Catecholamine Depletion in Thyrotoxicosis

Effect of Guanethidine on Cardiovascular Dynamics

By Sidney Goldstein, M.D., and Thomas Killip III, M.D.

An intimate relationship between the sympathetic nervous system and the cardiovascular effects of thyroid hormone has been extensively documented during the past several decades.\(^1\)\(^-\)\(^9\) In hyperthyroidism in both man and the experimental animal there is an increased susceptibility to cardiac arrhythmia after parenteral administration of epinephrine.\(^2\)\(^-\)\(^6\) The frequent occurrence of atrial fibrillation in patients with thyrotoxicosis in the apparent absence of organic heart disease is well known. In addition, hyperthyroidism enhances the pressor effect of injected epinephrine and norepinephrine.\(^7\)\(^-\)\(^8\)

The similarities between the cardiovascular effects of excess thyroid hormone and epinephrine administration have stimulated an evaluation of the therapeutic effects of sympathetic blockade in hyperthyroidism. Spinal anesthesia has been reported to prevent hyperkinetic cardiovascular responses during thyroid surgery.\(^10\) Brewster et al.\(^9\) showed that injection of procaine into the epidural space in hyperthyroid dogs reduced the elevated oxygen consumption, heart rate, cardiac output, and blood pressure to control levels. In the treated animals, infusion of epinephrine and norepinephrine restored the hyperthyroid state. They assumed that the procaine had blocked spinal autonomic outflow and concluded that there is an augmentation of the physiologic actions of epinephrine and norepinephrine in thyrotoxicosis.

The advent of newer drugs that inhibit sympathetic adrenergic functions, has prompted their clinical trial in thyrotoxicosis. Reserpine decreases pulse, blood pressure, basal metabolic rate, and stare in patients with thyrotoxicosis.\(^11\) In normal volunteers made hyperthyroid by the administration of triiodothyronine, Gaffney and co-workers\(^12\) reported that oral guanethidine reduced the tachycardia, basal metabolic rate, systolic blood pressure, and tremor without affecting serum cholesterol or weight loss. Similar effects have been observed by others in spontaneous thyrotoxicosis.\(^13\)

Hemodynamic data describing the effect of catecholamine depletion in spontaneous hyperthyroidism in man are scant. DeGroot et al.\(^14\) administered reserpine or guanethidine orally to thyrotoxic patients and found no significant change in basal metabolism or cardiac output although heart rate decreased. The present study was designed to evaluate the effect of parenteral guanethidine on cardiovascular functions in patients with previously untreated thyrotoxicosis. The data show that after the administration of large doses of guanethidine intramuscularly, the elevated heart rate, blood pressure, cardiac output, and cardiac work return toward normal. Although the cardiovascular responses to exercise were reduced after this therapy, the effects of exercise were qualitatively similar to those observed prior to treatment.

Materials and Methods

Nine patients with previously untreated thyrotoxicosis were admitted to a metabolic ward and maintained on an isocaloric diet. The diagnosis of hyperthyroidism was initially made on clinical grounds and was substantiated by elevation of the basal metabolic rate, increased uptake of orally administered tracer doses of \(^1\)^\(^3\)I, and increased serum protein-bound iodine (table 1). Seven of the patients had no evidence of heart
Table 1

Clinical Data in Nine Patients with Thyrotoxicosis Receiving Parenteral Guanethidine

