A permanent pacemaker was inserted in eight patients with the long QT syndrome. All had recurrent syncope or seizures, six had documented torsade de pointes and four had aborted sudden death. Among the eight patients, permanent pacing was instituted in three who were unsuccessfully treated with both a beta-adrenergic blocking agent and left cardiothoracic sympathectomy, and in two who proved refractory or intolerant to beta-blockers. Another three patients had pacemaker implantation and long-term beta-blocker therapy because of spontaneous atrioventricular (AV) block in one, aborted sudden death in one and patient preference in one.

After pacing (70 to 85 beats/min), there was no significant change in the mean corrected QT interval, but the mean QT interval decreased significantly (534.4 ± 51.4 to 425.6 ± 18.9 ms, \( p < 0.0001 \)). Over a mean follow-up period of 35.1 ± 18.9 months, all patients are alive and currently free of syncope. One patient without a history of stress-induced syncope had two syncopal episodes (believed to be due to hyperventilation) while under severe emotional stress, but has been symptom free for the past 5 years. One patient with an atrial demand (AAI) pacemaker developed dizziness due to documented episodes of AV block, but remains asymptomatic after conversion to atrial rate-responsive dual chamber (DDD) pacing.

Either atrial or ventricular pacing combined with beta-blocker therapy appears to be effective treatment for a subset of patients with the long QT syndrome, by either preventing episodes of torsade de pointes or alleviating symptoms due to bradycardia from beta-blocker therapy.

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apy alone, one to beta-blocker therapy and phenytoin (Dilantin), one to left cervical thoracic sympathectomy alone and another to left cervical thoracic sympathectomy and beta-blocker therapy. Six patients had permanent pacemaker implantation (Cases 1 to 5 and 8) and are part of this report. Two additional patients are among five patients with the long QT syndrome treated at the University of Southern California and the University of Minnesota (Cases 6 and 7) and are included in this report. Three of these patients were treated with beta-blockers and two with a permanent pacemaker. There was no significant difference in age, sex distribution or cardiac diagnosis between those treated with or without a pacemaker. None of the paced patients experienced syncope related to emotional upset, startle, fright or exercise. In contrast, 3 of the 17 patients who were not treated with a pacemaker had a history of adrenergic-mediated episodes of syncope.

**Clinical characteristics (Table 1).** There were eight women, ranging in age from 16 to 57 years mean ± SD 32.1 ± 11.8. Congenital bilateral hearing loss was diagnosed in one patient (Case 4). The long QT syndrome was familial in five patients (Cases 3 and 8 are relatives), and sporadic in three patients.

All patients had recurrent syncopal episodes (abrupt loss of consciousness) over a period of 5 to 49 years (mean ± SD 15.2 ± 13.6), and four patients had one to four episodes of aborted sudden death (requiring cardiopulmonary resuscitation) before the insertion of a permanent pacemaker. Two of the four had one episode of aborted sudden death, while two had repeated episodes. Episodes of torsade de pointes were recorded in six patients. Second degree atrioventricular (AV) block (Mobitz type II) was documented in two patients. All patients were free of associated cardiac disease, except for Patient 2, who had mitral valve prolapse.

The eight patients had a prolonged QT interval at rest, which was unrelated to drugs, electrolyte abnormalities, myocardial ischemia or central nervous system disease. The QT interval was measured from at least three 12 lead electrocardiograms using the technique of Lepschkin (9), and the corrected QT interval (QTc) was determined by normalizing the QT interval for heart rate (QTc = QT/√RR) (10). A QTc 0.44 second or greater was considered abnormal (11).

**Diagnostic testing.** Maneuvers such as fright, startle, Valsalva maneuver and exercise treadmill testing proved ineffective in eliciting episodes of torsade de pointes. The QT interval shortened with exercise in all patients. Invasive electrophysiologic studies were performed in six of the eight patients before the implantation of a permanent pacemaker using a protocol previously reported (12).

**Therapy.** Four patients underwent left cervical thoracic sympathectomy in which a thoracotomy was used to resect the left stellate ganglion together with four to six thoracic ganglia. The lack of effective response to surgery for three patients (Cases 2 to 4) was previously reported (5).

**Indications for permanent pacemaker implantation included** failure to respond (or drug intolerance) to treatment with left cervical thoracic sympathectomy or beta-blockers, a history of aborted sudden death, a family history of sudden death in symptomatic patients or occurrence of torsade de pointes associated with bradyarrhythmias. Three different types of permanent pacemakers were implanted: atrial demand (AAI), atrial rate-responsive dual chamber (DDD) or ventricular demand (VVI) pacemaker. The pacing rates were guided by the magnitude of QT shortening achieved by atrial or ventricular pacing, or both, over a physiologic range (70 to 90 beats/min) after full beta-blockade was achieved with drug therapy. Maximal shortening of the QT interval within this heart rate range served as the end point for choice of the permanent paced rate.

