Fifty years ago, in separate studies, thoracic surgeon Sir Russell Brock and pathologist Donald Teare published manuscripts on a new cardiac disease entity; these manuscripts are recognized as the initial description of the disease entity we now know as hypertrophic cardiomyopathy (HCM). “These publications launched a remarkable, and often controversial, evolution in the understanding of HCM; currently, it is recognized as the most common genetically mediated cardiovascular disease, present in approximately 1 in 500 individuals,” according to Steve R. Ommen, MD, director of the Hypertrophic Cardiomyopathy Clinic at Mayo Clinic in Rochester, Minnesota.

Although the majority of patients with HCM can live a normal life span with normal quality of life, subsets of patients develop limitations due to effort-related dyspnea and angina; approximately 20% develop atrial fibrillation, and there is a higher rate of sudden cardiac death in patients with HCM. Importantly, HCM is the most common genetically mediated cardiovascular disease, present in approximately 1 in 500 individuals,” according to Steve R. Ommen, MD, director of the Hypertrophic Cardiomyopathy Clinic at Mayo Clinic in Rochester, Minnesota. Although the majority of patients with HCM can live a normal life span with normal quality of life, subsets of patients develop limitations due to effort-related dyspnea and angina; approximately 20% develop atrial fibrillation, and there is a higher rate of sudden cardiac death in patients with HCM. 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“Importantly, this form of outflow tract obstruction is highly dynamic, and the severity can vary literally from minute to minute in individual patients,” says Dr Ommen. Physiologically, the obstruction is augmented in states of increased ventricular contractility, decreased preload (low-volume states), and a decreased afterload (systemic resistance). This dynamic nature has spurred interest in the use of pharmacologic agents to relieve the obstruction. Specifically, β-blockers, verapamil, diltiazem, and disopyramide improve symptoms by decreasing the strength of ventricular contraction and slowing the heart rate, which maximizes filling of the left ventricle during diastole. It is equally important to remove medications such as pure vasodilators, which may augment obstruction. Many patients can be successfully treated and have normal quality of life with appropriate medication adjustments.

Despite pharmacologic therapy, however, some patients continue to have lifestyle-limiting symptoms. Surgical treatment has always been an option; the initial description of HCM occurred well after cardiopulmonary bypass became routinely available. There was intense interest in the use of dual-chamber pacing in the 1980s and 1990s; however, in carefully performed randomized controlled trials, pacemaker therapy did not prove to have substantial, predictable long-term benefit. Over the past
Hypertrophic Cardiomyopathy Clinic

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Figure. History of HCM treatment at Mayo Clinic in Rochester. Initially patients were treated with myectomy. Percutaneous alcohol septal ablation was introduced in 1997.

decade, an alternative approach, percutaneous alcohol septal ablation (described elsewhere in this issue), has been proposed whereby alcohol is injected into a coronary artery providing perfusion to the septum such that a tactically located myocardial infarction is created. This infarction can result in local thinning and akinesis in the septum, thus widening the outflow tract. This procedure does appear to be an acceptable alternative for those patients who are not ideal candidates for a surgical approach. To this day, surgical septal myectomy (discussed elsewhere in this issue), whereby the portion of the basal septum integral to the left ventricular outflow tract obstruction is removed, remains the gold standard therapy for patients with symptoms despite pharmacologic therapy. At Mayo Clinic in Rochester, this procedure can be performed with minimal perioperative morbidity and mortality, excellent immediate- and long-term results, and improvements in long-term survival.

Mayo Clinic in Rochester has a long history of involvement and investigation into HCM, and more than 3,000 patients have been evaluated for HCM at Mayo Clinic (Figure). The first Mayo Clinic paper was published in 1961; in this paper, cardiovascular surgeon John Kirkland, MD, described his approach to relieving dynamic left ventricular outflow tract obstruction.

