Studies on Tolerance to Ganglionic Blocking Agents in Man
Reversal of Depressor Action of Quaternary Ammonium Compounds

By A. S. DONTAS, M.D., and S. W. HOOBLER, M.D.

The hypotensive effects of intravenous injections of tetraethylammonium and hexamethonium chloride diminish and finally become pressor during the course of short-term treatment with subcutaneous hexamethonium. Evidence is presented to indicate that this “tolerance” is associated with a decreased sympathetic tone in the feet and forearm and is not due to increased amounts of circulating adrenal medullary or cortical hormones. Possibilities are discussed for this apparent vascular autonomy and the locus of vasoconstriction. Cross tolerance appeared between several ganglionic blocking agents tested and extended to a minor degree to adrenergic blocking agents.

ONE of the main disadvantages of ganglionic blocking agents in the treatment of hypertension is the development of “tolerance.” The present study seeks to identify the mechanisms and vascular areas involved in this phenomenon and also in the development of cross tolerance between several different ganglionic blocking agents.

METHOD

Twelve patients, with moderate to severe essential hypertension, were studied in the Cardiovascular Unit of the University of Michigan Hospital for a period of 10 to 15 days, prior to, during and after a short period of treatment with parenteral hexamethonium. Of the twelve, three (A.P.,* H.T., J.P.) had been submitted to bilateral supradiaphragmatic splanchnicectomy, three months to six years previously, and one (E.B.) had a dorsal subthoracic sympathectomy three years previously and an additional extension of the original operation 12 months before the study. Their renal status was variable, but at the time of the study, only two (L.G.* and M.P.) had elevated serum creatinine or nonprotein nitrogen levels, while the others were definitely within normal limits. The patients were kept on a low sodium diet and remained ambulatory in the ward during their treatment with hexamethonium. The daily dose was usually constant for each patient for the period of observation and varied between 30 and 100 mg. per day, given subcutaneously in four equal doses every six hours. In six of the patients, foot and forearm blood flows were measured by venous occlusion plethysmography in a temperature-controlled room (70 to 74 F.) with a collecting cuff pressure of 80 mm. Hg. In no case did collecting pressure exceed diastolic pressure. After the subject had rested, three series of blood flow determinations at five-minute intervals were performed, each series consisting of five observations made at 20-second intervals. After drug injections, blood flows were determined in successive series of five observations every 20 seconds until a maximum had been reached. The average of three control series was designated as the “resting” blood flow and of five consecutive determinations at the time of maximum increase as average “maximum” blood flow for the respective area.

The effects of intravenous injections of 50 to 300 mg. of tetraethylammonium chloride (TEAC) and 7 to 30 mg. hexamethonium chloride (C-6) given about 45 minutes later were studied at frequent intervals before, during and for one or two days after the treatment. The injections were given two to four hours after the therapeutic subcutaneous hexamethonium injection on the ward.

RESULTS

A. Effects on Blood Pressure

Injection of tetraethylammonium chloride in all our patients prior to therapy by hexa-
methonium (see fig. 1) had the following effects: (1) A rapid initial rise in blood pressure, mainly systolic, developed. This lasted about 30 seconds and was associated with the well-known disagreeable tingling sensations. At the same time, the heart rate usually showed a slight increase. The peripheral vasodilatation, as measured by plethysmography, was already obvious at this stage. (2) A subsequent hypotensive response to tetraethylammonium chloride occurred. This was usually accompanied by subsidence of the initial disagreeable feelings and only a sensation of "cold" over the entire body persisted somewhat longer. The heart rate at this stage had returned to or slightly below the preinjection levels, although in occasional patients showing marked blood pressure drops there was a moderate tachycardia, as evidence of the incomplete blockade of the cardiac ganglia. Peripheral vasodilatation reached its peak during this stage, the foot and forearm resistance being reduced to one-third to one-fifth of the original values. (3) A phase during which blood pressure returned to the control levels, and the peripheral vasodilatation receded partially, lasted from 20 to 30 minutes. It was apparent that blood pressure-compensating mechanisms preceded the recovery of vasoconstrictor tone in the foot and forearm.

