

# A study of a family with inherited disease of cardiac and skeletal muscle

## Part I. Clinical, electrocardiographic, echocardiographic, haemodynamic, electrophysiological and electron microscopic studies

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### Summary

A family consisting of parents and their 6 sons were investigated to elucidate the relationship between a hypertrophic cardiomyopathy, musculoskeletal abnormalities and mental subnormality. The proband was diagnosed as having definite hypertrophic obstructive cardiomyopathy and the remaining family members were shown to have a spectrum of hypertrophic non-obstructive cardiomyopathy. Mild muscle weakness was present in 3 sons. All the subjects except for 1 son showed definite signs of electromyographic abnormality, whereas sensory and motor conduction velocities were normal. All the EEGs except for that of the proband were normal. Testicular hypoplasia was present in 3 sons. The inheritance pattern appears to be polygenic autosomal recessive in type. Definite evidence of linkage between hypertrophic cardiomyopathy and HLA awaits further data.

*S. Afr. med. J.*, 59, 363 (1981).

Structural abnormality of muscle mitochondria has been demonstrated in a large variety of neuromuscular diseases.<sup>1-5</sup> An association of cardiac and neurological disease as in progressive muscular dystrophy, myotonia dystrophica and Friedreich's ataxia is well known.<sup>6-9</sup> Involvement of the central nervous system was described previously.<sup>10-12</sup> Although most papers deal with case reports, familial cases have been increasingly reported.<sup>11,13,14</sup> Lactic acidemia associated with muscle mitochondrial disorders has been described in adults.<sup>12,15</sup>

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In the present report we describe the clinical, electrophysiological, histological, electron microscopic, histochemical and biochemical features in a family of 8 with a multisystem disease affecting the heart, skeletal muscle and central nervous system in varying degree. The associated skeletal myopathy in this family is interesting and there are those who feel that patients with hypertrophic obstructive cardiomyopathy (HOCM) probably always have involvement of skeletal muscle.<sup>16</sup> It is not yet clear whether these patients have a widespread myopathic disorder of which the cardiomyopathy forms only a part or whether the skeletal muscle involvement represents the result of faulty muscle fibre innervation.

### Patients and methods

The proband (patient 3) was referred to the Cardiac Clinic at Tygerberg Hospital on account of chest pain. Following extensive investigation it was decided to examine his 5 brothers as well as his parents. The investigation protocol was approved by the Ethics Committee of this hospital and all invasive procedures were undertaken following informed consent from each of the subjects.

EEGs were recorded on all patients. Electromyography was carried out on several muscles in the left upper and lower limbs; motor conduction velocities were determined in the median and lateral popliteal nerves and sensory action potentials were recorded from the median nerve. Holter monitoring was carried out on all patients apart from patient 8, and psychological testing on all 8 patients. A wide range of investigations on blood and urine were carried out, including serum lactate and pyruvate estimations and amino acid chromatography on 24-hour urine specimens. HLA tissue typing was performed.

Cardiac studies included echocardiography, cardiac catheterization and endomyocardial biopsy.

### Case 1

This patient was the proband's father and was 42 years of age. His development had been normal. After a motorcycle accident in which he had sustained head injuries he had been treated as an outpatient at a psychiatric institution. There was a history of excessive alcohol intake, and he had not worked since the accident. He was reputedly asymptomatic. On clinical examination he was slightly overweight. His IQ was 61. The neurological and musculoskeletal systems were normal, examination of the cardiovascular system was unremarkable, and he had a blood pressure of 130/90 mmHg. The respiratory system and the abdomen were also normal.

The chest radiograph showed a normal heart and lungs, and the ECG was within normal limits. Echocardiography demonstrated an interventricular septum to left ventricular posterior wall thickness (IVS/LVPW) ratio of 1,2. There was no asymmetrical septal hypertrophy (ASH) or anterior systolic

motion of the anterior leaflet of the mitral valve (SAM). The chamber dimensions were normal. Cardiac catheterization gave negative results.

Electromyography showed many short and polyphasic potentials. Light microscopy of heart muscle demonstrated cells in cross-section which appeared hypertrophied although there was quite marked variation in fibre size. Fibres cut longitudinally showed predominantly long runs with little evidence of any cellular branching. There was considerable interstitial fibrosis. Nuclei of myocytes were large with perinuclear haloes, but the nuclei were not crenated. Electron microscopy showed that most longitudinally cut myofibres were in normal parallel orientation, but in several small areas cells were more haphazardly arranged at angles to one another. In such areas there was evidence of end-to-end and occasional side-to-side intercellular junctions. Focal areas with myofilament disarray with some myofilaments coursing perpendicular to others were observed. Z bands were slightly widened. Other positive features included masses of densely packed small mitochondria with abundant lipofuscin pigment between them. Most mitochondria had densely compacted cristae with partial or complete loss of cristal structure. An occasional completely degenerate cell was noted as well as an increase in interstitial connective tissue.

### Case 2

The mother of the proband was 39 years old and was asymptomatic. On clinical examination she was rather overweight, short in stature, but strong in physique. Her IQ was 71. Examination of the neurological and musculoskeletal systems revealed nothing abnormal, but the cardiovascular system demonstrated some abnormal findings. Her radial pulse was regular but had a collapsing quality. All the remaining peripheral pulses were palpable. The jugular venous pressure was 2 cm and revealed the presence of prominent 'a' waves. The blood pressure was 150/90 mmHg. There was a short grade 2/6 ejection systolic murmur at the 4th left sternal space which radiated poorly to the mitral and pulmonary areas. This murmur increased significantly on squatting, but there was no alteration in quality after the Valsalva manoeuvre. The remainder of the clinical examination was negative. The ECG showed no abnormal features.

Electromyography showed an increased number of short and polyphasic potentials. Cardiac catheterization demonstrated some abnormal findings. The left ventricular end-diastolic pressure (LVEDP) was markedly elevated at 27 mmHg and the mean wedge pressure was also very raised at 24 mmHg ('a' wave 27 mmHg and 'v' wave 25 mmHg). The rest of the intracardiac pressures were within normal limits. There was no resting subaortic gradient, and this could not be evoked following a Valsalva manoeuvre or isoprenaline infusion. The cardiac indices were normal. Left ventricular cine angiography showed a normally contracting ventricle, but clear SAM was seen. These features were therefore suggestive of a hypertrophic non-obstructive cardiomyopathy (HCM). Light microscopy of heart muscle showed a near-normal appearance apart from an increase in the size of the cross-sectioned fibres. In the longitudinal cut long runs of fibres were seen with interstitial fibrosis. Some nuclei were enlarged with occasional haloes, but no crenated nuclei could be visualized. Electron microscopy demonstrated hypertrophy with normal orientation of cells and myofibrils. The only intercellular junctions seen were end-to-end. There was obvious mitochondriosis with masses of closely packed mitochondria of the small compact type. Abundant lipofuscin was present. Some of the Z bands appeared wider than normal.

