A GROWING BODY of clinical and experimental data indicates that the central nervous system exerts a major role in causing cardiac arrhythmias. Subjects suffering from cerebrovascular accidents, head injury, brain tumors, or undergoing brain operations exhibit a high incidence of electrocardiographic abnormalities and arrhythmias. Most of these data implicate cardiac sympathetic outflow with consequent activation of beta adrenergic receptors as the neural pathway involved in producing these arrhythmias. For this reason, propranolol commonly is employed to treat these cardiac rhythm disturbances. However, the arrhythmias, in some instances, do not respond to propranolol therapy but do respond to surgical removal of sympathetic cardiac ganglia. The reason for the disparity in the antiarrhythmic effects of propranolol and surgical sympathectomy is unclear.

The purpose of the present study was to examine central nervous system arrhythmias further to: (1) investigate the mechanism of central nervous system-induced arrhythmias, and (2) determine what drugs are effective in countering these arrhythmias. As a model, we chose to activate the central nervous system by administering the drug picrotoxin. This agent demonstratedly produces cardiac arrhythmias in experimental animals through activation of the central nervous system, with consequent augmentation of sympathetic outflow to the heart.

**Methods**

Cats unselected as to age and sex were anesthetized with alpha chloralose, 70–80 mg/kg, iv. A femoral vein and artery were isolated and cannulated for the purpose of drug administration and arterial blood pressure measurement, respectively. The trachea was isolated and cannulated and the cat was artificially respirated with room air. Rectal temperature was maintained at 37–38.5°C with an infrared lamp. Blood pressure and lead II of the electrocardiogram (ECG) were recorded on either a Grass polygraph or a Beckman Dynograph. Animals were immobilized with decamethonium bromide, 0.25 mg/kg, iv (Syncurine; Burroughs-Wellcome) every 45 minutes, or as needed. Picrotoxin (Aldrich) was made fresh daily in 10% ethanol in distilled water and protected from light until ready for use. The final concentration of this solution was 3 mg/ml. Each cat received the equivalent of 2 mg picrotoxin per kg, iv. The vehicle for picrotoxin had small transient effects on blood pressure and heart rate but these effects did not persist for more than 30 seconds.

Several procedures were used to examine the mechanisms involved in arrhythmias produced by central nervous system activation with picrotoxin, and these are as follows:

1. Three cats were subjected to spinal cord section at the C-1 level and bilateral cervical vagotomy 60–90 minutes prior to picrotoxin administration.
2. Six cats were pretreated with atropine sulfate, 1 mg/kg, iv (New York Quinine and Chemical Company) 10 to 15 minutes prior to picrotoxin administration.

**SUMMARY**

The mechanism of cardiovascular changes produced by activation of the central nervous system with picrotoxin (2 mg/kg, iv) was studied in chloralose-anesthetized cats. Effects occurred in two phases. During the early phase, there were decreases in arterial blood pressure and heart rate, and in a few cats, bradyarrhythmias. These changes were transient and superceded by an increase in arterial blood pressure and, in most cases, ventricular tachyarrhythmias. The early phase changes were mediated primarily by the cardiac vagus nerve whereas the later phase changes were mediated primarily by sympathetic nerves and the adrenal medulla. The ventricular tachyarrhythmias were unaffected by pretreatment with atropine, bilateral vagotomy, or beta adrenergic blocking agents. On the other hand, bilateral extirpation of the stellate ganglia and adrenal glands prevented the ventricular arrhythmias from occurring. In addition, administration of drugs that blocked alpha adrenergic receptors effectively counteracted picrotoxin-induced ventricular arrhythmias. These results indicate that the centrally induced ventricular arrhythmias were mediated by cardiac sympathetic nerves and/or release of catecholamines from the adrenal medulla. More importantly, these results indicate that one cannot equate beta adrenergic blockade with elimination of sympathetic influence on the heart. Finally, sympathetically induced arrhythmias resistant to beta adrenergic blockade appear to respond to drugs that block cardiac adrenergic alpha receptors.
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3. Seven cats were subjected to bilateral cervical vagotomy prior to picrotoxin administration.

