	+	+	N	—	No			RA, LA, LV	Renal, pulmonary spleen	+	—	—	—	—	+	—	Congestive heart failure ” ” ”
2	510	++	+	+	+	N	Slight	No	1.2	0.6	—	Pulmonary	—	—	—	—	—	+	—	
3	400	++	+	+	+	N	Slight	No	1.3	0.5	—	—	+	+	—	—	+	+	+	
4	650	++	++	+	++	N	Slight	No	1.7	0.7	LA, RV, LV	Renal, colon, pulmonary	+	+	—	—	+	+	+	
5	505	+	++	+	+	N	—	No	—	—	LV +	Pulmonary	+	—	—	—	LA +	+	—	”
6	575	++	++	+	+	N	—	No	1.6	0.7	—	—	+	—	+	+	+	+	—	”
7	675	++	+	+	+	N	Slight	No	1.4	0.4	RA +	Pulmonary, renal	+	—	—	—	—	—	—	”
8	455	++	++	+	+	N	Slight	No	1.7	—	—	Pulmonary	+	+	—	—	—	+	—	”
9	540	+	+	+	+	N	Slight	No	1.1	0.6	RA, RV	Renal	+	—	—	—	—	+	—	”
10	480	++	+	+	+	N	Slight	No			—	—	+	—	—	—	—	+	—	”
11	—	+	+	+	+	N	Slight	No			RV, LA	Pulmonary, cerebral	+	—	—	—	—	+	—	
12	670	+++	+	++	+	N	—	No	0.7-2.1	1.0	—	—	+++	—	—	—	LA +	+	—	”

N, normal; M, myocardium; E, endocardium; P, pericardium.

disease, but the remaining 7 cases were of unknown aetiology. No history of any considerable intake of alcohol was recorded in any.

Infective Cardiomyopathy. Case 6, a boy of 15 years, most closely resembles the descriptions of subacute myocarditis. He was initially unwell with an influenza-like illness and his main symptom was tiredness and exhaustion. The total white cell count rose to 12,050/c.mm. There was precordial pain and he died within 2 months of the appearance of heart failure. Histology showed leucocytic infiltration of the myocardium. No virus studies were performed.

Idiopathic Group with or without Family History of Heart Disease. Histological evidence of an infective process was not found in any of these 11 cases. Absence of inflammatory changes is in keeping with the observations of Dye *et al.* (1963) who studied 32 patients with heart failure and cardiomegaly for which no aetiology was evident. Of their 12 patients who died, 9 came to necropsy. Inflammatory reactions were not a feature in any. Similarly, Correo *et al.* (1963) studied the histology of 28 cases of heart disease of undetermined aetiology, and infection was not considered to be an aetiological agent. Fowler, Gueron, and Rowlands (1961) reported 18

patients who died of heart failure without clinical or pathological evidence of a primary cause.

Of the 11 patients in this group, 4 gave a family history of heart disease (Fig. 11). Fig. 4 shows the electrocardiogram of Case 1 and of his mother, who died of undiagnosed heart disease a few years earlier. The maternal grandmother also died at 45 years of heart disease.

A second patient (Case 2) gave a history that both his parents died of heart disease aged 45 and 52 years. Of a family of 5 boys (Case 7), 2 were known to have died suddenly of heart disease while young.

The family history of Case 11 shows that 6 of 10 members are already dead of heart disease. Her 2 sisters and 2 children both died suddenly, and necropsy findings of her 2 children confirmed the diagnosis of primary myocardial fault. Her own illness was unlike all the others in this report in that the course was protracted. This is the only feature suggesting that her heart disease may be aetiological different from the rest.

We have not felt justified in assuming that those patients with a family history of heart disease are necessarily any different from the rest. It is clearly possible that they may be aetiological distinct. It is equally possible that the entire group of patients have the same disease and that there is a family

FIG. 10.—(A) Gross appearance of the heart (Case 1), and (B) section of the myocardium showing the absence of inflammatory reactions.

incidence. The essential myocardial abnormality or abnormalities may be genetically determined or acquired.

Table V compares the two groups separated on the basis of family history. The only feature suggesting

a difference in the nature of the disease is the longer survival of those with a positive family history. Thus, the average duration from the onset of heart failure to death is 23 months in those with a family history and 7 months in those without. This longer

FIG. 11.—Family trees.

course is also reflected in the fact that 4 of 5 patients were found to have heart disease before congestive heart failure supervened. In 2, the onset of arrhythmia was the first evidence. Atrial fibrillation was not found in the group with the more rapid course and this may again represent only the effect of chronicity. The rather greater average heart

weight in those with a family history is in keeping with Brigden's (1957) statement that heart weights are greater in familial cardiomyopathy than in the other groups. However, the longer duration of the disease in our patients probably accounts for this difference. The numbers are small and the average difference may be entirely fortuitous.