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age, years</th>
<th>Sex</th>
<th>Duration of symptoms, mos.</th>
<th>Parenteral Guanethidine Dose, mg./Kg.</th>
<th>Duration, hrs.</th>
<th>24-hr. % thyroid uptake, per cent</th>
<th>Serum protein-bound iodine, µgm./ml.</th>
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</thead>
<tbody>
<tr>
<td>Lu</td>
<td>41</td>
<td>M</td>
<td>3</td>
<td>1.0</td>
<td>48</td>
<td>87</td>
<td>16.0</td>
</tr>
<tr>
<td>Cu</td>
<td>45</td>
<td>F</td>
<td>12</td>
<td>1.8</td>
<td>48</td>
<td>82</td>
<td>16.8</td>
</tr>
<tr>
<td>Ci</td>
<td>30</td>
<td>F</td>
<td>24</td>
<td>1.2</td>
<td>24</td>
<td>78</td>
<td>30.4</td>
</tr>
<tr>
<td>Fe</td>
<td>39</td>
<td>M</td>
<td>5</td>
<td>1.8</td>
<td>48</td>
<td>83</td>
<td>14.2</td>
</tr>
<tr>
<td>Ma</td>
<td>29</td>
<td>M</td>
<td>12</td>
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<td>48</td>
<td>87</td>
<td>22.2</td>
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<tr>
<td>Fi</td>
<td>47</td>
<td>F</td>
<td>12</td>
<td>1.4</td>
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<td>93</td>
<td>15.0</td>
</tr>
<tr>
<td>Ha*</td>
<td>65</td>
<td>F</td>
<td>6</td>
<td>0.9</td>
<td>48</td>
<td>99</td>
<td>14.4</td>
</tr>
<tr>
<td>Co</td>
<td>35</td>
<td>F</td>
<td>4</td>
<td>0.7</td>
<td>24</td>
<td>81</td>
<td>16.4</td>
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<tr>
<td>Ga†</td>
<td>32</td>
<td>F</td>
<td>1</td>
<td>0.7</td>
<td>24</td>
<td>79</td>
<td>12.4</td>
</tr>
</tbody>
</table>

*Arteriosclerotic heart disease with angina.
†Rheumatic heart disease, mitral stenosis, atrial fibrillation, digitalis therapy.

disease. One patient had arteriosclerotic heart disease. One patient had rheumatic heart disease with mitral stenosis and was maintained on 0.2 mg. of digitoxin daily. During a control period of 3 to 5 days, the patients adjusted to the ward routine and became familiar with the laboratory procedures and personnel. Oxygen uptake was measured daily before breakfast throughout the period of study with a 9-liter Benedict-Roth spirometer. No antithyroid or sedative medication was given at any time during the study.

After an overnight fast, hemodynamic studies were performed. Following local anesthesia with procaine hydrochloride, polyethylene no. 160 catheters were placed in the left median arm vein and in the right brachial artery by the Seldinger technic. The distal end of the venous catheter was advanced into the innominate vein. Catheters of identical length were used for repeat studies in the same patient. Arterial pressure was measured with a Statham transducer. Venous pressure was measured with a saline-filled, calibrated, glass tube. Manometric zero was the estimated level of the tricuspid valve in the horizontal plane.

Cardiac output was measured by the indicator-dilution technic. After injection of indocyanine green from a calibrated cuvette, arterial blood was withdrawn at a constant rate of 38 ml./min. through a Waters 300A densitometer. Indicator-dilution curves were inscribed on a Texas Instrument recorder. Calibration of the densitometer was accomplished by passing arterial blood containing known concentrations of green dye through the densitometer at the rate used for arterial sampling. Cardiac output and central volume were calculated from the formulas of Stewart and Hamilton, after the curves had been replotted on semilogarithmic paper.

Indicator-dilution measurements that did not include a calibration curve containing four points on a straight line were discarded. Resting cardiac output was measured in duplicate. In 18 paired determinations from the nine patients, the average cardiac output was 7.50 L./min., with an average variation from the mean of the pairs of ±180 ml. The average per cent variation from the mean of the pairs was ±2.07 per cent with a standard deviation of 1.25 per cent.

Measurements were obtained at rest and during exercise. The exercise was standardized, bicycling motion of the legs at a rate of 60 to 70 per minute performed while the patient was supine. The rate and the range of leg excursion were kept constant. Venous and arterial pressure, heart rate, oxygen consumption, and cardiac output were obtained between the third and fifth minute of exercise. The product of arterial pressure and systolic ejection time, equivalent to the tension time index, also termed pressure time per minute (PTM), was calculated as: PTM = MSP \times LVET \times HR in mm. Hg in which MSP is mean systolic pressure in mm. Hg, LVET is left ventricular ejection time in seconds, and HR is heart rate in beats per minute. Duration of left ventricular systole and mean systolic pressure were obtained from the brachial arterial pressure tracing. Because the dicrotic notch was frequently poorly defined on the brachial arterial pressure pulse during exercise, these data were derived only at rest.