4. Six cats were pretreated with propranolol hydrochloride, 1 mg/kg, iv (a gift from Ayerst Laboratories) 20 to 30 minutes prior to picrotoxin administration.

5. Seven cats were pretreated with a combination of atropine (1 mg/kg) and propranolol (1.5-2.0 mg/kg) 20 to 30 minutes prior to picrotoxin administration. Three of these cats also received practolol, 3.0 mg/kg, iv, during this time period. (Practolol was a gift from Ayerst Laboratories.) In two of the seven cats, stellate ganglia and adrenal medullae were exposed. These structures were left intact, and these cats served as controls for those that underwent bilateral stellate ganglionectomy and bilateral adrenalectomy as described below.

6. Seven cats were subjected to bilateral stellate ganglionectomy prior to picrotoxin administration. These animals also underwent bilateral vagotomy.

7. Seven cats were subjected to bilateral stellate ganglionectomy plus bilateral adrenalectomy prior to picrotoxin administration. These animals also underwent bilateral cervical vagotomy.

8. Six cats were pretreated with phentolamine mesylate, 3-7 mg/kg, iv (Regitine, Ciba-Geigy) 10-15 minutes prior to picrotoxin administration.

9. Five cats exhibiting a picrotoxin-induced ventricular arrhythmia were given alpha adrenergic blocking drugs, iv [either phentolamine mesylate, 5 mg/kg, or tolazoline hydrochloride-Priscoline HCl (Ciba-Geigy), 1 mg/kg] in an attempt to convert the abnormal rhythm to sinus rhythm. These drugs were administered over a period of 15-20 seconds to cats with a picrotoxin-induced ventricular arrhythmia of at least 1 minute.

Presence of either beta adrenergic blockade or alpha adrenergic blockade was assessed by observing no significant heart rate response to iv administration of 1-isoproterenol HCl, 0.5-1.0 μg/kg (Sigma), and no significant pressor response to iv administration of norepinephrine bitartrate, 0.5 to 1.0 μg/kg (Sigma), respectively. These agonists given prior to administration of the antagonists gave heart rate and arterial pressure responses exceeding 45 beats/min and 50 mm Hg, respectively.

The data were analyzed by paired comparisons, analysis of variance, Duncan’s multiple range test, and Fisher’s exact test. The criterion for statistical significance was P < 0.05.

Results

CARDIOVASCULAR CHANGES PRODUCED BY ACTIVATION OF THE CENTRAL NERVOUS SYSTEM WITH PICROTOXIN

Eleven cats received a bolus iv injection of picrotoxin, 2 mg/kg. The first cardiovascular effects observed were a fall in arterial pressure and a decrease in heart rate. These changes became maximal 2.6 ± 0.6 and 2.9 ± 0.4 (SEM) minutes after picrotoxin administration, respectively (Table 1, phase I changes). Four of the 11 animals exhibited arrhythmias during the time period when sinus bradycardia and hypotension occurred. Three developed junctional rhythms with rates ranging from 95 to 138 beats/min. One cat developed a ventricular rhythm with a rate of 42 beats/min. These rhythm disturbances were preceded by an increase in the P-R interval and sinus bradycardia. The arrhythmias occurred within 1-5 minutes after picrotoxin administration and were of short duration (i.e., no longer than 4 minutes).

Hypotension and bradycardia also were short lived and were superceded by an increase in arterial pressure and a return of sinus rate to control values. These changes began to develop at 4.9 ± 0.2 and 5.6 ± 0.6 minutes, respectively, and either became maximal 11.0 ± 1.5 (arterial pressure), or attained a plateau 14.0 ± 2.0 (SEM) minutes (sinus rate) after picrotoxin administration (Table 1, phase II changes). Nine of the 11 cats developed cardiac arrhythmias during the time when the phase II changes occurred. These arrhythmias were different from those that occurred