### Case 3

This patient (the proband) was 18 years old and his main complaint was of a nonspecific stabbing precordial pain, as well as generalized muscle weakness in recent months. He had always realized that he was weak in both arms and legs, and he had a history of drop attacks, possibly epileptic seizures, for which he was treated medically. He attended special classes at school and obviously had a low IQ. On admission he was diagnosed as having Friedreich's ataxia and was referred to the Cardiac Clinic on account of his history of chest pain and a very abnormal ECG. On clinical examination the patient was rather small, his cranial vault being markedly smaller than his face. The testes were very small but hair distribution was masculine. Except for some dysarthria and a decreased palatal reflex his cranial nerves were intact. There was moderately severe proximal muscle weakness, especially with regard to the hip-girdle distribution. Muscle power in the trapezius, latissimus dorsi, deltoid, glutei, biceps brachii and intrinsic hand muscle was therefore graded as 4, and in quadriceps femoris and hamstrings as 3-4 (British Medical Research Council grading). The patient was unable to climb stairs without applying support to his lower limb with his hands. Muscle wasting and fasciculation were not evident, nor was there any pseudohypertrophy. The facial muscles were normal. Moderate inversion of the feet was present; his gait was uncoordinated for finer movements and was definitely waddling. Intelligence tests indicated an IQ of 46.

Examination of the cardiovascular system demonstrated striking findings. The pulse was regular but collapsing in nature. The jugular venous pressure was not elevated, but there were prominent 'a' waves, and the blood pressure was 120/60 mmHg. The apex was normally placed but had a double character. Auscultation revealed both 3rd and 4th heart sounds. A grade 2/6 ejection systolic murmur was maximally heard at the 4th left sternal border with slight radiation to the pulmonary and mitral areas. This murmur decreased dramatically on squatting and increased post-Valsalva manoeuvre. The remainder of the clinical examination was negative.

The ECG showed sinus rhythm of 80/min with a P-R interval of 0,12 second and a mean QRS axis of plus 75°. Right atrial hypertrophy was seen. There were prominent Q waves in the inferior and anterolateral leads. Asymmetrical T-wave inversion was seen in the inferior leads and an incomplete right bundle-branch block was in evidence (Fig. 1). The chest radiograph demonstrated a normal cardiac shadow and lung fields. Echocardiography showed ASH with a IVS/LVPW ratio of 1,6. There was no evidence of SAM, and pump function and contractility indices were normal. These features were in keeping with the diagnosis of hypertrophic cardiomyopathy (Fig. 2).

Electromyography showed numerous short and polyphasic potentials. Skull and spine radiographs, and sensory and motor conduction velocities were normal. The EEG was slightly abnormal with no specific features. Urinary amino acid levels were normal. Serum creatine phosphokinase, and basal blood lactic acid and pyruvate levels were also normal. Cardiac catheterization showed normal resting pressures in all the chambers, but after isoprenaline infusion there was a clear subaortic gradient of 44 mmHg. The Valsalva manoeuvre failed to elicit a gradient. Angiography did not demonstrate any SAM. This investigation therefore confirmed the presence of hypertrophic obstructive cardiomyopathy (HOCM).

Light microscopy of heart muscle revealed short runs in the longitudinally cut cells with distinct whorling in places. The cells varied in shape from being polygonal to branched. The runs of fibres were frequently interrupted by fibrous tissue, and some apparently normal fibres were seen between the hypertrophied ones. Cell nuclei were enlarged and crenated with perinuclear haloes. Electron microscopy showed that although cell orientation was apparently predominantly normal in the longitudinally cut fibres, there was some side-to-side and

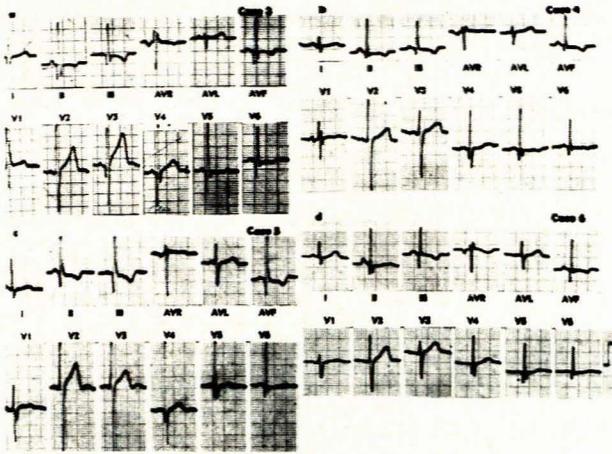


Fig. 1. ECGs featuring prominent inferolateral Q waves, left and right atrial enlargement and left ventricular hypertrophy.

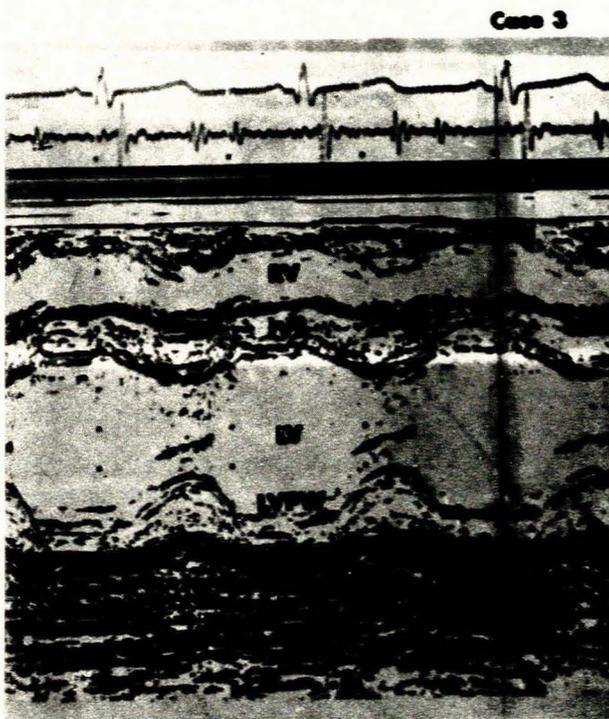


Fig. 2. Echocardiogram showing ASH (IVS/LVPW ratio of 1.6). There is no evidence of SAM.

abundant end-to-end anastomosis. The degree of myofibrillar disorientation was not as marked as one would have expected from the semi-thin sections. Cell nuclei were, however, bizarre and crenated and had pools of glycogen around them. Mitochondria were present in giant groups with their cristae dense and compact. There was some widening of Z bands, fairly abundant lipid droplets, little lipofuscin, dilated T tubules and abundant Golgi apparatus.

#### Case 4

This patient was 21 years of age and initially denied that he had any symptoms. However, on interrogation he admitted having had some difficulty in climbing stairs for some years. He also admitted to about 1 year's progressive dyspnoea on effort. At times he experienced burning precordial pain, radiating into the right hypochondrium and back, brought on by moderate exertion and relieved after some 10 minutes of rest; he had never

participated in school sport on account of muscle weakness. He had been unable to complete secondary school and was employed as a greaser. His IQ was 92. On clinical examination the upper half of his body appeared to be less developed than the lower half. His extremities also tended to be short. The relevant feature on neurological examination was slight dysarthria. The ankle reflexes were somewhat depressed and his gait was strikingly waddling. Sensation was entirely normal. The musculoskeletal system demonstrated significant hip-girdle weakness, and he used the Gower manoeuvre in order to rise from the sitting position. Muscle power in the deltoids, quadriceps femoris, glutei, anterior tibialis and peroneals was graded as 4 and in the hamstrings as 3. There was no atrophy.

Examination of the cardiovascular system revealed a regular, collapsing-type radial pulse, all peripheral pulses being easily palpable. The jugular venous pressure was not abnormally elevated but there was an easily discernible 'a' wave present. The blood pressure was 160/70 mmHg. The apex beat was not displaced but had a double quality to it. On auscultation the 1st and 2nd heart sounds were normal, but there was a prominent 3rd heart sound at the apex. A grade 2/6 ejection systolic murmur was audible at the fourth left sternal space and radiated to the mitral area and the base of the heart. This murmur softened markedly on squatting and increased in intensity following the Valsalva manoeuvre. The remainder of the clinical examination proved negative.