Mean left ventricular external work was calculated as

\[
LV \text{ work} = CI \times 1.055 \times 13.6 \times MSP \times 1000
\]

in Kg. M./min./M.² in which CI is cardiac index in L./min./M.² and MSP is mean systolic arterial pressure in mm. Hg. The mean rate of left ventricular ejection was calculated

\[
MRLVE = \frac{SI}{LVET}
\]

in ml./sec./M.² in which SI is stroke index in

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Table 2
Cardiodynamic Data before and after Guanethidine in Nine Patients with Thyrotoxicosis

<table>
<thead>
<tr>
<th>Patient</th>
<th>Oxygen consumption, ml O2/min./M^2</th>
<th>Heart rate, beats/min.</th>
<th>Cardiac index, L./min./M^2</th>
<th>Stroke volume, ml./M^2</th>
<th>Arterial pressure, systolic/diastolic, mm. Hg</th>
<th>Peripher. resistance, Dynes sec. cm.^-5</th>
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<tr>
<td></td>
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<td>Before/After</td>
<td>Before/After</td>
<td>Before/After</td>
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<td></td>
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<td></td>
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<tr>
<td>Lu</td>
<td>Rest 225/221</td>
<td>104/67</td>
<td>5.8/4.0</td>
<td>55/59</td>
<td>132/68, 76</td>
<td>121/56, 74</td>
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<tr>
<td></td>
<td>Ex. 649/535</td>
<td>126/84</td>
<td>7.8/5.0</td>
<td>36/59</td>
<td>177/82, 112</td>
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<td>Rest 311/234</td>
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<td>Rest 226/232</td>
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<td>111***/78***</td>
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<td>51/54</td>
<td>147*/69**, 91**</td>
<td>131*/56**, 76*</td>
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</table>

Note: Statistical data presented for group I only. Heterogeneous makeup and small sample preclude statistical evaluation of group II.
*P < 0.05
**P < 0.01
***P < 0.001
Table 3

Indices of Left Ventricular Function, at Rest, and before and after Guanethidine in Nine Patients with Thyrotoxicosis

<table>
<thead>
<tr>
<th></th>
<th>Ejection time, sec.</th>
<th>Mean rate ventricular ejection, ml./sec./M.²</th>
<th>Pressure time, mm. Hg</th>
<th>Ventricular work, Kg. M/min./M.²</th>
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<td>After</td>
<td>Before</td>
<td>After</td>
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<tr>
<td>Lu</td>
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<td>0.29</td>
<td>230</td>
<td>200</td>
</tr>
<tr>
<td>Cu</td>
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<td>0.28</td>
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<td>Ci</td>
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<td>Ma</td>
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<td>Ha</td>
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<td>0.25</td>
<td>180</td>
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<tr>
<td>Co</td>
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<td>0.24</td>
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<td>0.26</td>
<td>194</td>
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</table>

Note: See footnote table 2.

*P < 0.05

**P < 0.025

***P < 0.001

ml./M.² and LVET is left ventricular ejection time in seconds.

Results

Clinical data and the dose of parenteral guanethidine for nine patients with previously untreated thyrotoxicosis are recorded in table 1. For purposes of analysis the patients have been divided into two groups. Group I comprises six patients who received 1.0 mg./Kg. or more of guanethidine (total patient dose ranged from 60 to 147 mg.) between the first and second tests. Group II comprises the three patients who received less than 1.0 mg./Kg. of guanethidine (patient total dose ranged from 35 to 42 mg.) before the second set of measurements. All patients in Group I but one (Ma) developed postural hypotension after guanethidine administration prior to the second set of measurements. None of the patients in group II developed postural hypotension. Data obtained before and after guanethidine are presented in tables 2 and 3.