<table>
<thead>
<tr>
<th>Group</th>
<th>No. of cats tested</th>
<th>Arterial BP (mm Hg)</th>
<th>Sinus rate (beats/min)</th>
<th>Arterial BP (mm Hg)</th>
<th>Sinus rate (beats/min)</th>
<th>Arterial BP (mm Hg)</th>
<th>Sinus rate (beats/min)</th>
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<tbody>
<tr>
<td>Controls</td>
<td>11</td>
<td>158 ± 8</td>
<td>217 ± 10</td>
<td>-63 ± 9*</td>
<td>-89 ± 15*</td>
<td>+56 ± 7*</td>
<td>+13 ± 12</td>
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<tr>
<td>Atropine pretreated</td>
<td>8</td>
<td>140 ± 7</td>
<td>229 ± 12</td>
<td>-37 ± 14*</td>
<td>-24 ± 6*</td>
<td>+71 ± 15*</td>
<td>+70 ± 16*</td>
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<tr>
<td>Bilateral vagotomy</td>
<td>9</td>
<td>170 ± 5</td>
<td>225 ± 4</td>
<td>-21 ± 5*</td>
<td>-7 ± 3</td>
<td>+58 ± 7*</td>
<td>+43 ± 5*</td>
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<td>Propranolol</td>
<td>6</td>
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<td>184 ± 8</td>
<td>-76 ± 16*</td>
<td>-68 ± 11*</td>
<td>+48 ± 13*</td>
<td>-23 ± 9*</td>
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<td>Atropine + propranolol (+ pracoit)</td>
<td>7</td>
<td>153 ± 7</td>
<td>183 ± 7</td>
<td>-34 ± 10*</td>
<td>-4 ± 1*</td>
<td>+62 ± 5*</td>
<td>+39 ± 8*</td>
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<td>Bilateral vagotomy + bilateral stellate ganglionectomy</td>
<td>7</td>
<td>116 ± 16</td>
<td>171 ± 13</td>
<td>-20 ± 10*</td>
<td>-5 ± 3</td>
<td>+67 ± 9*</td>
<td>+50 ± 6*</td>
</tr>
<tr>
<td>Bilateral vagotomy + bilateral stellate ganglionectomy + bilateral adrenalectomy</td>
<td>7</td>
<td>112 ± 6</td>
<td>147 ± 9</td>
<td>-33 ± 5*</td>
<td>-7 ± 4</td>
<td>+47 ± 8*</td>
<td>+13 ± 9</td>
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<tr>
<td>Phenolamine pretreated</td>
<td>6</td>
<td>113 ± 10</td>
<td>229 ± 10</td>
<td>-47 ± 8*</td>
<td>-105 ± 21*</td>
<td>+26 ± 13*</td>
<td>+4 ± 11</td>
</tr>
</tbody>
</table>

Values are mean ± SEM.

P < 0.05 with paired comparisons (comparison was made between data obtained during picrotoxin administration and data obtained prior to picrotoxin administration).

P < 0.05 using analysis of variance and Duncan’s multiple range test (comparison was made between data obtained from cats subjected to autonomic nervous system interventions and data obtained from controls).
in the four cats during the period of the phase I pressure and rate changes. They consisted of ventricular premature beats, bigeminal and trigeminal runs of ventricular beats, multifocal ventricular extrasystoles, and ventricular tachycardia. Ventricular rates that occurred during the latter two types of arrhythmias ranged from 138 to 316 beats/ min. The onset of the phase II arrhythmias ranged from 5 to 16 minutes \( \bar{x} = 7.5 \pm 1.2 \) (SEM) minutes after picrotoxin administration and persisted for approximately 30 seconds to 50 minutes \( \bar{x} = 18.5 \pm 4.5 \) (SEM) minutes. One cat had an arrhythmia duration of 30 seconds, and the duration of the others ranged from 6 to 50 minutes. Representative experiments depicting the ECG, heart rate, and blood pressure changes produced by picrotoxin administration are shown in Figures 1 and 2.

Three of the 11 cats died from the effects of the bolus injection of picrotoxin (2 mg/kg). Death occurred as a result of either hypotension (one cat) or a combination of hypotension and ventricular arrhythmia (two cats). Six of the remaining cats were used to examine the cardiovascular effects of a second bolus injection of picrotoxin, 2 mg/ kg, while the other two cats were used to examine the cardiovascular effects of a bolus injection of picrotoxin of 4 mg/kg. These doses were administered 30–75 minutes after the initial dose. None of the six cats exhibited the ventricular tachyarrhythmias observed with the first injection of picrotoxin. Only the phase I cardiovascular changes occurred, i.e., sinus bradycardia (six of six cats) and hypotension (five of six cats). One cat developed a slow ventricular arrhythmia. The two cats that received 4 mg/kg developed these same phase I cardiovascular changes, including slow ventricular escape arrhythmias. The times to onset of the rhythm disturbances were 25 and 40 seconds after drug administration and the durations were 80 and 190 seconds.