The chest radiograph revealed a rather prominent main pulmonary artery. The ECG (Fig. 1) demonstrated sinus rhythm of 80/min with a P-R interval of 0.12 second and a mean QRS axis of 90°. Bi-atrial hypertrophy was in evidence. There were striking Q waves and asymmetrical T-wave inversion in the inferolateral leads. Left ventricular hypertrophy by voltage criteria was also evident. Incomplete right bundle-branch block was present. Echocardiography (Fig. 3) demonstrated a IVS/LVPW ratio of 1.32, both the IVS and LVPW being grossly hypertrophied. There was no obvious SAM. The aortic valve showed some systolic flutter with early systolic closure. Pump function and contractility indices were normal. The features were compatible with hypertrophic cardiomyopathy.

Electromyography showed several short and polyphasic potentials. Cardiac catheterization showed features of hypertrophic cardiomyopathy without a resting subaortic gradient. A gradient could also not be provoked with

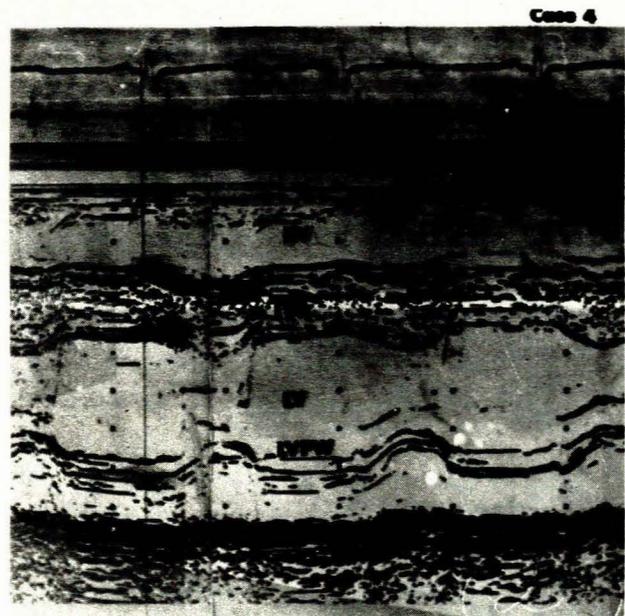


Fig. 3. Echocardiogram showing ASH (IVS/LVPW ratio of 1.32) with gross hypertrophy of the IVS and LVPW.

isoprenaline infusion or post-Valsalva manoeuvre. There was mild pulmonary hypertension. Left ventricular cine angiography showed a hypercontractile ventricle with a reduced end-diastolic volume, but no SAM.

Light microscopy of the heart muscle was virtually identical to that in patient 3. Electron microscopy showed that although the myofibrillar orientation was predominantly normal there was some degree of myofibrillar and myofilamentous disarray. Numerous end-to-end and side-to-side intercellular junctions were evident. The cell nuclei were very large and truly bizarre. Masses of compacted mitochondria were conspicuous. There was some dilatation of T tubules as well as numerous lipid droplets. An increase in interstitial connective tissue was noted. Abundant glycogen but very little lipofuscin was present.

### Case 5

This patient was 19 years of age and was asymptomatic. He had attended special classes at school and had never engaged in any sporting activity, and was employed in kitchen work at a hotel. On clinical examination a striking feature was the relatively small cranium compared with the face. His mouth was also rather broad. The limbs, especially the fingers and toes, were short. His speech was not well articulated and his gait somewhat unco-ordinated. The patient's testes were small, being approximately the size of beans, but body hair was normal and masculine in character. His IQ was 66.

Examination of the cardiovascular system revealed prominent 'a' waves in the jugular venous pressure curve. The blood pressure was 115/60 mmHg. Heart sounds were normal, but a prominent 4th heart sound was heard, and a grade 2/6 ejection systolic murmur was present at the 4th left sternal space which radiated poorly to the axilla. This murmur became softer on squatting and louder following the Valsalva manoeuvre.

The ECG was grossly abnormal (Fig. 1). There was sinus rhythm at 76/min, with a P-R interval of 0,12 second and a mean QRS axis of plus 70°. Deep Q waves were seen in the inferolateral leads and the T waves were asymmetrically inverted in these leads. Left ventricular hypertrophy by voltage criteria was also in evidence.

Electromyography showed very short, high-amplitude muscle potentials, as well as the presence of increased numbers of polyphasic potentials. There was no evidence of any denervation and the contraction pattern could be interpreted as being an 'interference pattern'. The 'myopathic' features were far more prominent in the shoulder girdle than the hip-girdle muscles.

Cardiac catheterization revealed normal intracardiac pressures apart from a marginally elevated LVEDP of 14 mmHg. Left ventricular cine angiography and aortography demonstrated no abnormality. Light microscopy of heart muscle showed changes practically identical to those in patients 3 and 4, with fairly marked increase in interstitial connective tissue. The nuclei were large and pleomorphic with short runs of fibres in obvious disarray. Electron microscopy showed features similar to those described in 3 and 4 but the degree of myofibrillar disarray was more marked with myofibrils arranged in a criss-cross pattern.

### Case 6

This 17-year-old patient was asymptomatic but was investigated on account of the family history. He had had to attend special classes at school and was disinterested in any form of sporting activity. His IQ was 58. On clinical examination there was an obvious discrepancy between the smaller cranial and larger facial parts of his head. Apart from a first-degree horizontal nystagmus to the right and left the cranial nerves showed no abnormalities. The tendon reflexes, sensation and co-

ordination were within normal limits but his gait was somewhat clumsy. Only the trapezius muscles were somewhat reduced in volume and power. He had bean-sized testes but normal hair distribution and other secondary male characteristics.

There was a grade 2/6 ejection systolic murmur heard at the 4th left interspace which radiated to the apex and base of the heart. This murmur softened slightly on squatting but did not change in intensity post-Valsalva manoeuvre. The ECG showed sinus rhythm at 84/min with a P-R interval of 0,15 second and a mean QRS axis of plus 67°. The right atrium was hypertrophied. Very striking Q waves were seen in the inferolateral leads and left ventricular hypertrophy by voltage was present.

Electromyography indicated the presence of many muscle potentials of short duration. Many more polyphasic potentials than normal, with low amplitude, were also seen. There was no denervation or fasciculation. The features were thus in keeping with a mild proximal 'myopathy' affecting both the upper and lower limbs. Cardiac catheterization showed an elevated LVEDP of 17 mmHg. Left ventricular cine angiography and aortography were negative. Light microscopy of heart muscle showed that most of the myofibres in cross section were round to oval. In sections cut lengthwise the orientation was mostly normal but most muscle cells were short and squat with myofibrillar disarray. Nuclei were round or somewhat crenated with occasional haloes. Abundant interstitial connective tissue was present. Electron microscopy demonstrated a definite slight degree of myofibrillar disarray. The myofilaments were disorganized and in the same cells myofilaments could be observed running at right angles to others. There was obvious mitochondriosis with small, dense, compacted organelles. Only end-to-end intercellular junctions were present and there was slight spreading of Z-band material. A minor degree of lipofuscin was also present.

### Case 7

This patient was 15 years old and completely asymptomatic. He took part normally in school sports and apparently had no difficulty with his academic work. On clinical examination his physique was normal; and all muscles were well developed and of normal strength. Full neurological investigation showed nothing abnormal. The IQ was 84. Cardiovascular examination was negative apart from a grade 1/6 short systolic murmur at the base which did not radiate and was not altered by squatting or Valsalva manoeuvre.