Group I. Data during Rest

Resting oxygen consumption obtained at the time of the cardiovascular measurements, was not significantly different from the control values after guanethidine administration, averaging 218 ml./min./M.² before and 241 ml./min./M.² after therapy. Daily oxygen consumptions showed considerable individual variability, but no trend was apparent either before or after therapy.

Heart rate fell significantly, averaging 111 beats/min. before and 78 beats/min. after guanethidine (p < 0.001) (fig. 1).

Mean, systolic, and diastolic brachial arterial pressures fell significantly with administration of guanethidine, averaging 91 and 147/69 mm. Hg before, and 76 and 131/56 mm. Hg after therapy (p < 0.05 for systolic and mean, p < 0.01 for diastolic pressures).

The average cardiac index decreased significantly from a value of 5.8 L./min./M.² before to 4.2 L./min./M.² after guanethidine (p < 0.001). Mean stroke volume index rose slightly from 51 ml./beat/M.² to 54 ml./beat/M.², but the difference between the means was not statistically significant.

Calculated peripheral resistance tended to rise as the blood pressure fell after guane-
Guanethidine therapy. Mean resistance rose from 800 to 910 dynes sec. but the difference between the means was not significant.

Mean venous pressure rose from 45 to 58 mm. of saline. Mean "central" volume decreased from 2,100 to 1,800 ml. The changes in venous pressure and central volume were not significant.

Several indirect indices of left ventricular function were calculated (table 3). Guanethidine administration was associated with a fall in average left ventricular work from 7.5 to 4.6 Kg. M./min./M.² (p < 0.001). Average left ventricular ejection time lengthened from 0.24 to 0.28 second/beat (p < 0.05). Average mean left ventricular ejection rate did not change significantly after guanethidine therapy. The pressure time per minute decreased significantly in all patients, averaging, 52.4 before and 36.3 mm. Hg (p < 0.025).

Group II. Data during Rest

In the three patients receiving a lower dose of guanethidine oxygen consumption, cardiac index, brachial arterial pressure, venous pressure and central volume were essentially unchanged from control values after guanethidine administration. Heart rate, and pressure time per minute were decreased following the drug, whereas stroke volume, ejection time, cardiac work, and mean rate of left ventricular ejection increased. Peripheral resistance fell in two patients and rose in one.

Response to Exercise

Satisfactory data from five patients in group I during exercise before and after guanethidine therapy are available for analysis (table 2).

Before therapy, exercise in the patients with thyrotoxicosis was associated with an increase in oxygen consumption, heart rate, cardiac index, and arterial pressure. Stroke volume and peripheral vascular resistance were essentially unchanged. After guanethidine administration, although resting values were lower, the patients were able to increase oxygen consumption, heart rate, cardiac index, and arterial pressure in response to the demand of exercise. Stroke volume and calculated peripheral vascular resistance remained unchanged.

To evaluate the effect of guanethidine on the cardiovascular responses to exercise, the data are compared in two ways. Both the level of function attained during exercise and the change in function above the resting state are analyzed. When the levels of function are compared, it is apparent that during exercise, following guanethidine, mean heart rate is lower (p < 0.05), mean cardiac index is lower (p < 0.01), mean systolic pressure is...
Changes in cardiodynamics from resting levels during exercise before and after high doses, > 1.0mg/Kg., of guanethidine in six patients with untreated thyrotoxicosis. Resting (fig. 1) and exercise (fig. 2) indices of cardiac function are lower after guanethidine. However, the changes from resting level induced during exercise after the drug are not significantly different from control for each variable shown.

lower (p < 0.01), mean diastolic pressure is lower (p < 0.05), average mean arterial pressure is lower (p < 0.05), and the calculated peripheral vascular resistance is higher (p < 0.05) than under control conditions (table 2, fig. 2).