The Hypertrophic Cardiomyopathy Clinic was founded by A. Jamil Tajik, MD. It is a multidisciplinary clinic staffed by 8 cardiologists, 2 nurse educators, a medical genetics counselor, and 2 cardiovascular surgeons. The team includes a broad range of clinical expertise, including expertise in cardiovascular imaging, invasive and noninvasive hemodynamics, electrophysiology, percutaneous and surgical interventions, and medical genetics.

“A key objective of the Hypertrophic Cardiomyopathy Clinic is to educate patients and their families about the disease, including appropriate activity levels and potentially dangerous situations such as competitive athletics,” says Dr Ommen. “The ultimate goal is to optimize quality of life using individualized treatment recommendations.”

Patients may be referred to the Hypertrophic Cardiomyopathy Clinic at Mayo Clinic in Rochester by contacting the appointment coordinator at 507-538-1434.
Septal Myectomy for Obstructive Hypertrophic Cardiomyopathy

Transaortic septal myectomy is one of the most appropriate treatments for patients with obstructive hypertrophic cardiomyopathy (HCM) and severe symptoms unresponsive to medical therapy. A decrease in the left ventricular outflow tract (LVOT) gradient is accomplished by physical enlargement of the outflow tract and by interruption of the pathophysiologic sequence of events (primarily systolic anterior motion [SAM] of the anterior mitral leaflet) that are responsible for the outflow gradient. “Complete relief of LVOT obstruction by septal myectomy also eliminates mitral regurgitation caused by SAM,” says Joseph A. Dearani, MD, a cardiovascular surgeon at Mayo Clinic in Rochester. “Residual mitral valve regurgitation after adequate septal myectomy is almost always due to intrinsic mitral valve abnormalities such as ruptured chordae, leaflet prolapse, or annular dilation and can be corrected by direct valve repair.”

Indications for Operation
Symptoms of exertional dyspnea, chest pain, presyncope, syncope, fatigue, and occasionally orthopnea or paroxysmal nocturnal dyspnea can result from LVOT obstruction. However, despite appropriate medical treatment, symptom relief can be incomplete, transient, or accompanied by intolerable medication adverse effects. For such patients, septal myectomy is the preferred treatment when the resting or provokable gradient is more than 50 mm Hg. Surgery may also be advised initially for young patients and children who are asymptomatic or mildly symptomatic with particularly marked LVOT obstruction of more than 75 to 100 mm Hg. In these patients, operative risk is less than 1%, relief of obstruction is predictably good, and such patients are unlikely to have persistent symptoms related to diastolic dysfunction.

Replacement of the mitral valve, once proposed as an alternative to septal myectomy, can eliminate the LVOT gradient and improve symptoms. The chief disadvantage of this procedure is that outflow obstruction is replaced with the attendant risks associated with prosthetic valves. Mitral valve replacement is now reserved for patients with primary mitral valve pathology (eg, rheumatic valve disease) that is not amenable to surgical repair.

Results of Septal Myectomy
Between January 1961 and January 2007, over 1,300 patients have had septal myectomy for obstructive HCM at Mayo Clinic in Rochester. For all patients in this 45-year experience, early mortality was 2.1%. Importantly, risk of death with isolated myectomy has been 0.8% in 549 patients younger than 65 years. On the basis of the experience and data assembled from Mayo Clinic and more than 25 centers worldwide over almost 45 years, septal myectomy is a proven approach for reversing the consequences of heart failure by providing permanent amelioration of obstruction (and relief of mitral regurgitation) at rest and restoring functional capacity and an acceptable quality of life at any age. These outcomes exceed those achievable with chronic administration of cardioactive drugs. “The benefits of surgery are demonstrable subjectively by patient history and objectively by increased treadmill time, maximum workload, peak oxygen consumption, and improved myocardial oxygen demand, metabolism, and coronary flow,” says Dr Dearani.