The ECG showed normal sinus rhythm at 76/min with a P-R interval of 0,11 second and a mean QRS axis of plus 63°. Echocardiography revealed a IVS/LVPW thickness ratio of 1,00 with no evidence of ASH or SAM. All the chamber dimensions were within normal limits.

Electromyography showed increased numbers of short-duration potentials in the proximal arm and thigh muscles, with normal nerve conduction times. Fasting serum lactate levels were normal, but the pyruvate level was subnormal. Cardiac catheterization demonstrated normal intracardiac pressures and indices. Light microscopy of heart muscle showed subtle abnormalities. Myofibres were round to oval and moderately hypertrophied. Longitudinally the runs were longer with occasional short runs and very little interstitial connective tissue. There was some nuclear enlargement but the nuclei were not crenated. These cells were shorter and more square than the rest. On electron microscopy fibre orientation was found to be predominantly normal, but some myofibres coursed at right angles to others. Some of the Z bands appeared wider than normal. Mitochondriosis was obvious and there were numerous lipid droplets. The mitochondria appeared distinctly abnormal with exaggerated cristae and focal cristolysis.

## Case 8

This patient was 20 years old. He denied any symptoms and had just completed his 2-year period of military service. His IQ was 83. The cardiovascular system appeared normal, as did the respiratory, gastro-intestinal, musculoskeletal and neurological systems. The chest radiograph, ECG, echocardiogram and electromyograms were within normal limits. Cardiac catheterization was negative.

Light microscopy of heart muscle demonstrated some slight hypertrophy, but otherwise the myocardium appeared normal. Electron microscopy showed that there was no myofibrillar disorganization. Occasional nuclei were enlarged and crenated and in some areas groups of mitochondria were small and compact. Apart from these changes the heart muscle was unremarkable. Tiny droplets of lipids and slight lipofuscinosis were to be seen.

## Results

### Neurological investigations

The parents and their 6 sons were all of short stature (Fig. 4); in some of them (patients 5 and 6) there was a discrepancy between the relatively small cranial vault and larger face with a broad mouth. Mental retardation was obvious and verified by psychological testing. All the children failed to achieve elementary school requirements and were socially unsuccessful (except for patient 8, who had an IQ of 83). Reflexes and sensation were intact in all the patients, but co-ordination was slightly affected in patients 3, 4, 5 and 6, including some dysarthria.

On funduscopy nothing abnormal could be demonstrated and the hearing tests were negative. A horizontal nystagmus was

present in patient 6, but cranial nerve investigation was otherwise negative. In patients 3 and 4 upper and lower extremities were equally affected as regards loss of power in proximal and distal muscles, but atrophy was not a feature. Patient 6 showed some loss of power and atrophy in the trapezius muscles only. The peripheral nerves were normal on palpation in all cases.

### Electrophysiological investigations

All patients except No. 3 had a normal EEG. The EEG in patient 3 showed diffuse high-frequency theta activity, and he had experienced some episodes of unexplained loss of consciousness.

Electromyography revealed in all cases (except patient 8) numerous short and polyphasic potentials in both proximal and distal muscles, their amplitudes not usually exceeding  $400 \mu V$  (Fig. 5 and 6). (Compare with a normal 22-year-old control subject (Fig. 7).)

In patients 5 and 6 polyphasic potentials with a relatively high amplitude were recorded. Fibrillation potentials, positive denervation potentials or fasciculations were not observed. With the exception of patient 3 all subjects showed a full interference pattern on maximum voluntary effort.

Motor conduction velocities and distal latencies were within normal limits for all patients. Sensory conduction velocities of the median nerves measured from stimulus to initial deflection were also normal; the range of their peak-to-peak amplitudes was between  $18,5$  and  $39 \mu V$ , which was within the limits of our normal controls.

During rapid repetitive stimulation of the abductor digiti quinti muscles no abnormal tapering was seen. This test was done because most subjects said that they were easily fatigued on

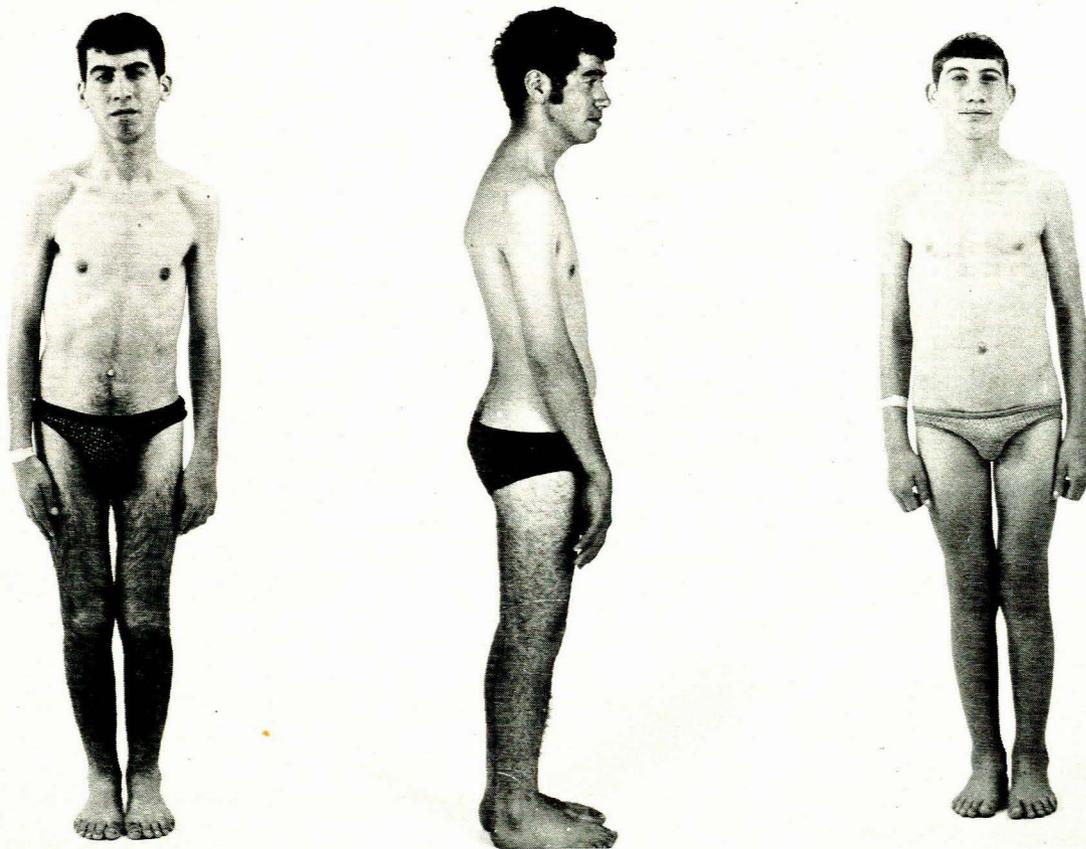


Fig. 4. General body build of 3 of the 6 sons, showing quite short extremities, as well as discrepancy between cranial vault and lower face in the subject on the right.