TABLE V
COMPARISON OF TWO GROUPS SEPARATED ON BASIS OF FAMILY HISTORY OF HEART DISEASE

	No. of cases	Average age at death (yr.)	M:F ratio	First objective evidence of cardiac involvement	Average total duration of symptomatic state until death	Average duration in congestive heart failure until death (mth.)	Atrial fibrillation	Mural thrombosis	Embolic complications	Average weight of heart (g.)
Those with family history of heart disease	5	42.8	3:2	Atrial fibrillation, murmur, cardiac enlargement	36.2 mth.	23	3 cases	3 cases	4 cases	557.33
Those without family history of heart disease	7	40	6:1	Congestive heart failure	10.3 mth.	6.7	None	3 cases	4 cases	516

Note: The mother of Case 1 has been included in the first group, while Case 12 was excluded from the second group because of the different pathological features.

Until there is evidence as to the fundamental biochemical fault or faults in this group of diseases, it will not be possible to be dogmatic as to which cases are genetically determined and which are acquired.

Affected Families. It is clear that in affected families the disease may run a quite different course in different members. Whitfield (1961) describes 10 members of a family affected with cardiomyopathy: 3 died suddenly and 3 others died of congestive heart failure. The age at which the disease becomes evident may also differ in succeeding generations. Thus, in Whitfield's family of 4 generations the first and second generations were affected in the third to sixth decade, 5 members of the third generation in the second to fourth decade, and 4 of the fourth generation in the first decade. The 2 families described by Kariv, Sherf, and Solomon (1964) also showed the disease appearing at an earlier age in the second generation. It may not be relevant to compare families with hypertrophic obstructive type of cardiomyopathy, but Hollman *et al.* (1960) reported more severe affection at an earlier age in the latest generation of a family with 9 affected members. On the other hand, Braunwald *et al.* (1964) reported 23 patients with hypertrophic obstructive cardiomyopathy with a family history, and he found no evidence that the disease was more severe in the later generations.

In our patients (Table III) there is good evidence that the disease ran a similar course in Case 1 and in his mother. Both developed atrial fibrillation and were dead within 2 years of the onset of congestive heart failure. On the other hand, Case 11 ran the most protracted course of the entire series, while her 2 children both died suddenly and unexpectedly: it is believed that both her sisters died suddenly. There is a suggestion that the disease is tending to occur earlier in later generations. For instance, Case 1 died at the age of 33 years, whereas his mother survived to 53 years. Case 11 and her 2 sisters died at the age of 40 years, whereas her 2 children died in their teens.

Genetics. Brigden (1957) and Whitfield (1961) considered that the female was responsible for transmission of the defect. In the present series in the two families in which evidence of transmission was strong (Case 1), or proved (Case 11), this was also true; but the father of Case 11 also died at 40 years of age, of heart disease (Fig. 11). Kariv *et al.* (1964) and Braunwald *et al.* (1964), on the other hand, considered transmission was on the basis of an autosomal dominant gene.

There may be more than one form of genetically

determined heart disease to account for the various clinical types and the different modes of inheritance. On the other hand, these differences have been found among clinically similar cases of Duchenne type of muscular dystrophy (Walton, 1964). As Nirenberg (1963) has shown, intracellular transmission of abnormally coded DNA information occurs within the cell when RNA carries the code into metabolic steps which terminate in a quantitative or qualitative alteration of a particular enzyme. Walton (1964) has pointed out the difficulties in understanding the similarities and differences between neuromuscular entities which depend upon different genes, owing to the overlap of the metabolic pathways associated with the expression of various specific genes, which in turn may cause an overlap in clinical stigmata.

Further evidence of the genetic pattern of the disease is highly desirable, as advice is now being sought by members of these families as to the risk to future progeny.

Hypertrophic Obstructive Cardiomyopathy. Although no pressure measurements were made during life, it seems probable that Case 12 was an example of hypertrophic obstructive type of cardiomyopathy. For instance, she was under observation at the age of 6 years with a loud apical systolic murmur. The electrocardiogram showed higher voltage over left ventricular leads than in any other patient. Finally, the post-mortem appearance of the heart was similar to that described by Teare (1958) as asymmetrical hypertrophy of the outflow tract of the left ventricle. In our patient the hypertrophy was most marked over the upper anterior portion of the left ventricular wall (2.1 cm.); posteriorly the thickness of the wall was 0.7 cm. (Fig. 12). Histologically the hypertrophied portion showed interstitial fibrosis dividing the hypertrophied muscle into coarse bundles. The course of this patient's illness was protracted, as it was in 2 of the 4 in Braunwald's series who died of their disease (Braunwald *et al.*, 1964).