Comparison of the change in cardiovascular function induced by exercise before and after guanethidine reveals, however, that the differences between the mean change in heart rate, oxygen consumption, cardiac index, diastolic and mean arterial pressure and calculated peripheral vascular resistance from the resting state are not statistically significant (fig. 3). These data suggest that guanethidine does not inhibit a relatively normal qualitative response to exercise in thyrotoxicosis.

Values measured during exercise are lower after treatment because function is at a lower base. The increment above the base induced by the exercise is similar before and after guanethidine (fig. 3).

Satisfactory measurements during exercise were obtained from only one patient in group II (table 2).

Discussion

The cardiovascular alterations found in thyrotoxicosis are strikingly similar to the responses following epinephrine administration. Since adrenergic autonomic blockade inhibits the hemodynamic alterations of hyperthyroidism, it has been postulated that many of the effects of catecholamines are augmented by thyroid hormone. Wurtman et al.8 studied the distribution and metabolism of catecholamines in the heart of hyperthyroid rats. They found that the hypertrophied hearts had a decreased ability to inactivate by binding circulating epinephrine, which is delivered in larger amounts than normal because of the shunting of an increased fraction of the cardiac output to the myocardium. They concluded that the increased sensitivity of the cardiovascular system to epinephrine in thyrotoxicosis was due to increased availability of "free" epinephrine to act on physiologic receptors. Whether this mechanism can be invoked in man is unclear. Rowe et al.9 found an identical fractional increase in both coronary and systemic blood flow in patients with thyrotoxicosis.

The present study has shown that depletion of catecholamines with large doses of guanethidine partially depresses the hyperkinetic circulation in thyrotoxicosis. The elevated heart rate, blood pressure, cardiac output, and cardiac work are reduced by the drug in patients with untreated thyrotoxicosis. These observations are in contrast to the effect of guanethidine on normal subjects, in whom only the pulse rate falls.20 Although the dosage schedules varied between the present study and Kahler's et al.,20 in both studies the drug was given to the point of postural hypotension, suggesting that maximal doses were used.

The depression of the hyperkinetic circulation in thyrotoxicosis by guanethidine is compatible with the thesis that many of the cardiovascular effects of excess thyroid hormone are mediated by catecholamines. Guanethidine is a potent adrenergic blocking agent which selectively blocks the reflex responses to sympathetic stimulation, inhibits the uptake of circulating norepinephrine, enhances the action of injected catecholamines, releases
norepinephrine from bound tissue stores, and causes a slow but continuous release of norepinephrine. The mechanism responsible for the guanethidine response in thyrotoxicosis may be (1) blockade of the effect of tonic sympathetic discharge on the heart, (2) reduction in myocardial catechol content, or (3) reduction of myocardial response to circulating catechols.

Evidence for a relationship between catecholamines and the metabolic effects of thyroid hormone is conflicting. In the present study guanethidine did not reduce significantly the elevated oxygen consumptions. Both similar and opposite results have been reported by others. Bray found that reserpine inhibits the oxygen consumption in vitro in liver but not in myocardium from triiodothyronine-treated rats.

One might postulate a reduction in venous tone (increase in compliance) with venous "pooling" as partial explanation for the fall in cardiac output. Lack of significant change in either "central" volume or venous pressure after administration of guanethidine argues against such a postulation. In descriptive terms, cardiac output fell after high doses of guanethidine because stroke volume remained unchanged despite the sharp decline in heart rate. Although maximally tolerated doses of guanethidine were administered, resting cardiac output and stroke volume remained above normal, but pulse returned to a normal rate.

Heart rate fell in the patients receiving the lower doses of guanethidine although cardiac output did not change. With higher doses cardiac output was reduced. Because the number of patients studied is small, the differences in response must be interpreted with caution. A two-stage effect, depending on dosage, may be postulated. Guanethidine has been shown to block the response to sympathetic stimulation (cardio-accelerator nerve) prior to a reduction in myocardial catechol content. Neither the mechanism of action nor the completeness of the catecholamine depletion can be accurately delineated from the present study.