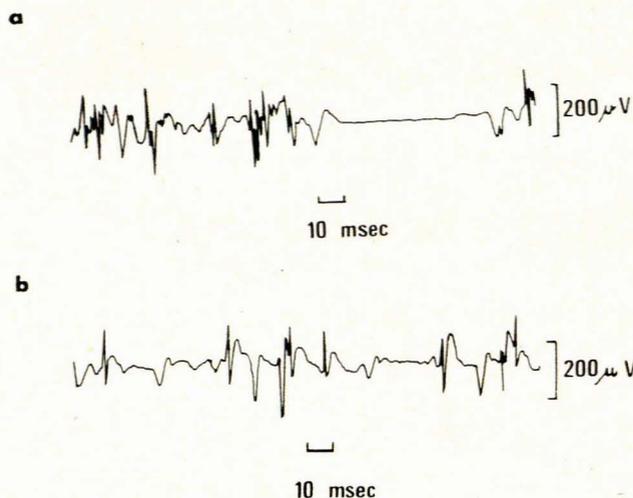


Fig. 5 (a and b). Deltoid muscle (patient 3) showing many short potentials usually not exceeding 200  $\mu$ V. Reference to (a) shows conspicuous polyphasic potentials of low amplitude.

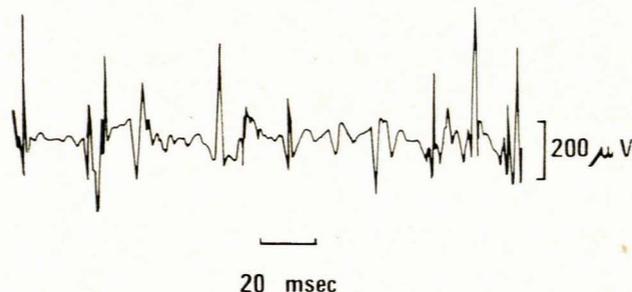


Fig. 6. Deltoid muscle (patient 6) demonstrating short potentials with amplitudes not exceeding 500  $\mu$ V.

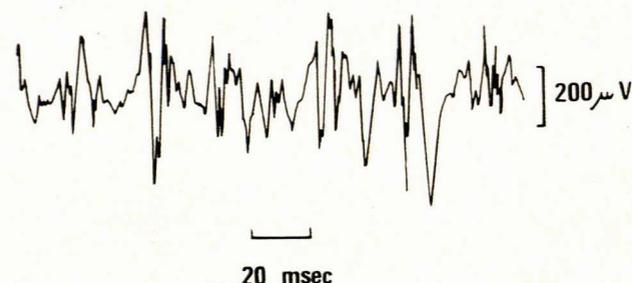


Fig. 7. Deltoid muscle of normal subject (22 years of age). Note the difference in amplitude and duration of the potentials when compared to Figs 5 and 6.

exertion, which made lactate and pyruvate testing under such conditions difficult.

### Holter monitoring

This investigation failed to reveal any bradyarrhythmia or tachyarrhythmia in any of the 7 out of 8 patients studied. There was no evidence of supraventricular or ventricular extrasystoles or arrhythmias, and conduction appeared to be entirely normal.

### Psychological testing

The family's IQs ranged between 46 and 92, well below the normal limits. Whether this is part of the clinical condition or the results of socio-economic and inherited factors is not entirely clear.

### Serum lactate and pyruvate estimations

No fasting lactic acidemia was present in any of the cases. Serum lactate and pyruvate levels were slightly elevated in patients 2, 6 and 7, and the lactate/pyruvate ratio was increased in patients 2, 4, 6 and 7. An ischaemic lactate test was attempted in patients 3 and 4, but the amount of work was slight due to muscle weakness and lack of co-operation. Only a slight increase in plasma lactate values occurred and the lactate/pyruvate ratio rose minimally, viz. less than twice the resting value.

### HLA tissue typing

All patients inherited the paternal A2, B27, Cw2 haplotype and the maternal A11, B18,— haplotype, except for patient 7, who inherited the paternal A2, Bw16,— haplotype (Table I).

TABLE I. RESULTS OF HLA TISSUE TYPING

Case	Haplotypes				
1 Father	A2, B27,	Cw2/A2,	Bw16,	Cw—	
2 Mother	A1, B8,	Cw—/A11,	B18,	Cw—	
3 Proband	A2, B27,	Cw2/A11,	B18,	Cw—	
4 Son	A2, B27,	Cw2/A11,	B18,	Cw—	
5 Son	A2, B27,	Cw2/A11,	B18,	Cw—	
6 Son	A2, B27,	Cw2/A11,	B18,	Cw—	
7 Son	A2, Bw16,	Cw—/A11,	B18,	Cw—	
8 Son	A2, B27,	Cw2/A11,	B18,	Cw—	

No evidence of skeletal myopathy or HCM was found in the 16 maternal relatives, but 3 relatives had the maternal A11, B18,— haplotype. The 2-year-old son of one of these relatives died of a condition diagnosed as 'congestive cardiomyopathy'. Some features which could be consistent with HCM were seen in the father (patient 1) as well as in all the children except patient 8; although conclusive evidence of HCM was not present in the mother (patient 2) or in patient 8, myocardial biopsy showed some features of hypertrophy.

### Electrocardiography

Five out of the 8 patients had an abnormal ECG (patients 1, 7 and 8 had normal tracings). The predominant abnormalities were pathological Q waves (especially in the inferior and lateral leads), left ventricular hypertrophy by voltage criteria, and left atrial abnormality. Patients 3, 4 and 6 also demonstrated right atrial hypertrophy. An incomplete right bundle-branch block pattern and repolarization abnormalities in the anteroseptal leads were also found. The proband (patient 3), who was diagnosed as having HOCM, showed a combination of all these abnormal features. One of the 2 symptomatic, non-obstructive HCM patients (patient 4) has a combination of these abnormal ECG findings except that there was no evidence of repolarization changes. It was also interesting to see that 1 of the 2 asymptomatic patients with HCM (patient 6) displayed abnormal ECG features almost identical to those in patient 4, who was symptomatic. The 2 patients (No. 2 and 5) with possible HCM were both asymptomatic and showed very abnormal ECG characteristics.

### Echocardiography

On echocardiography none of the patients exhibited paradoxical septal motion or SAM. ASH was seen in only 2 of the 8 patients, patient 3 (the proband) with symptomatic HOCM and patient 4 with symptomatic non-obstructive HCM. Contractility and pump function indices were normal in all patients. Only 2 of the 5 patients with an abnormal ECG therefore had an abnormal echocardiogram.

## Haemodynamic findings and cine angiography

Table II summarizes the cardiac catheterization features. Four patients had abnormal intracardiac pressures, two of the most salient abnormalities being a raised mean pulmonary capillary wedge (PCW) pressure and an elevated LVEDP. Both of these abnormalities occurred in the same patients. One of the patients (No. 4) had mild pulmonary hypertension; none had a resting subaortic gradient. Apart from the proband, in whom isoprenaline infusion induced a 44 mmHg gradient, no subaortic gradient could be elicited by the Valsalva manoeuvre or isoprenaline infusion. The cardiac output ranged from 6.3 to 8.5 l/min and there was no increase in  $dp/dt_{max}$ .

Left ventricular cine angiography demonstrated SAM in the mother (patient 2) and a hypercontractile ventricle in patient 4, although SAM could not be verified by echocardiography in the former.

## Relationship between ECG, echocardiographic and haemodynamic findings

There appeared to be a very poor correlation between the electrocardiographic and echocardiographic features, apart from patients 3 and 4 who showed ASH and multiple abnormalities on ECG. Left ventricular hypertrophy on ECG was also not verified by an increase in the absolute left ventricular wall thickness echocardiographically. In addition, the pathological Q waves sometimes suggesting prominent septal forces on ECG did not accurately correlate with increased septal thickness or IVS/LVPW ratio.