Three additional cats underwent spinal cord transection at the C-1 level and bilateral cervical vagotomy prior to administration of picrotoxin. None of these animals exhibited significant changes in cardiovascular function after picrotoxin, indicating the total dependency of the arrhythmogenic response on the presence of the central nervous system.

**EFFECT OF PHARMACOLOGICAL AND SURGICAL INTERVENTIONS ON THE CARDIOVASCULAR CHANGES PRODUCED BY PICROTOXIN**

The arterial blood pressure and sinus rate responses to picrotoxin are summarized in Table 1. Briefly, these data indicate that: (1) interruption of cardiac vagal function largely prevented the early (phase I) slowing in sinus rate and fall in blood pressure and also eliminated the slow "escape" arrhythmias. In addition, these cats exhibited an increase in sinus rate during phase II. Blockade of cardiac adrenergic receptors with propranolol had no significant effect on these early responses. (2) The increase in sinus
rate observed in cats with vagal function impaired during phase II was not prevented either by propranolol or by bilateral stellate ganglionectomy but was prevented by a combination of bilateral stellate ganglionectomy and bilateral adrenalectomy. (3) The rise in arterial pressure during phase II was counteracted by alpha adrenergic receptor blockade but not by propranolol or the other antiadrenergic procedures employed.

The effects of pharmacological and surgical interventions on the incidence of picrotoxin-induced phase II tachyarrhythmias are summarized in Table 2 and Figure 3, and indicate: (1) pharmacological or surgical interruption of cardiac vagal function had no significant effect on the capacity of picrotoxin to produce arrhythmias, (2) bilateral stellate ganglionectomy performed in cats with vagus nerves sectioned significantly reduced the incidence of picrotoxin-induced arrhythmias, (3) bilateral stellate ganglionectomy plus bilateral adrenalectomy performed in cats with vagus nerves sectioned totally prevented the arrhythmogenic effect of picrotoxin, and (4) blockade of cardiac beta adrenergic receptors with propranolol and propranolol plus practolol in cats with or without pharmacological blockade of cardiac vagal function had no significant effect on the capacity of picrotoxin to produce arrhythmias. An experiment depicting the inability of blockade of cardiac beta adrenergic receptors in an atropinized animal to prevent a picrotoxin-induced arrhythmia appears as the upper two panels of Figure 3. The lower two panels of this figure illustrate the antiarrhythmic effect of bilateral stellate ganglionectomy.

**EFFECT OF ALPHA ADRENERGIC BLOCKADE ON THE ARRHYTHMOGENIC EFFECT OF Picrotoxin**

There is evidence that activation of cardiac alpha adrenergic receptors can result in significant electrophysiological changes in cardiac cells that exert an influence over cardiac rhythm. Accordingly, two alpha receptor blocking agents were tested for their effects on modifying arrhythmias produced by activation of the central nervous system with picrotoxin. Six cats were pretreated with phentolamine (5 mg/kg) and then challenged with a bolus injection of picrotoxin of 2 mg/kg. None of these cats developed phase II tachyarrhythmias, although one developed an escape rhythm 2-4 minutes after picrotoxin administration. In addition, cats with alpha adrenergic blockade did not exhibit a statistically significant rise in arterial pressure with picrotoxin (table 1).

Five experiments also were performed wherein either phentolamine (5 mg/kg in three experiments) or tolazoline (1 mg/kg in two experiments) was administered during a ventricular arrhythmia induced by picrotoxin. In each instance, administration of the alpha adrenergic blocking agent resulted in conversion of the ventricular arrhythmia to sinus rhythm. Conversion occurred within 35 seconds after the start of the infusion with the alpha adrenergic blocking agent. Conversion with phentolamine was associated with a fall in arterial pressure in two instances (—8 and —13 mm Hg), while in one instance and in the experiments with tolazoline, arterial pressure did not change significantly with conversion. Sinus rate at the time of conversion with the alpha adrenergic blocking agents was either reduced relative to the preexisting ventricular rate (two experiments by approximately 5 beats/min) or unchanged (three experiments).