Gradient reduction results from basal septal thinning with resultant enlargement of the LVOT area (and redirection of forward flow with loss of the drag and Venturi effects on mitral valve) and consequent abolition of SAM of the mitral valve. Mitral regurgitation is usually eliminated without the need for additional mitral valve surgery, left atrial size (and possibly the long-term risk for atrial fibrillation) is reduced, and LV systolic wall stress and LV end-diastolic pressures are normalized. Thus, heart failure from obstructive HCM can be regarded in part as surgically correctable.

Whether relief of outflow obstruction by septal myectomy also extends the longevity of patients with HCM has been an important but largely unresolved issue, because of the impracticality and ethical considerations involved in designing a controlled trial comparing patients randomly assigned to surgery and to other treatments. Nevertheless, previous reports and a recently available large retrospective and controlled analysis of the Mayo Clinic surgical series suggest that myectomy results in excellent long-term survival and may improve the natural history of the disease. After septal myectomy, long-term actuarial survival
The gold standard therapy for the relief of left ventricular outflow tract (LVOT) obstruction in patients with hypertrophic cardiomyopathy (HCM) is surgical myectomy, pioneered in the 1970s. “Myectomy was also associated with reduced long-term risk for sudden cardiac death,” according to Hartzell V. Schaff, MD, a cardiovascular surgeon at Mayo Clinic in Rochester. “Nonetheless, surgical myectomy does not eliminate the need to assess each patient’s risk for sudden cardiac death and consider placement of an implantable cardioverter-defibrillator in those with severe risk burden.”

**Septal Myectomy in Children**
Symptomatic pediatric patients with obstructive HCM have a higher mortality rate (6% annually) than adults. Although operation is technically more challenging because of difficulty of exposure of children’s smaller structures, there is a role for surgery in pediatric patients with obstructive HCM. The prognosis for symptomatic pediatric patients with obstructive HCM is much worse than that for symptomatic adults. To determine whether surgical relief of LVOT obstruction had a favorable influence on this poor prognosis, Mayo Clinic cardiovascular surgeons recently analyzed the outcomes in 56 consecutive pediatric patients who underwent septal myectomy. Mean intraoperative premyectomy direct pressure LVOT gradients were 60±27 mm Hg, postmyectomy gradients were 6±6 mm Hg, and no patient required mitral valve replacement. There was no early mortality, and age younger than 14 years at operation was the only predictor of late reoperation. As is true for adults, extended septal myectomy in children is a safe and effective means of relieving cardiac symptoms and LVOT obstruction, and late survivorship compares favorably with the natural history of the disease.

In summary, septal myectomy effectively relieves LVOT obstruction and cardiac symptoms in both adults and children with obstructive HCM. “Abnormalities of the mitral valve and subvalvar mitral apparatus can be addressed without the need for mitral valve replacement in almost all circumstances,” says Dr Dearani. “The operative mortality rate for isolated septal myectomy in both children and adults is low (about 1%), and overall results continue to improve.” Symptomatic improvement with myectomy is gratifying; 90% of patients improve by at least 1 functional class, and most remain improved on late follow-up. Late survivorship is improved over that among nonoperated patients with obstructive HCM, and myectomy may be associated with reduced long-term risk of sudden cardiac death.

**Percutaneous Alcohol Septal Ablation**
An Alternative Therapy for Symptomatic Obstructive Hypertrophic Cardiomyopathy

The gold standard therapy for the relief of left ventricular outflow tract (LVOT) obstruction in patients with hypertrophic cardiomyopathy (HCM) is surgical myectomy, pioneered in the 1970s. As an alternative to surgical myectomy, percutaneous alcohol septal ablation (ASA) emerged in 1995. The aim of this procedure is to induce a localized myocardial infarction of the proximal ventricular septum, thereby reducing septal thickness and systolic excursion of the septum and alleviating LVOT obstruction. ASA typically results in an infarct that involves 5% to 10% of the left ventricular mass. In other percutaneous methods (eg, vascular coils, covered stent placement), septal infarction may not occur because of septal collateralization that is either preexisting or develops during follow-up.