In contradistinction, the relationship between the ECG and haemodynamic findings was reasonably close. Thus, patients 2, 4 and 6 demonstrated elevated LVEDP (patients 2 and 4 in addition had increased PCW pressures) as well as left ventricular hypertrophy, left atrial enlargement and pathological inferolateral Q waves. However, it was somewhat surprising that the proband (patient 3), in spite of having a grossly abnormal ECG, displayed very little haemodynamic abnormality apart from a subaortic gradient provoked by isoprenaline infusion.

## Endomyocardial biopsies

All subjects in this series had myocardial hypertrophy as indicated by nuclear enlargement and the fact that the maximal transverse diameters of cells (Table III) ranged from 22 to 55  $\mu\text{m}$  (normal 10 - 15  $\mu\text{m}$ ). On light microscopy one could see short runs of myofibres with some degree of whorling in patients 3, 4 and 5. The same patients showed areas where the normal orientation of myocardial cells was lost. End-to-end junctions, as well as an increase in the number of side-to-side junctions were noted in 4 cases. Obvious myofibrillar disarray was found in patients 3, 4 and 5 (Figs 8 and 9). In patients 1, 6 and 7, although the myocardial cells were predominantly normal in their longitudinal orientation, a careful search revealed slight and focal myofibrillar disarray (Fig. 10). All patients with myofibrillar disarray showed disorganization of myofilaments ranging from gross myofibrillar disarray (Fig. 11) to much more subtle and focal changes. Patients 2 and 8 showed no myofibrillar or myofibrillar disorganization. All patients, except No. 8, showed some degree of widening of Z bands, most conspicuous in No. 5. Nuclear haloes were seen in all cases. All subjects had some degree of mitochondriosis and as a rule the mitochondria were of the small compact type with closely packed cristae.

Additional findings included some degree of lipid accumulation in patients 1, 3, 4, 7 and 8, and apparent increase in interstitial connective tissue in all but No. 8.

In summary, it would appear that sufficient collective criteria were present in patients 3, 4 and 5 to suggest a diagnosis of ASH.

TABLE II. RESULTS OF HAEMODYNAMIC STUDIES

Case	RA	RV	PA	Ao	LV	$dp/dt_{max}$ (mm/s)	CO (l/min)	CI (l/min/m <sup>2</sup> )	SVR (U)	PVR (U)	SV (ml)	PCW A = 8 V = 7(6) A = 27 V = 25(24) A = 12 V = 13(10) A = 23 V = 23(22) A = 9 V = 11(8) A = 17 V = 17(12) A = 11 V = 12(8) A = 11 V = 13(9)
1	(2)	18/0-5	18/8(12)	129/90 (109)	129/6-9	2 146	7.7	3.4	13.9	0.8	76	
2	(7)	31/3-9	31/19(25)	139/87 (111)	139/12-27	2 068	6.8	3.3	15.3	0.1	73	
3	(1)	16/0-3	16/7(13)	109/76 (89)	109/2-5	1 982	6.3	4.4	13.9	0.5	56	
4	(2)	40/0-8	40/15(28)	125/82 (103)	125/0-23	1 475	6.7	4.1	15.0	1.2	76	
5	(1)	20/0-3	20/7(12)	108/77 (94)	108/0-14	2 562	8.5	5.6	10.9	0.5	94	
6	(2)	23/0-4	23/8(14)	100/67 (85)	100/1-17	1 862	6.9	4.6	12.4	0.3	99	
7	(3)	14/1-5	14/9(11)	90/73 (79)	90/0-12	1 987	8.0	5.7	9.5	0.4	96	
8	(1)	22/0-3	22/10(14)	101/77 (90)	101/2-12	1 857	7.0	3.9	12.9	0.7	63	

RA = right atrium; RV = right ventricle; Ao = Aorta; LV = left ventricle; CO = cardiac output; CI = cardiac index; SVR = systemic vascular resistance; PVR = pulmonary vascular resistance; SV = stroke volume; PCW = pulmonary capillary wedge. All pressures in mmHg. Mean pressure in brackets.

TABLE III. CARDIAC MUSCLE HISTOLOGY

Case	Max. transverse diameter (µm)	Runs	Cellular orientation	Junctions	Myofibrillar & myofilamentous disarray	Z-band widening	Nuclei	Haloed	Mitochondriosis	Lipid	Interstitial fibrosis
1	35	Long	Normal	e/e	Slight	Slight	Large	Present	+++	+	+++
2	32	Long	Normal	s/s	Absent	Slight	Large	Occas.	+++	-	++
3	54	Short whorling	Variable	e/e	Moderate	Slight	Bizarre, crenated	Prominent	+++	+++	++
4	55	Short whorls	Variable	s/s	Moderate	Slight	Bizarre, crenated	Present	+++	+++	++
5	38	Short runs	Variable	e/e	Moderate	Definite	Large, pleomorph.	Prominent	+++	-	+++
6	56	Long	Normal	s/s	Slight	Slight	Large, occas. crenated	Occas.	+++	-	+++
7	30	Long	Normal	e/e	Slight	Slight	Enlarged	Occas.	+++	+++	+
8	22	Long	Normal	e/e	Absent	Normal	Enlarged	Occas.	++	+	-



Fig. 8. Near-normal heart muscle (patient 8) with myofibrils in normal parallel orientation surrounding stacks of mitochondria (x 6225).



Fig. 9. Moderate myofibrillar disarray (patients 3, 4, 5) with myofibrils running at angles to one another. Note focal widening of Z bands and mitochondriosis (x 6225).

In patients 1, 6 and 7 some of the ultrastructural changes seen in ASH were present in a mild form. Patients 2 and 8 revealed only mild signs of myocardial hypertrophy.

### Discussion

#### Echocardiographic features

An attempt at finding the inheritance pattern in this family could be made because there were 6 male offspring. Brent *et al.*<sup>17</sup> were the first to propose inheritance of hypertrophic

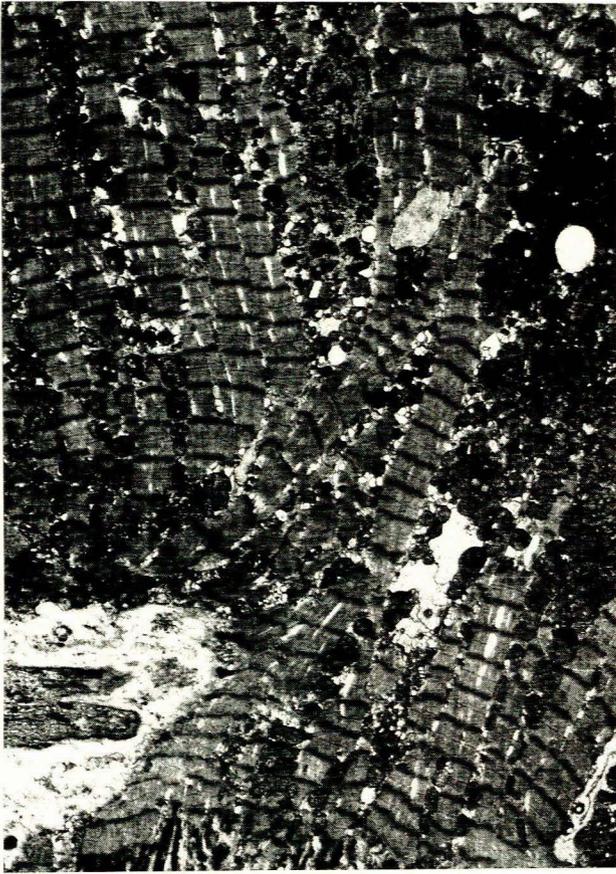


Fig. 10. Less obvious myofibrillar disarray as seen in patients 1, 6 and 7. Marked mitochondriosis (x 6 225).