**Discussion**

Picrotoxin proved to be a useful tool for eliciting cardiovascular responses through activation of the central nervous system. The effects produced could be divided into two phases and are as follows: phase I, decreases in arterial blood pressure and heart rate and, in some animals bradyarrhythmias; and phase II, increase in arterial blood pressure, increase in sinus rate in some animals and, in most animals, ventricular tachyarrhythmias. The phase I changes were primarily due to activation of the vagus, as the responses were either prevented or attenuated by bilateral vagotomy. The phase II changes were primarily due to activation of the sympathetic nervous system (including the adrenal medulla), as the responses were either prevented or attenuated by bilateral stellate ganglionectomy and bilateral adrenalectomy, and phentolamine.

The fact that picrotoxin administration results in cardiac

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<table>
<thead>
<tr>
<th>Group</th>
<th>No. of cats tested</th>
<th>No. of cats exhibiting arrhythmias</th>
<th>% of cats exhibiting arrhythmias</th>
<th>Duration of arrhythmias (min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Controls</td>
<td>11</td>
<td>9</td>
<td>82</td>
<td>18.5 ± 4.5</td>
</tr>
<tr>
<td>Atropine pretreated</td>
<td>6</td>
<td>4</td>
<td>67</td>
<td>31.0 ± 15.0</td>
</tr>
<tr>
<td>Bilateral vagotomy</td>
<td>9</td>
<td>7</td>
<td>73</td>
<td>11.0 ± 4.0</td>
</tr>
<tr>
<td>Propranolol pretreated</td>
<td>6</td>
<td>6</td>
<td>100</td>
<td>16.0 ± 6.0</td>
</tr>
<tr>
<td>Atropine + propranolol (+ practolol)</td>
<td>7</td>
<td>6</td>
<td>86</td>
<td>36.5 ± 17.2</td>
</tr>
<tr>
<td>Bilateral vagotomy + bilateral stellate ganglionectomy</td>
<td>7</td>
<td>1</td>
<td>14*</td>
<td>4.0</td>
</tr>
<tr>
<td>Bilateral vagotomy + bilateral stellate ganglionectomy + bilateral adrenalectomy</td>
<td>7</td>
<td>0</td>
<td>0*</td>
<td>–</td>
</tr>
<tr>
<td>Phentolamine pretreated</td>
<td>6</td>
<td>0</td>
<td>0*</td>
<td>–</td>
</tr>
</tbody>
</table>

* P < 0.05 using Fisher's exact test (comparison was made between data obtained from cats subjected to autonomic nervous system interventions and data obtained from controls).
Arrhythmias of central nervous system origin has been previously demonstrated by Bircher and colleagues and Lee and coworkers. The latter study was performed using cats; one finding that contrasts with our data is that three of four cats given picrotoxin, iv, developed arrhythmias that were terminated by vagotomy. We observed vagally induced arrhythmias in only a few cats (four of 11). The predominant arrhythmias in our study were ventricular tachyarrhythmias that were unaffected by procedures that excluded cardiac vagal tone. Possible reasons for the discrepancy between the two studies might be differences in the doses of picrotoxin employed in the two studies (we used 2 mg/kg, whereas Lee and coworkers used 4 mg/kg), and the fact that we employed vagotomy as pretreatment whereas Lee and coworkers employed vagotomy as a treatment. When used as a treatment, one would expect sinus rate to increase and this might result in "overdrive suppression" of the ventricular pacemaker.