“In the majority of ASA procedures, obliteration of the septal artery occurs, with immediate relief of LVOT obstruction,” says Paul Sorajja, MD, an interventional cardiologist at Mayo Clinic in Rochester. The published periprocedural mortality of ASA patients is 1% to 2%. Procedural failure is most commonly attributable to lack of an appropriate septal artery, which occurs in approximately 20% of patients. In these instances, it is important to carefully examine the left and right coronary angiograms for candidate arteries because septal perforators frequently arise from vessels other than the left anterior descending artery.

The major complication of ASA is pacemaker dependency from complete atroventricular block, the occurrence of which depends in part on the presence of underlying conduction system disease. Because ASA results in right bundle branch block in approximately 50% of cases, patients with preexisting left bundle branch block are at the highest risk of permanent pacemaker dependency; however, the risk
of complete atrioventricular block is about 10% even in patients with normal electrocardiograms. Thus, all patients undergo placement of a temporary pacemaker during the procedure followed by intensive care unit monitoring with the pacemaker in place for at least 4 days.

Other acute complications of ASA that have been reported include dissection of the left anterior descending artery, free wall infarction from collateralization or untoward extravasation of alcohol, and cardiac perforation caused by temporary pacemaker placement. Cardiac perforation also may result from transseptal puncture, which is preferred over retrograde crossing of the aortic valve in the evaluation of LVOT obstruction in HCM. “At Mayo Clinic in Rochester, transseptal puncture is avoided in elderly women, and small-bore, temporary screw-in pacemaker leads are used in all patients to mitigate the risk of cardiac perforation,” says Rick A. Nishimura, MD, an interventional cardiologist at Mayo Clinic in Rochester.

Reports on clinical outcomes after ASA have been favorable. In the Mayo Clinic series, ASA led to relief of severe symptoms in more than 75% of patients. Younger patients (≤65 years) tend to have longer symptom-free survival after surgical myectomy (Figure). Although the reason for this difference is not clear, younger patients may not tolerate the relatively higher residual gradients present after ablation (10-15 mm Hg) than after myectomy (<5 mm Hg). Overall, there is about a 25% to 30% increase in objective functional capacity, which was comparable to surgical myectomy in 2 published series.

Ventricular remodeling with further reduction of both septal and free-wall hypertrophy has been reported in mid-term follow-up studies using both echocardiography and cardiac magnetic resonance imaging. The reductions in septal thickness coincide with further reduction in the LVOT gradient.

Nevertheless, the long-term effects of ASA raise concerns. “Because of their myocardial substrate, patients with HCM are predisposed toward ventricular arrhythmias, and this predisposition may be exacerbated by induction of a myocardial scar with ASA,” says Dr Nishimura. In the Mayo Clinic series, survival up to 4 years was similar for patients with ASA and myectomy. However, long-term data (>3- to 5-year follow-up) continue to be lacking. Further study is needed before definitive conclusions can be drawn about the effect of ASA on survival, especially since normal survival of HCM patients after myectomy has recently been demonstrated.

Proper patient selection for ASA is crucial. Criteria include 1) severe, drug-refractory cardiac symptoms (class III/IV dyspnea and/or angina) due to obstructive HCM; 2) dynamic LVOT obstruction due to systolic anterior motion of the mitral valve (gradient ≥30 mm Hg at rest or ≥50 mm Hg with provocation); 3) ventricular septal thickness ≥15 mm; 4) absence of severe intrinsic mitral valve disease; 5) absence of need for concomitant cardiac surgical procedure (eg, bypass grafting, valve replacement); and 6) informed patient consent. “Informed patient consent requires full understanding of the paucity of long-term data on survival after ASA, the relatively lower success rate because of ASA’s dependence on coronary anatomy, risk of pacemaker dependency, and the need for observation with a temporary pacing wire in place after the procedure,” says Dr Sorajja.