### Table 1. Clinical Characteristics of the Eight Patients

<table>
<thead>
<tr>
<th>Case No.</th>
<th>Age (yr) &amp; Sex</th>
<th>FH</th>
<th>Syncope (no)</th>
<th>ASD (no)</th>
<th>Duration of Symptoms (yr)</th>
<th>Torsade de Pointes</th>
<th>Bradycardia</th>
<th>Unsuccessful Therapy</th>
<th>Current Therapy</th>
<th>Follow-up (mo)</th>
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<tbody>
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<td>1</td>
<td>33F</td>
<td></td>
<td>10</td>
<td></td>
<td>7</td>
<td>+</td>
<td></td>
<td>Propranolol, 80 mg/day; phenytoin LCTS</td>
<td>32</td>
<td></td>
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<tr>
<td>2</td>
<td>32F</td>
<td></td>
<td>5</td>
<td>1</td>
<td>9</td>
<td>+</td>
<td>SB(BB)</td>
<td>Nadolol, 120 mg/day; phenytoin LCTS</td>
<td>35</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>16F</td>
<td>+</td>
<td>&gt;20</td>
<td>4</td>
<td>9</td>
<td>+</td>
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</tr>
<tr>
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<td>1</td>
<td>21</td>
<td>+</td>
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<td></td>
</tr>
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<td>27F</td>
<td></td>
<td>7</td>
<td></td>
<td>7</td>
<td>–</td>
<td>SB(BB)</td>
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<td></td>
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<tr>
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<td>&gt;10</td>
<td>2</td>
<td>5</td>
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<td></td>
</tr>
<tr>
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<td>24F</td>
<td>+</td>
<td>8</td>
<td></td>
<td>15</td>
<td>+</td>
<td>AVB, SB</td>
<td>Phenothiazine 43</td>
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<td></td>
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<tr>
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<td>+</td>
<td>&gt;40</td>
<td></td>
<td>49</td>
<td>–</td>
<td>–</td>
<td>Phenothiazine 12</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

ASD = aborted sudden death; AVB = atrioventricular block (Mobitz type II); BB = after beta-blocker therapy; FH = family history of recurrent syncope, or sudden death, or both; LCTS = left cervicothoracic sympathectomy; SB = sinus bradycardia.
All patients were followed up by one of us or the referring physician at intervals of 3 to 6 months.

Statistics. Values are expressed as mean values + standard deviation. The two-tailed Student's t test for paired data was used to compare QT values before and after pacemaker implantation in the same patients.

Results

The eight patients are divided into three groups, depending on the indications for pacemaker insertion.

Group I. This group included three patients who underwent cardiac pacing after failure of response to both beta-blockers and left cervical thoracic sympathectomy. Patient 1 had documented torsade de pointes after removal of the left stellate ganglion. Repeated episodes of torsade de pointes, which were not related to bradycardia, occurred in spite of more extensive resection of the left thoracic chain (to T4) and treatment with propranolol (800 mg/day). She has been without symptoms for 2.5 years after treatment with a permanent cardiac pacemaker and beta-blocker therapy.

Patient 2 suffered from recurrent episodes of dizziness and syncope, and was referred after an episode of aborted sudden death. Episodes of polymorphous ventricular tachycardia were not related to bradycardia (Fig. 1). She underwent left cervical thoracic sympathectomy and had recurrent dizzy spells in spite of maximally tolerable doses of nadolol (120 mg/day). The Holter electrocardiographic (ECG) recordings showed chronic sinus bradycardia (42 to 53 beats/min), and episodes of dizziness were correlated with bouts of polymorphous ventricular tachycardia that occurred after pauses induced by ventricular ectopic beats (Fig. 2). She underwent insertion of the AAI pacemaker and remains asymptomatic over a follow-up period of 30 months.