Our results demonstrate that surgical removal of both stellate ganglia, both adrenal medullae, and both vagus nerves prevented the arrhythmias. Surgical or pharmacological removal of cardiac vagal tone had no effect on the development of the arrhythmias, indicating that these arrhythmias are mediated by the sympathetic nervous system. Since extirpation of both cardiac sympathetic ganglia and both adrenal glands prevented the arrhythmias, it was surprising that pharmacological blockade of cardiac beta adrenergic receptors did not reproduce this result. A disparity in the antiarrhythmic effects of propranolol and surgical sympathectomy also has been observed in clinical studies. In one case, the authors conclude "that failure to respond to beta-blockade does not preclude a beneficial response to sympathectomy." A somewhat analogous situation to this was reported by Lown and colleagues. They observed that the number of ventricular premature beats occurring in subjects with heart disease was significantly reduced by sleep. The explanation for the antiarrhythmic effect of sleep was proposed as being due to a decrease in cardiac sympathetic tone, but, as pointed out by Lown and colleagues, "it is hard to account for the failure of large doses of propranolol to reduce VPB's in three patients, though such a result was observed with sleep alone."

The reason for the disparity in the antiarrhythmic effects of propranolol and surgical sympathectomy is unclear. An obvious explanation is incomplete beta adrenergic blockade with propranolol. It is doubtful that this would explain our results, since we employed a dose of propranolol capable of blocking sinus tachycardia evoked by isoproterenol. (Ledsome and colleagues have demonstrated that a dose of propranolol that blocks isoproterenol-induced tachycardia also blocks tachycardia produced by sympathetic nerve stimulation.) In addition, in many experiments we administered not only a full beta-blocking dose of propranolol but also a beta-blocking dose of practolol. No antiarrhythmic effect was observed with this combination.

An alternative explanation is that the arrhythmogenic response elicited by central nervous system stimulation with picrotoxin was mediated via alpha adrenergic receptors on the heart. This is strongly suggested by our data demonstrating that drugs which block alpha adrenergic receptors (phenolamine and tolazoline) antagonize the picrotoxin-induced ventricular arrhythmias. Although the role of cardiac alpha receptors on arrhythmias has generally been considered unimportant, some evidence favors their significance. Cardiac electrophysiological changes result from interaction of norepinephrine with alpha adrenergic receptors on Purkinje cells. This alpha adrenergic agonist has been shown to increase refractory period duration of in vitro Purkinje cell preparations. If these changes in the refractory period occur nonuniformly in the heart (as demonstrated with cardiac sympathetic nerve stimulation by Han and colleagues), reentrant ventricular arrhythmias might result.

It is interesting to speculate that cardiac alpha adrenergic receptors may play a role in some instances in the arrhythmias associated with the prolonged Q-T interval syndromes. Clinically, arrhythmias in this syndrome are usually blocked by propranolol, but there are cases wherein the arrhythmias are resistant to beta adrenergic blockade but do respond to left stellate sympathectomy. The peripheral sympathetic mechanism mediating the arrhythmias associated with Q-T interval syndromes resistant to propranolol treatment therefore may not be beta adrenergic, but may be alpha adrenergic. This
may also be an important mechanism in selected subjects with recurrent ventricular tachyarrhythmias not associated with the prolonged Q-T interval syndrome. The arrhythmias described in these subjects were resistant to beta adrenergic blockade but responded to stellate ganglionectomy.

A third explanation is that the antiarrhythmic effect of these alpha adrenergic blocking agents occurs within the central nervous system. This hypothesis is suggested by the study of Share and Melville in which arrhythmias produced by central administration of picrotoxin were prevented by central pretreatment with phenoxybenzamine. However, the antiarrhythmic effect of phenoxybenzamine observed in their study might be entirely explained by "over-drive suppression" of the ventricular pacemaker. After phenoxybenzamine administration, picrotoxin caused an increase in the sinus rate of 84 ± 12 beats/min, resulting in a sinus rate significantly faster than the rate of the ventricular tachycardia observed in control animals given picrotoxin. Furthermore, experiments performed wherein central sympathetic outflow was monitored during conversion with phentolamine revealed no significant effect of this alpha adrenergic blocking agent on sympathetic nerve discharge to the heart (DiMicco and Gillis, unpublished observations).

Acknowledgments

The authors express their appreciation to Dr. Daya R. Varma, Department of Pharmacology, McGill University, for suggesting the use of picrotoxin for evoking cardiac arrhythmias of central nervous system origin.

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J A DiMicco, T Prestel, D L Pearle and R A Gillis

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