In some instances, ASA may be the only option because the patient is a poor candidate for surgery. Among 160 patients who have undergone ASA at Mayo Clinic in Rochester, 20% were at greatly increased operative risk for myectomy (>5%) because of patient age or comorbid conditions. Although younger age has not been a contraindication to the procedure, ASA generally has been reserved for older adults because of the limited data on long-term survival. Given all these considerations and the procedural complexity of ASA, current guidelines recommend its performance in tertiary care centers with expertise in both the medical and surgical care of HCM patients.
Risk of Sudden Cardiac Death in Hypertrophic Cardiomyopathy

Sudden cardiac death (SCD) in hypertrophic cardiomyopathy (HCM) is the paradigm of unexpected death occurring as “a bolt from the blue” and is the most frequent HCM-related cause of death in younger patients and in athletes. In one series, most patients with SCD had no or mild symptoms, and 68% of SCDs occurred while sedentary or during mild exertion. In patients with implantable cardioverter-defibrillators (ICDs) in a Mayo Clinic series, the development of ventricular arrhythmias after a prolonged period of arrhythmic quiescence was frequently characterized by the clustering of episodes, emphasizing the unpredictability of ventricular arrhythmias and SCD. Moreover, the potential arrhythmic substrates are complex and multifactorial, including the presence of left ventricular hypertrophy (LVH), myocardial disarray, subendocardial ischemia, myocardial fibrosis, autonomic dysfunction perhaps interacting with outflow tract obstruction, concomitant coronary artery disease, and a strong genetic component in many cases (Figure 1).

“Earlier studies probably overemphasized the unfavorable natural history of HCM and were likely influenced by referral bias—that is, sicker patients comprised the majority of referrals to the relatively few centers around the world with expertise in the management of HCM at that time,” says Bernard J. Gersh, MD, PhD, an electrophysiologist at Mayo Clinic in Rochester. Subsequent natural history studies and, in particular, community-based studies highlighted a complex of diseases that have a more favorable prognosis, with a community mortality rate of approximately 0.7% to 1.3% per year. In younger patients, HCM does have an unfavorable natural history, and SCD is the leading cause of death. In symptomatic middle-aged patients, morbidity is considerable, but the prognosis is probably better than that seen in patients with coronary artery disease. In elderly patients, with or without symptoms, the Mayo Clinic series demonstrated normal survival compared with age- and sex-matched controls (Figure 2).

The specter of SCD has prompted attempts at risk stratification for several decades. The results are somewhat disappointing; current techniques are imprecise, the positive predictive value is low, and there is considerable heterogeneity within each risk factor. In 1 recent large registry study, it appeared that the predictive value of 1, 2, or 3 risk factors was similar, a highly unusual finding. To compound the problem, although the ICD is highly effective in the primary and secondary prevention of SCD, its implantation entails considerable late morbidity, particularly in younger patients, including inappropriate shocks, lead problems, and infection.

The possibility that genotyping might identify patients at high- and low-risk of ventricular arrhythmias is intriguing, and it is the stimulus for a series of genotype and phenotype correlative studies. These have identified mutations involving the sarcomeric genes (actin and myosin) in the majority, highlighting the genetic complexity of HCM in that over 450 mutations involving approximately 20 genes (including extrasarcomeric mutations) have been identified. Initial prognostic series based on familial linkage studies in families with a high prevalence of genetic mutations were promising and suggested that within the context of these families, certain mutations were associated with a poor prognosis in contrast to other mutations. “Unfortunately, the clinical consequences for the patient and the family following an SCD in the face of a prior diagnosis of a supposedly ‘benign’ mutation are profound,” says Dr Gersh. Moreover, an important question is whether these genetic observations in specific families would apply to a consecutive series of unrelated outpatients—a pivotal question in regard to the role of routine genetic screening for prognosis.