In normal human subjects, guanethidine impairs the expected increase in cardiac output, arterial pressure, and cardiac work during exercise. Despite the high resting values, both cardiac output and heart rate increased during exercise prior to therapy in the patients with thyrotoxicosis. After high doses of guanethidine the resting values were lower, but heart rate and cardiac output still increased during exercise by approximately the same amount as during the control study. These observations suggest that either the depletion or blockade caused by guanethidine was incomplete or that nonadrenergetic factors continued to sustain cardiac hyperfunction both at rest and during exercise.

Guanethidine reduced left ventricular work and the product of mean arterial systolic pressure, ejection time, and heart rate. The latter has been shown to correlate with myocardial oxygen consumption in acute preparations. A reduction in cardiac work and oxygen demand might improve cardiac function in patients with thyrotoxicosis and heart disease. Reversion of atrial fibrillation to sinus rhythm after guanethidine administration has been reported.

In patients severely ill with thyrotoxicosis, catecholamine depletion may provide immediate respite and allow time for standard forms of medical therapy directed toward thyroid hyperfunction itself to become effective. The narrowed arterial-mixed venous oxygen difference in thyrotoxicosis indicates that cardiac output is increased out of proportion to total body metabolic needs. However, splanchnic arteriovenous oxygen difference widens in thyrotoxicosis despite an increased splanchnic blood flow which is not sufficient to meet the increased oxygen demand. Central necrosis of the liver, a sign of hepatic circulatory insufficiency, has been reported in patients dying from thyroid storm.

Guanethidine has been reported to reduce the fraction of systemic blood flow perfusing the splanchnic bed in hypertensive subjects. It is possible that in thyrotoxicosis guanethidine may reduce blood flow to certain vascular beds out of proportion to any change in oxygen demand. Since such an imbalance
may have adverse effects, we suggest that sympathetic blockade be utilized in thyrotoxicosis with caution.

Summary and Conclusions

The effect of catecholamine depletion on cardiovascular dynamics has been studied in nine patients with untreated thyrotoxicosis. Measurements were made at rest and during exercise before and after large doses of parenteral guanethidine. Six patients received maximally tolerated doses of guanethidine (1.0 mg./Kg. or more). Three patients received lesser amounts.

In the patients receiving the higher doses, heart rate, cardiac index, arterial pressure, left ventricular ejection time, left ventricular pressure time per minute, and left ventricular work were significantly reduced, from 16 to 39 per cent, at rest after guanethidine. The elevated oxygen consumption was not significantly changed. Despite maximally tolerated doses of guanethidine, cardiac index and stroke volume remained above normal, suggesting that either catecholamine depletion or blockade was incomplete or that nonadrenergic factors continued to maintain a hyperkinetic circulatory state.

In the patients receiving the lower dose of guanethidine heart rate fell, but cardiac index was not changed.

During exercise cardiovascular response was significantly lower in the patients receiving the higher doses of guanethidine than control for heart rate, cardiac index and arterial pressure; peripheral vascular resistance was higher. However, the resting values after drug therapy were lower, and the changes from baseline resting cardiac function induced by exercise were similar before and after guanethidine. Hence catecholamine depletion did not inhibit a relatively normal qualitative response to supine exercise in thyrotoxicosis.

The reduction of left ventricular work and pressure time by guanethidine suggests that the drug may be useful as a short-term aid in the occasional patient with severe heart failure and thyrotoxicosis. A note of caution is sounded, however, since it is possible that guanethidine may reduce blood flow to some vascular beds out of proportion to change in oxygen demand.

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GUANETHIDINE IN THYROTOXICOSIS

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The History of Science

They that know the entire course of the development of science will, as a matter of course, judge more freely and more correctly of the significance of any present scientific movement than they, who limited in their views to the age in which their own lives have been spent, contemplate merely the momentary trend that the course of intellectual events takes at the present moment.—Ernst Mach in Science of Mechanics.
Catecholamine Depletion in Thyrotoxicosis: Effect of Guanethidine on Cardiovascular Dynamics

SIDNEY GOLDSTEIN and THOMAS KILLIP III

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