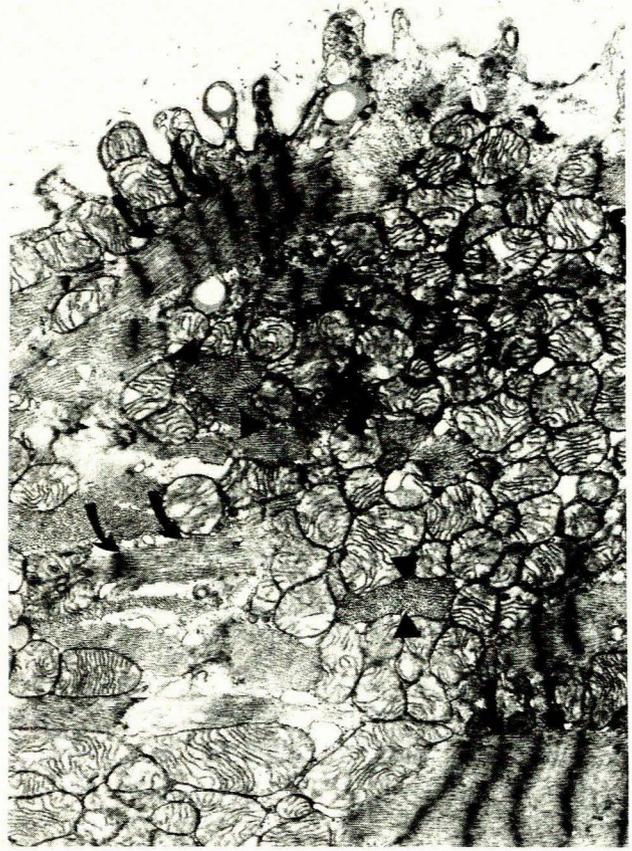


Fig 11. Myofilamentous disorganization. Some myofilaments cut longitudinally (arrows) and others coursing at right angles to them (arrowheads) (x 15 000).

cardiomyopathy (HCM) as an autosomal dominant one. This claim was later supported by work showing a 25% familial incidence in a large series.<sup>18</sup> In fact, Clark *et al.*<sup>19</sup> were of the opinion that most, if not all, cases were familial when he used echocardiographic ASH as the genetic marker. This was subsequently shown to be the case by Ten Cate *et al.*<sup>20</sup> who also demonstrated the presence of a decreased systolic septal thickening of less than 25% and in some cases an abnormal left ventricular shape on cross-sectional echocardiography.

However, ASH cannot be considered pathognomonic for HCM since it can also be seen in severe pulmonary stenosis, primary pulmonary hypertension (right ventricular hypertrophy out of proportion to left ventricular hypertrophy), coronary artery disease and posterior wall myocardial infarction. In this family only 2 patients had ASH, despite most of the other family members having some features of HCM.

In an attempt to establish whether ASH was familial 20 maternal sibs and their descendants had full clinical examination, chest radiographs, ECGs and echocardiograms; all results were negative. Unfortunately, at the time of writing this article the paternal sibship had not yet been examined. It is possible that there is polygenic autosomal recessive inheritance.

### Electrocardiographic features

It is widely accepted that the ECG is rarely normal in HCM, especially if the subjects have symptoms or have left ventricular outflow obstruction. In one series<sup>21</sup> 73% of asymptomatic patients without outflow obstruction had ECG abnormalities, and 93% of those with or without either symptoms or outflow obstruction. Some workers<sup>22</sup> have suggested that the classic abnormality is a combination of left ventricular hypertrophy and right atrial enlargement. Left axis deviation, repolarization

abnormalities and left atrial abnormality have also been documented. Furthermore, no ECG features pathognomonic of either obstructed or non-obstructed HCM have been reported. However, it has been stated that the frequency of abnormal ECGs in children with HCM may increase as they approach adulthood.

The pattern of pseudo-transmural myocardial infarction is known to occur in HCM. Goldberger<sup>23</sup> claims to be able to differentiate the two conditions electrocardiographically. He states that there is a unique 'Q wave-T wave vector discordance' in HCM, the T wave being positive with ST-segment elevation in those leads with significant Q waves, and attributes this feature to a pattern of septal hypertrophy and strain. This feature he regards as the exact opposite of infarction, as well as the classic picture of left ventricular hypertrophy and strain, that is, large amplitude R waves with inverted T waves and ST-segment depression. The ECG features in our patients clearly disprove this assertion, and more strongly underline the lack of agreement in the concept of a 'classic' ECG pattern in HCM, whether obstructive or non-obstructive. More recently Chen *et al.*<sup>24</sup> emphasized the changes seen in the mid-precordial leads and standard lead II in non-obstructive HCM. In 66% of the 33 patients there were the tallest R waves with T-wave inversion in leads V3 and V4, as well as tall R waves in lead II in the presence of a normal QRS axis. They also noted the lack of Q waves in leads I, V5 and V6 ('incomplete left bundle-branch block'), accepted as a feature of systolic overload caused by systemic hypertension or aortic valvar stenosis. Many mechanisms have been postulated for this pattern, one being the replacement of conduction tissue by septal fibrosis.

There are features in keeping with left ventricular hypertrophy in our patients (Fig. 1) but the most striking changes are the prominent inferolateral Q waves, as well as the

ST-T wave abnormalities which suggest a pseudo-infarction.

Right atrial hypertrophy is clearly visualized in patients 3, 4 and 6; patient 4 shows additional left atrial enlargement. Mid-precordial abnormalities were not seen, but the early ventricular repolarization in the anteroseptal leads is obvious. In summary, therefore, the ECG changes did not indicate whether the HCM was obstructive or non-obstructive.

### Relationship between ECG, echocardiographic and haemodynamic findings

Most studies have shown a fairly close correlation between ECG, echocardiographic and haemodynamic measurements in HCM. Our findings differ from those reported by Joye *et al.*<sup>25</sup> and Savage *et al.*<sup>21</sup> who found that normal ECGs were associated with less septal thickening. However, our results are similar to theirs in that our patients with ECG signs of left ventricular hypertrophy had no increased incidence of left ventricular outflow obstruction. We also did not show that left ventricular hypertrophy on ECG was associated with increased left ventricular free wall thickness, a finding which agrees with the study of Savage *et al.*<sup>21</sup> but differs from that of Joye *et al.*<sup>25</sup>

In summary, therefore, our study demonstrates a close correlation between left ventricular hypertrophy on ECG and haemodynamic increased LVEDP pressure and PCW pressure. Also, we failed to show a significant correlation between ECG and echocardiographic features, suggesting that in our subgroup of patients haemodynamic findings were of more use diagnostically than echocardiography. Presumably with follow-up of this series of patients the correlation between ECG and echocardiographic features will become more close.

### HLA tissue typing in hypertrophic cardiomyopathy

In Darsee *et al.*'s study<sup>26</sup> familial HCM was linked to the HLA haplotype containing the B12 or B5 antigen complex. In Matsumori *et al.*'s study<sup>27</sup> HCM was linked to a HLA haplotype A9, B7. To the best of the authors' present knowledge there are no other published data in this field.

Insufficient data are at present available to link HCM in our cases to any specific HLA haplotype or antigen. If linkage is present, it could be either the paternal A2, B27, Cw2 haplotype or the maternal A11, B18, — haplotype, or both. This would confirm that HCM is linked to HLA, but as is evident in the two previous studies the specific antigen or haplotype differs from population to population.