Studies from the laboratory of Michael J. Ack-
erma, MD, PhD, of approximately 300 consecutive outpatients at Mayo Clinic in Rochester provided firm though unexpected conclusions. First, the frequency of the previously described “malignant” mutations involving the beta-myosin heavy chain gene, troponin, and alpha-tropomyosin genes were fairly common, occurring in approximately 1% of patients. The prevalence of “benign” mutations was 1.7%. It appears, therefore, that the vast majority of genetic HCM is the result of new or novel mutations, and screening for previously demonstrated mutations, irrespective of their originally demonstrated prognostic impact, is of no clinical value. Second, the majority of patients are sarcomere gene–negative; specific mutations (either benign or malignant) are rare. This indicates that multiple other genetic substrates probably lie outside the sarcomeric proteins, and much more needs to be learned in regard to the interactions between genetic mutations and environmental modifiers. Another area of increasing interest is the interrelationship among specific mutations, septal shape, age, ventricular mass and morphology, and the predisposition to ventricular arrhythmias.

It is generally accepted that a history of prior SCD, a positive family history of SCD, a history of unexplained syncope, and severe or “massive” septal hypertrophy (≥30 mm) are strong risk factors for future SCD. Other risk factors, which are perhaps less well established, include the presence of nonsustained ventricular tachycardia on ambulatory monitoring, an exercise-induced decline in blood pressure, and young age at onset. In fact, the prognostic import of severe LVH has been a contentious issue, although most would agree that its presence in patients younger than 40 years is a concern. Data are limited on the isolated risk posed by a positive family history of SCD, but results of recent and ongoing studies appear to show that family history alone is a risk factor, although its strength as a risk factor is undetermined. The emotional impetus to implant a device in surviving family members of an SCD patient is strong. Documentation that family history alone is a risk factor supports the recommendations of a 2003 American College of Cardiology/European Society of Cardiology Consensus Conference, in addition to a more intuitive clinical perspective, that an ICD is indicated in this setting.

Figure 3 illustrates current clinical approaches to risk stratification. In patients at high risk (ie, 1 or more of the risk factors discussed above), the therapeutic objective is to improve survival; the only proven strategy is placement of an ICD. In patients at intermediate risk, many of whom are symptomatic but without risk factors for SCD, the therapeutic objective is to relieve symptoms. The initial approach is aggressive medical therapy followed by either surgical myectomy/myotomy or alcohol septal ablation. Low-risk patients are those with minimal or no symptoms and none of the previously mentioned risk factors and include the majority of elderly patients with HCM. The cornerstone of management in these patients is reassurance, careful and regular surveillance with attention to the development of symptoms, and adequate control of hypertension.

The question is whether the availability of genotyping will alter this diagnostic and therapeutic construct. Currently, the answer is a categorical negative. Nonetheless, the future for routine genotype determination is optimistic, particularly in light of rapid technological development and enhanced comprehensive, rapid genotyping capabilities. Genotyping should result in establishment of disease patterns based on longitudinal studies in larger numbers of patients, refinement in current models of risk stratification, and genotype determination for genetic counseling. “A fascinating potential application lies in the prevention of expression of a phenotype in mutation-positive individuals who have not developed the clinical picture or phenotype of HCM,” says Dr Gersh. Animal models exist, and the first clinical trials of prevention either have begun or are in the planning phase. “We now know a great deal more about what it is we do not know,” he says, “but for the present, risk stratification for SCD in HCM is imprecise, and genotyping in this context is not a routine clinical tool.”

Figure 2. Patient age plays an important role in determining risk of SCD in patients with HCM.

Figure 3. Approach to determining risk of SCD in patients with HCM.
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RECOGNITION

Kevin L. Greason, MD, has joined the cardiovascular surgery practice at Mayo Clinic in Rochester.

Alfred A. Bove, MD, professor of medicine at Temple University, Philadelphia, Pennsylvania, presented the 12th Annual Robert L. Frye Lecture. Dr Bove is pictured (right) with Dr Frye.