Patient 3 had recurrent episodes of syncope and required cardiac resuscitation on three occasions. Multiple episodes of syncope due to torsade de pointes were documented and were not associated with bradycardia (Fig. 3). At the age of 7 years, she underwent left stellate ganglion resection at another institution, but continued to have recurrent syncope in spite of daily treatment with propranolol (120 mg/day) and dilantin (300 mg/day). She was referred to our center at 14 years of age after another episode of aborted sudden death. She underwent left cervical thoracic sympathectomy and an atrial pacemaker was inserted because of undue sinus bradycardia associated with beta-blocker therapy. She had no evidence of AV conduction disturbances. She remained asymptomatic for 2 years and then had a recurrence of her original symptoms (syncope) when pacemaker malfunction due to fractured leads was found. She remains without symptoms after appropriate pacing was instituted. Her follow-up course is discussed in detail later in this report.

Group II. This group included two patients who proved refractory or intolerant to beta-blocker therapy alone. Patient 4 had sinus node dysfunction and documented torsade de pointes, both associated with as well as unrelated to sinus bradycardia. Treatment with propranolol (120 mg/day) was associated with increased episodes of syncope and one episode of aborted sudden death. She subsequently underwent concomitant left cervical thoracic sympathectomy and AAI pacemaker implantation. In Patient 5, maximally tolerated doses of beta-blockers (nadolol, 120 mg/day) relieved her of syncope, but produced fatigue owing to profound sinus

Figure 1. Patient 2. Twelve lead electrocardiogram showing a heart rate of approximately 82 beats/min, a markedly prolonged QT interval (0.60 second) and repolarization abnormalities. The rhythm strip shows a sinus rate of 75 beats/min followed by an episode of torsade de pointes. The heart rate remained within normal limits throughout the hospital stay.
bradycardia. She is currently without symptoms after pacemaker insertion and continued beta-blocker therapy.

**Group III.** Three patients (Cases 6 to 8) were treated with permanent pacing and beta-blocker therapy without a trial of beta-blocking agents alone. All three had a history of recurrent syncope. One patient (Case 8) declined beta-blocker therapy alone because both her daughter (treated with left cervical thoracic sympathectomy) and granddaugh-

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**Figure 2.** Patient 2. A, Nonsustained episode of polymorphous ventricular tachycardia recorded by Holter electrocardiographic monitoring after left cervicothoracic sympathectomy during treatment with a beta-blocking agent. This patient developed chronic sinus bradycardia with beta-blocker therapy, and episodes of symptomatic polymorphous ventricular tachycardia occurred after pauses associated with ventricular ectopic complexes. B, Atrial pacing at a rate of 85 beats/min with absence of ventricular ectopic activity.

**Figure 3.** Patient 3. Twelve lead electrocardiogram (ECG) showing sinus rhythm at rate of 72 beats/min and a prolonged QT interval (0.60 second). Shortly after the 12 lead ECG was recorded, a monitored rhythm strip shows an episode of torsade de pointes. The sinus rate immediately preceding the arrhythmia was not recorded.
shortening of the QT interval in all. Two patients had 2:1 AV block, which proved to be infra-Hisian in one (Case 3) who underwent electrophysioligic studies (Fig. 4). The right ventricular effective refractory period for this patient was 250 ms.

**Chronic pacemaker therapy and the QT interval (Table 2).** Four patients had an atrial demand (AAI) pacemaker, two had an atrial rate-responsive dual chamber (DDD) pacemaker and two had a ventricular demand (VVI) pacemaker implanted. The pacing rates (or lower rate for DDD pacemakers) were 70 to 85 beats/min (mean 79.2 ± 4.8).

The electrocardiogram in all eight patients with a permanent pacemaker showed shortening of the QT interval. The QTc interval shortened in five patients, did not change in one and lengthened in two. For the group as a whole, permanent pacing resulted in a significant shortening of the mean QT interval (from 534.4 ± 51.4 before to 425.5 ± 18.9 ms after pacing, p < 0.0001). The QTc interval shortened (from 526.2 ± 35.6 to 483 ± 43.0 ms), but these changes were not statistically significant. The degree of QT shortening was similar among those treated with an AAI (472.5 ± 13.0 to 405.0 ± 29.6 ms), DDD (560.0 ± 40.0 to 440.0 ± 0 ms) or VVI (555.0 ± 5 to 445 ± 35 ms) pacemaker.

**Follow-up (Table 1).** The patients have been followed up for 35.1 ± 18.9 months. All patients are alive and currently without symptoms; none had recurrence of aborted sudden death. Repeated continuous ECG recordings in these patients showed, at most, ventricular couplets. Patient 3 had an atrial pacemaker inserted at the time of her cervical thoracic sympathectomy and was maintained on long-term beta-blocker therapy. She remained without symptoms for 2 years when she had recurrent syncope and was found to have a fractured pacemaker lead. The ECG showed sinus rhythm without evidence of AV block. Her symptoms were identical to those manifested before surgery and thought to be related to recurrence of torsade de pointes (not documented). The lead was replaced by an endocardial unipolar atrial lead and programmed in the AAI mode. Six months before her last admission, she discontinued the beta-blocker treatment and shortly afterward sustained two episodes of dizziness documented to be due to episodic 2:1 AV block with a ventricular rate of 45 beats/min. In this patient, cessation of beta-blocker therapy allowed for an increase in the sinus rate, and rate-dependent infranodal block was documented (Fig. 4). A DDD pacemaker was implanted, and the patient remains asymptomatic 5 months later.