Speculation as to the Nature of the Disease. Histological examination of these hearts gives no clue as to the nature of the disease. All genetically determined diseases are basically "inborn errors of metabolism" (Carter, 1964). Future work should be directed more towards biochemical analysis and histochemical studies. The similarities in the clinico-pathological features in our material between those with or without family history of heart disease, may be due to the fact that in some cases there are both genetic predisposition and environmental triggers, operating as suggested in schizo-

FIG. 12.—Case 12. Note the asymmetrical left ventricular hypertrophy in (A) and hypertrophy of the myocardial fibres with interstitial fibrosis in (B).

phrenia, duodenal ulcer, and coronary thrombosis (Carter, 1964). Kobernick *et al.* (1963) studied the heart of a patient with idiopathic cardiomegaly and found evidence of succinic dehydrogenase deficiency in the myocardium. The suggestion has also been made that there may be overactivity of the sympathetic supply to the heart in hypertrophic obstructive cardiomyopathy (Braunwald *et al.*, 1964). In the group without evidence of obstruction, the possibility of deficiency of sympathetic activity comes to mind. Recent studies reveal abnormal circulating enzymes in primary disorders of skeletal muscle (Walton, 1964). Whorton, Hudgins, and Connors (1961) report abnormal spectrophotometric appearances of myoglobin in patients with muscular dystrophy and cardiac involvement. Auto-immune processes may be of importance in some, as is suggested in idiopathic pericarditis (Bridgen and Robinson, 1963). Infection may play a part in some instances. Bridgen (1957) reported 15 patients who had no history of familial heart disease, hypersensitivity, alcoholism, or puerperal disorder, and no amyloidosis at necropsy; 9 of these had a history of serious infection and 4 had suffered streptococcal fevers. He suggests that an acute myocarditis may later produce symptoms of chronic myocardial damage. Goodwin (1964) also considered an initial infection, which may be viral in nature, as a possible cause for many cases of congestive cardiomyopathy. Van Creveld (1960) has reviewed the subject of acute infantile myocarditis due to Coxsackie B 3/4 viruses, and has drawn attention to possible long-term sequelæ such as chronic myocarditis and cardiac failure, while Burch, Walsh, and Mogabgab (1961) have conducted a study during the Asian influenza epidemic and demonstrated myocardial involvement, and Pearce (1960) has shown that many viruses can infect the heart in animals and that this action depends on coexisting deprivation of oxygen to the heart rather than on the type of the virus. Virus infection may have been the causative agent in one of our cases (Case 6). It is obvious that the reactions of the myocardium to any injury must be limited and different ætiological factors may produce the same picture.

Treatment. Routine administration of digitalis compounds and the use of diuretics usually gave some relief when these patients first presented with heart failure. The idea of adding sympathomimetic agents under close supervision is worth trying. In view of the very bad prognosis of the condition, Burch and Walsh (1960) advocate prolonged bed-rest for patients with considerable cardiac enlargement.

SUMMARY

The findings on clinical examination and at necropsy in 12 patients who died of primary myocardial disease of obscure origin are presented. All developed congestive heart failure, and 10 died less than 2 years after the development of symptoms.

In 4 there was a family history of heart disease, and in 2 of these records are presented to show that the heart disease of other members was of similar type.

In one patient an infective origin is postulated, and another is considered to be an example of asymmetrical hypertrophy. The other 10 are of unknown ætiology. Those with a family history are compared with the others and no clear differences are found.

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Dr. O. C. Lloyd reviewed the pathological findings.

