Br Heart J 1989;61:144-8.

3 Lee CH, Xiao HB, Gibson DG. Presystolic tricuspid valve closure: An alternative mechanism of diastolic sound genesis. *Cardiology* 1990;77:340-5.

4 Laennec RTH. *Traité de l'auscultation médiate*. 2nd ed. Paris: Brosson et Chaude, 1826.

5 Ozawa Y, Smith D, Craige E. Origin of the third heart sound: I. Studies in dogs. *Circulation* 1983;67:393-8.

6 Ozawa Y, Smith D, Craige E. Origin of the third heart sound: II. Studies in human subjects. *Circulation* 1983;67:399-404.

7 Tyberg TI, Goodyer AVN, Langou RA. Genesis of a pericardial knock in constrictive pericarditis. *Am J Cardiol* 1980;46:570-5.

8 Lee CH, Gibson DG. Isovolumic relaxation sound: a new class of added heart sound? *Br Heart J* 1991;65:357-9.

9 Traill TA, Fortuin N. Presystolic mitral closure sound in aortic regurgitation with left ventricular hypertrophy and first degree heart block. *Br Heart J* 1982;48:78-80.

10 Mackenzie J. Valvular defects (continued). In: Mackenzie J, ed. *Diseases of the heart*. London: Oxford University Press, 1908:229-34.

11 Groedel FM, Miller M. Studies on the acoustic phenomena over the vessels of the neck in the healthy and diseased heart. *Exper Med Surg* 1944;II:193-215.

12 Dock W. Loud presystolic sounds over the jugular veins associated with high venous pressure. *Am J Med* 1956;20:853-9.

ABSTRACTS IN CARDIOLOGY

Prediction of sudden death in hypertrophic cardiomyopathy

Abnormalities of heavy chain myosin account for perhaps 50% of hypertrophic cardiomyopathy (HCM). It now seems that the site and nature of the aminoacid change influence survival. Why should this be? One possibility is that the substitutions interfere to a different degree in myofibrillary organisation within the myocyte. It is probably significant that the substitution leading to a change in charge has the greatest deleterious effect on survival. Abnormal myofibrillary organisation probably leads in turn to misshapen cells and

abnormalities in cell to cell organisation producing disarray and an ideal substrate for arrhythmias. Family history remains a cheap way of identifying those with HCM at high risk of sudden premature death but a good case can be made for determining the exact gene abnormality. The understanding of how HCM affects myocyte structure will be further forwarded when the other genes unrelated to heavy chain myosin are discovered. These are exciting times for those interested in HCM.

M J DAVIES

Characteristics and prognostic implications of myosin missense mutations in familial hypertrophic cardiomyopathy

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Abstract Background—Familial hypertrophic cardiomyopathy is characterized by a variable degree of myocardial hypertrophy and a wide range of symptoms. Different mutations in the β cardiac myosin heavy-chain gene have been identified in three affected families. However, neither the proportion of cases attributable to myosin mutations nor the effects of different mutations on clinical outcome are known.

Methods—Using a ribonuclease protection assay, we screened the β cardiac myosin heavy-chain genes of probands from 25 unrelated families with familial hypertrophic cardiomyopathy; this assay is a sensitive method for detecting the presence and location of mutations. We further defined the mutations by analyzing their nucleotide sequences. The clinical features of the disease were compared in families with various myosin mutations.

Results—Seven mutations in the β cardiac myosin heavy-chain gene were identified in 12 of the 25 families. All were missense mutations (i.e., causing the substitution of a single amino acid) clustered in the head and headrod junction region of the molecule. Six mutations resulted in a change in the charge of the amino acid. Patients with mutations that changed the charge of the altered amino acid (such as that from arginine to glutamine at nucleotide 403 or from arginine to cysteine at nucleotide 453) had a significantly shorter life expectancy (mean age at death, 33 years), whereas patients with the one mutation that did not produce a change in charge (Val606Met) had nearly normal survival. However, patients with different mutations did not differ appreciably in their clinical manifestations of familial hypertrophic cardiomyopathy.

Conclusions—Different missense mutations in the β cardiac myosin heavy-chain gene can be identified in approximately 50 percent of families with hypertrophic cardiomyopathy. In those families, a definite genetic diagnosis can be made in all members. Since the location of a mutation or its DNA-sequence alteration (or both) appears to influence survival, we suggest that the precise definition of the disease-causing mutation can provide important prognostic information about affected members (*N Engl J Med* 1992;326:1108-14.)