Patient 4 underwent left cervical thoracic sympathectomy, and an atrial demand pacemaker was inserted at a rate of 70 beats/min. She had two syncopal episodes within 4 months after pacemaker insertion. These occurred when she was under extreme stress related to divorce proceedings. It was believed that these syncopal episodes were possibly due to hyperventilation since her syncopal episodes (or aborted

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**Figure 4.** Patient 3. A, Rest electrocardiogram shows a markedly prolonged QT interval (0.64 second). During exercise, the patient develops 2:1 atrioventricular (AV) block; P waves (P) are denoted by the arrows. B, Simultaneous recording of two surface leads (aVF and VI) and right atrial (RA) and His bundle (HBE) electrograms. Atrial stimulation (S) at a cycle length of 600 ms is followed by atrial depolarization (a) with a 2:1 AV block distal to the bundle of His (b) deflection. V = ventricular deflection.
sudden death) before surgery were not related to emotional upset or exercise. She has remained asymptomatic for the next 75 months.

**Discussion**

This study describes eight patients with symptomatic idiopathic long QT syndrome in whom a permanent pacemaker was implanted as a part of treatment. The most important finding was the efficacy of permanent pacing and beta-blockers therapy for three patients (Cases 1, 2 and 3) without bradycardia-mediated torsade de pointes who did not respond to combined medical and surgical treatment. This is of special importance in terms of the reported incidence of sudden death for those who fail to respond to available therapy. In addition, permanent pacing plays an obvious role in alleviating bradycardia-related symptoms induced by beta-blocking drugs. Our data showed that either spontaneous or beta-blocker-induced bradycardia may act as a provocative agent for episodes of torsade de pointes in patients with the long QT syndrome (Cases 2, 4 and 7) and that permanent pacing and beta-blocker therapy can control these arrhythmias.

**Mechanisms of torsade and rationale for pacing.** Several mechanisms have been invoked to explain the occurrence of torsade de pointes in patients with the long QT syndrome. The most popular relates to asynchronous cardiac sympathetic innervation and dispersion of ventricular refractoriness (3,13,14). Critically timed premature ventricular depolarizations in this milieu might initiate serious reentrant ventricular arrhythmias. An impressive array of data suggests that these arrhythmias may be neurogenically (adrenergic) mediated. Permanent pacing may be efficacious by decreasing the dispersion of refractoriness (14). In addition, if torsade de pointes is related to abnormal automatocity of two or more ventricular foci (15), permanent overdrive pacing may prove effective by decreasing automatocity (16,17). A more recently proposed mechanism of torsades de pointes relates to afterdepolarizations (18). It has been shown that triggered rhythms relating to early afterdepolarizations are enhanced by slow rates or factors that prolong repolarization, or both (19). In Purkinje fibers, cesium was found to induce bradycardia-dependent early afterdepolarizations (20). It was recently shown that early afterdepolarizations preceded the development of torsades de pointes in dogs given anthropleurin-A (21). Whether permanent cardiac pacing will abolish arrhythmias related to early afterdepolarizations is, of course, conjectural.

In patients with the long QT syndrome, the episodes of torsades de pointes are usually described as adrenergic dependent (1,2,22–24) (and the majority of symptomatic patients respond to anti-adrenergic therapy). Unexplained by this hypothesis is the finding of patients with the long QT syndrome who fail to respond to beta-blocker therapy or left cervical thoracic sympathectomy, or both. Described in this report is a subset of patients with the long QT syndrome in whom both symptoms and documented episodes of torsades de pointes appear to be exacerbated by the occurrence of bradyarrhythmias. The bradyarrhythmias occurred either spontaneously or as a result of beta-blocker therapy. We hypothesize that a subset of patients with the long QT syndrome may suffer from arrhythmia provocation by adrenergic-mediated mechanisms as well as by a decrease in heart rate. It is of interest that permanent pacing and beta-blocker therapy are the only therapeutic modalities that produce consistent long-term normalization of the QT interval. Although pacing alone would be expected to shorten the QT interval, these effects are minimal in patients with a normal heart rate if the desired pacing rate is to be maintained within the normal range. The QT shortening with pacing is, however, accentuated by concomitant use of beta-blocking agents that serve to slow the sinus rate.