REFERENCES

- Bercu, B. A., Diettert, G. A., Danforth, W. H., Pund, E. E., Jr., Ahlvin, R. C., and Belliveau, R. R. (1958). Pseudoaortic stenosis produced by ventricular hypertrophy. *Amer. J. Med.*, **25**, 814.
- Braunwald, E., Lambrew, C. T., Rockoff, S. D., Ross, J., Jr., and Morrow, A. G. (1964). Idiopathic hypertrophic subaortic stenosis: 1. A description of the disease based upon an analysis of 64 patients. *Circulation*, **30**, Suppl. 4, pp. 104, 106, 110.
- Bridgen, W. (1957). Uncommon myocardial diseases. The non-coronary cardiomyopathies. *Lancet*, **2**, 1179, 1243.
- , and Robinson, J. (1963). Immunological studies in the post-cardiotomy syndrome. *Brit. Heart J.*, **25**, 692.
- Brock, R. (1957). Functional obstruction of the left ventricle. (Acquired aortic subvalvar stenosis.) *Guy's Hosp. Rep.*, **106**, 221.
- Burch, G. E., and Walsh, J. J. (1960). Cardiac enlargement due to myocardial degeneration of unknown cause. Preliminary report on effect of prolonged bed rest. *J. Amer. med. Ass.*, **172**, 207.
- , —, and Mogabgab, W. (1961). A study of the response of the cardiovascular system to Asian influenza. *Amer. Rev. resp. Dis.*, **83** (No. 2, Part 2. International conference on Asian influenza), p. 68.
- Carter, C. O. (1964). Genetics. In *Recent Advances in Medicine* (Beaumont and Dodds), 14th edn., ed. D. N. Baron, N. Compston, and A. M. Dawson, pp. 15, 16. Churchill, London.
- Correa, P., Restrepo, C., Garcia, C., and Quiroz, A. C. (1963). Pathology of heart diseases of undertermined etiology which occur in Cali, Colombia. *Amer. Heart J.*, **66**, 584.
- Dye, C. L., Rosenbaum, D., Lowe, J. C., Behnke, R. H., and Genovese, P. D. (1963). Primary myocardial disease. Part 1. Clinical features. *Ann. intern. Med.*, **58**, 426, 442.
- Fowler, N. O., Gueron, M., and Rowlands, D. T., Jr. (1961). Primary myocardial disease. *Circulation*, **23**, 498.

- Goodwin, J. F. (1964). Cardiac function in primary myocardial disorders. *Brit. med. j.*, 1, 1527, 1595.
- , Gordon, H., Hollman, A., and Bishop, M. B. (1961). Clinical aspects of cardiomyopathy. *Brit. med. j.*, 1, 69.
- , Hollman, A., Cleland, W. P., and Teare, D. (1960). Obstructive cardiomyopathy simulating aortic stenosis. *Brit. Heart j.*, 22, 403.
- Hollman, A., Goodwin, J. F., Teare, D., and Renwick, J. W. (1960). A family with obstructive cardiomyopathy (asymmetrical hypertrophy). *Brit. Heart j.*, 22, 449.
- Kariv, I., Sherf, L., and Solomon, M. (1964). Familial cardiomyopathy with special consideration of electrocardiographic and vectorcardiographic findings. *Amer. j. Cardiol.*, 13, 734.
- Kobernick, S. D., Mandell, G. H., Zirkin, R. M., and Hashimoto, Y. (1963). Succinic dehydrogenase deficiency in idiopathic cardiomegaly. *Amer. j. Path.*, 43, 661.
- Morrow, A. G., and Braunwald, E. (1959). Functional aortic stenosis. A malformation characterized by resistance to left ventricular outflow without anatomic obstruction. *Circulation*, 20, 181.
- Nirenberg, M. W. (1963). The genetic code. II. *Sci. Amer.*, 208, No. 3, p. 80.
- Pearce, J. M. (1960). Heart disease and filtrable viruses. *Circulation*, 21, 448.
- Teare, D. (1958). Asymmetrical hypertrophy of the heart in young adults. *Brit. Heart j.*, 20, 1.
- Van Creveld, S. (1960). Virus myocarditis in infancy.—Acute phase and possible late sequelae. In *Viral Infections of Infancy and Childhood*, ed. H. M. Rose, p. 33. Harper, New York.
- Walton, J. N. (1964). Muscular dystrophy: some recent advances in knowledge. *Brit. med. j.*, 1, 1271, 1344.
- Whitfield, A. G. W. (1961). Familial cardiomyopathy. *Quart. j. Med.*, 30, 119.
- Whorton, C. M., Hudgins, P. C., and Connors, J. J. (1961). Abnormal spectrophotometric absorption spectrums of myoglobin in two forms of progressive muscular dystrophy. *New Engl. j. Med.*, 265, 1242.

ADDENDUM

Since this paper was completed a boy of 19 years was admitted to hospital with advanced congestive heart failure. Full investigation by catheterization and angiography showed a dilated left ventricle with high diastolic pressure. In spite of intensive treatment he died within six months of his first symptom. Necropsy showed that death was due to unexplained cardiomyopathy. Four years previously his mother had died of heart failure with an enlarged heart, at the age of 42. Her electrocardiogram (Fig. 13A) showed non-specific changes. Fig. 13 compares her electrocardiogram (A) with that of her son (B) who was proved to have cardiomyopathy.

FIG. 13. Electrocardiograms of the mother (A) and son (B). See addendum.