Studies on paternal and further maternal relatives will have to be undertaken before HLA linkage can be clarified in our patients. Additional HLA - D locus typing might yield more conclusive evidence.

### Endomyocardial biopsy features

It is well accepted that the characteristic histological abnormality in hypertrophic cardiomyopathy is disordered architecture of the myocardium. Previous studies<sup>28-32</sup> have consistently demonstrated abnormal cellular morphology in the interventricular septum in patients with ASH. Important questions, however, have to be answered regarding the nature and distribution of the myocardial hypertrophy and myocardial fibre disarray in patients with ASH.<sup>33,34</sup> Is there, for example, myocardial fibre disarray in the left and right ventricular free walls? If there is, is it present only in patients without obstruction to left ventricular outflow or is it also present in patients with obstruction? Maron *et al.*<sup>34</sup> studied myocardium obtained surgically or at autopsy from 22 patients with ASH. Of these 14 had obstruction while 8 were cases of non-obstructive

ASH. Many hypertrophied, bizarrely shaped and abnormally arranged cardiac muscle cells, presumably a morphological manifestation of the genetically transmitted defect, were present in the septum of all patients. In patients with obstructive ASH these abnormalities were either absent or rarely found in muscle from the left and right ventricular free walls. In contrast, numerous disorganized cells were extensively distributed in the left and right ventricular free walls in 7 out of 8 cases (symptomatic) with non-obstructive ASH.

In our material some degree of myofibrillar disarray and myofilamentous disorganization was found in a father and 5 of his 6 sons in the right ventricular free wall specimens. The mother (patient 2) was entirely normal, as was 1 son (patient 8). There appeared to be a spectrum of myocardial changes in the father and his affected sons. Very definite changes were present in the specimens of patients 3 and 4, both of whom also had clinical indications of ASH. Patients 5, 6 and 7 were clinically normal but had histological and ultrastructural signs indicative of myofibrillar and myofilamentous disarray, albeit of a relatively minor degree.

In summary, it can be said that the changes ranged from minimal in the clinically normal subjects to quite outspoken in the 2 with clinical ASH. The mildness of the changes can probably be related to the mildness of the disease in the 2 subjects with clinical ASH and it is also likely that the mild changes described in the clinically normal sons would be compatible with the disease in a latent state in which it may presumably continue or from which it may emerge clinically.

### Neurological and electrophysiological aspects

Several aspects of voluntary muscle involvement in hypertrophic obstructive cardiomyopathy (HOCM) have recently been investigated.<sup>16,35,36</sup> The results of the final analysis of electromyographic, histological, histochemical and electron microscopic studies have challenged some concepts concerning their mutual relationships. We have described and attempted to correlate some clinical and laboratory findings in a family consisting of the parents and their 6 sons. Prominent features were mental dullness, short stature, HCM and skeletal muscle involvement. Testicular hypoplasia was present in 3 and nystagmus could be demonstrated in 1 subject. Only the most seriously disabled patient (No. 3) had an abnormal EEG. Both sensory and motor conduction velocities were normal in all subjects but the EMGs of all, except patient 8, were abnormal. In all subjects very brief (1 - 3 ms) low amplitude potentials could be demonstrated with an excess of polyphasic potentials. No fibrillation potentials, positive denervation potentials or fasciculations were recorded and all subjects, except patient 3, produced an interference pattern on full voluntary effort. Similar electromyographic findings suggesting a 'myopathic EMG' have been described in patients with HOCM,<sup>16,36</sup> although others<sup>35</sup> found a neurogenic EMG.

The interpretation of these findings give no certain clue as to a 'myopathic' or 'neurogenic' cause and the following facts must be considered. During the last decade considerable doubt has been raised about the justification of the earlier concept 'myopathic EMG'.

Drachman *et al.*<sup>37</sup> designed a study on the histological effects of long-standing partial denervation in 9 elderly poliomyelitis patients. The EMG showed an excess of polyphasic potentials; no mention was made of short potentials. There were no signs of denervation and the pattern on full contraction was often somewhat reduced. Muscle biopsy in 7 of these patients gave evidence of combined denervation and 'myopathy' and 3 biopsies showed only 'myopathic' features. Gath *et al.*<sup>38</sup> described the electromyographic and histological findings in 4 patients with Wohlfart-Kugelberg-Welander disease. Both investigations showed signs of denervation and different degrees

of a myopathic pattern. Mastaglia and Walton<sup>39</sup> described the electromyographic and histological findings in 17 patients with the Kugelberg-Welander syndrome, and considered possible explanations for development of myopathic changes and transformation of the histochemical profile in surviving muscle fibres in chronically denervated muscle. The most important factor was considered to be the reinnervation of muscle fibres by collateral sprouts from surviving axons. Engel<sup>40</sup> offered alternative explanations for the so-called 'myopathic EMG'. Warmolts and Mendell<sup>41</sup> were the first to demonstrate by open biopsy electromyography that a pattern of excessively recruited, pathologically small and numerous polyphasic motor unit potentials could be recorded from a biopsy site demonstrating histological, histochemical and ultrastructural evidence for neuropathy alone.

These reports clearly demonstrate that pathologically small potentials with an excessive amount of polyphasic motor unit potentials in muscles showing a full interference pattern, are not diagnostic of myopathy; these muscles sometimes show the characteristics of neurogenic atrophy, as was confirmed in at least 3 of our cases (Nos. 4, 5 and 7). Comparison of the clinical, electromyographic and histological features in our series underlines the fact that prebiopsy diagnosis is virtually impossible. It is also obvious that both the myocardium and skeletal muscles can be affected without overt clinical dysfunction.

### Follow-up and therapeutic implications

Not all the patients with obvious myocardial involvement had symptoms. This poses the problem of having to administer potentially unpleasant and harmful drug therapy prophylactically in a disease without a definite known prognosis. The family's reduced intelligence makes patient compliance far from ideal, and genetic counselling appears even more difficult in this patient group.

Therapy with  $\beta$ -blockers, especially propranolol, has been used for many years in hypertrophic obstructive cardiomyopathy<sup>42</sup> with uncertain therapeutic benefit. Patients 3 and 4 have now been on a  $\beta$ -blocker for some 18 months without any objective improvement.

Because of the increased sensitivity to digitalis and catecholamines in this disease, it has been postulated that there is an increased availability of intracellular calcium. Thus, more recently, the calcium antagonist, verapamil, has been tried.<sup>43</sup> This drug, given in a mean oral dose of 480 mg daily, was shown to ameliorate symptoms. In addition, verapamil generally caused parallel reductions in QRS voltage, interventricular gradient, left ventricular muscle mass, heart volume, and coronary artery diameter. There is also good evidence that calcium antagonists are of more therapeutic benefit than  $\beta$ -blockers in this condition.

It is intended to follow up this family at 3-monthly intervals to determine whether the asymptomatic members develop symptoms of cardiac origin, and whether the symptomatic

patients improve or deteriorate subjectively. More objective information obtained by performing regular electrocardiography and echocardiography will be published later.

We wish to sincerely thank Miss H. Weymar of the Cardiac Clinic for her diligent preparation of the manuscript. We also appreciate help rendered in the cardiac catheterization by Dr F. Maritz, and wish to extend our thanks to Dr Du Toit and staff of the Provincial Blood Grouping Laboratory. Finally, we wish to thank the Medical Superintendent of Tygerberg Hospital, Dr C. Vivier, for permission to publish.

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