**AV block in the long QT syndrome.** Two of our patients had Mobitz type II AV block. In one of the two who underwent electrophysiologic studies, the site of block occurred distal to the recorded His bundle potential. The oc-

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**Table 2. QT and QTc Intervals Before and After Implantation of a Permanent Pacemaker**

<table>
<thead>
<tr>
<th>Case No.</th>
<th>Baseline QT (ms)</th>
<th>Baseline QTc (ms)</th>
<th>Type of Pacemaker</th>
<th>Pacing Rate (beats/min)</th>
<th>Pacing QT (ms)</th>
<th>Pacing QTc (ms)</th>
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<td>453</td>
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<td>400</td>
<td>476</td>
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<tr>
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<td>85</td>
<td>410</td>
<td>393</td>
</tr>
<tr>
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<td>566</td>
<td>DDD</td>
<td>80</td>
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<td>505</td>
</tr>
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</tr>
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</table>

AAI = atrial demand pacemaker; DDD = rate-responsive dual chamber pacemaker; VVI = ventricular demand pacemaker.
currence of AV block in patients with the long QT syndrome had been previously described (8,25), but its prevalence is not known. A recent study (26) has documented the coexistence of infranodal lesions in these patients. The documentation of infra-Hisian AV block in combination with relatively long ventricular repolarization (as judged by the prolonged QT intervals) suggests that the block in these patients might have been due to prolonged myocardial refractoriness. However, the patient with AV block who underwent electrophysiologic studies did not have abnormal right ventricular effective refractory periods, suggesting that the block occurred in the His-Purkinje system.

Type of implanted pacemaker. The long-term effectiveness of permanent pacing was independent of the mode of pacing (namely, atrial, ventricular or dual chamber). Medina-Ravell et al. (6) found that DVI pacing shortened the QT interval more than did ventricular pacing in one patient with the long QT syndrome. In our patients, the QT interval shortened to similar degrees with atrial and ventricular pacing. Roy et al. (8) believed that an atrial rather than a ventricular pacemaker should be implanted to avoid induction of ventricular arrhythmias. In the early 1970s, Olley and Fowler (24) described apparent aggravation of arrhythmias by ventricular pacemaker wires. In contrast, no arrhythmias were detected in four of our patients in whom ventricular leads were implanted. This finding confirms several recent reports (7,27). It is possible that more flexible wires with more reliable ventricular fixation may account for the difference.

Our results show that permanent ventricular pacing is not contraindicated in patients with the long QT syndrome and may, in fact, be desirable since some of these patients appear to be prone to develop AV block. A dual chamber pacemaker may be most appropriate for those requiring rate-responsive pacing.

The pacing rates in our patients are generally slower than those employed previously in patients with the long QT syndrome (7,24). This is likely due to concomitant use of a beta-blocking agent, which uniformly produced sinus slowing in treated patients. The pacing rate in our series was guided by achievement of “physiologic” rates that produced clear-cut shortening of the QT interval.

Limitations of study. In three patients (Cases 6 to 8) treated simultaneously with pacing and beta-blocking agents, it is unclear whether treatment with a single modality would have been effective. This group is nevertheless important because it demonstrates efficacy of combined therapy in a high risk group (syncope and aborted sudden death) and suggests that combined therapy may be a suitable alternative to more aggressive therapy (that is, sympatheticectomy or insertion of an automatic defibrillator).

Clinical implications. Our observations have several important practical implications. For patients with the long QT syndrome presenting with transient neurologic symp-
toms that are adrenergically mediated, a trial of beta-blocker therapy is indicated. On the basis of our observations, it would appear reasonable to use permanent cardiac pacing and beta-blocker therapy for those who do not respond to beta-blocker therapy and left cervical thoracic sympathectomy. In those patients in whom the mechanism of torsade de pointes appears to be both adrenergic- and bradycardia-dependent, treatment with permanent pacing and beta-blocker therapy might prove to be a suitable alternative to left cervical thoracic sympathectomy. Patients with the long QT syndrome who present with aborted sudden death are a particularly difficult group to treat. The incidence of sudden death even after left cervical thoracic sympathectomy is still 6% and some have suggested use of the automatic internal defibrillator for these patients. Our data raise the possibility that a less aggressive approach including long-term beta-blocker therapy and cardiac pacing might prove equally effective.

References