The main differences between the actions of tetraethylammonium chloride and those of the other ganglionic blocking agents tested (hexamethonium, pendiomide, and the trivalent ganglionic blocking agent SU-1194*) were the following: The initial blood pressure rise was missing, as were the sensations of cold and pricking with these latter drugs, and an agreeable feeling of general warmth was noted. The heart rate remained the same or decreased (especially with SU-1194), even during the initial sharp drop in blood pressure; the hypotension and peripheral vasodilatation were longer lasting and some differences in the loci of maximal response were occasionally observed. Figure 1 shows the difference in the forearm responses to tetraethylammonium chloride and hexamethonium, in a case where the foot increases were qualitatively similar.

When the injections of tetraethylammonium chloride were repeated on consecutive days

* We would like to express our thanks to Dr. F. F. Yonkman, Ciba Pharmaceutical Products, Inc., for the supply of this agent.
after therapy with hexamethonium had started, 
the following changes were observed: The 
initial rise remained the same, but the tran-
sition toward the hypotensive phase became less 
and less abrupt. Simultaneously, the maximum 
blood pressure drop became less and its dura-
tion shorter. In 11 of the 12 patients studied, 
a point was eventually reached where no blood 
pressure drop after the tetraethylammonium 
chloride injection occurred, while the initial 
rise now lasted occasionally as long as 10 
minutes. The subjective feelings in response 
to the injection of tetraethylammonium chlor-
ide were never altered. We defined as "com-
plete tolerance" the period when the hypo-
tensive response in the supine position was 
entirely missing. Resting recumbent blood 
pressures, as can be seen from tables 1 and 2, 
usually fell somewhat during treatment with 
hexamethonium and then gradually rose as 
"tolerance" developed. The mean control blood 
pressure of our six patients studied by plethys-
mography was 171.6 ± 6.2 and had dropped 
to 154 ± 5.7 at the time of tetraethylam-
monium chloride reversals; the pressor re-
sponses to tetraethylammonium chloride and 
hexamethonium did not seem to bear any rela-
tion to the resting supine blood pressures, oc-
curring at lower as well as occasionally at 
higher than the pretreatment levels. During 
this entire period, cold pressor responses were 
only moderately depressed, as further evidence 
of partial ganglionic blockade.

The other drugs were tested more rarely, 
usually not more than once or twice weekly. 
Hexamethonium given intravenously at the 
height of "tolerance" also exerted pressor 
effects in the majority of cases, while in the 
rest it was devoid of any depressor action. 
However, the rise occurred slowly and the 
decline also was delayed, occasionally lasting 
up to 30 minutes. In one instance, up to 60 mg. 
of hexamethonium given in infusion did not 
overcome the slow blood pressure rise. Pendio-
mide (30 mg.) also caused a reversal to a pressor 
response occurring simultaneously with the 
reversal to tetraethylammonium chloride. The 
onset and offset of effect were rapid, resembling 
those observed after tetraethylammonium chlo-
ride. The tertiary ganglionic blocking agent 
SU-1194 showed a considerable difference in 
the two patients tested. Refractoriness to its 
depressor action appeared much later than that 
to tetraethylammonium chloride, responses to 
it being quantitatively equal at a time when 
the "TEA-floor" had risen considerably. How-
ever, after complete "tolerance" to tetraethyl-
ammonium chloride had been reached for some 
days, the depressor action of SU-1194 gradually 
lessened, and one patient became completely 
tolerant to it (table 3). In our limited ex-
perience with this agent, we have not seen 
pressor responses following its injection.

B. Effects on Blood Flow

As mentioned above, in six of our patients 
we studied the changes in peripheral blood 
flow through a muscular (forearm) and a less 
muscular (foot) area after injection of the same 
amounts of tetraethylammonium chloride and 
hexamethonium chloride before, during and 
after the period of development of tolerance. 
The resting blood flows of both foot and fore-
arm did not present definite changes compared 
with those obtained during the pretreatment 
test (fig. 2). It is obvious, therefore, when the 
drug is given every six hours subcutaneously, 
that repeated vasodilations such as are 
demonstrated in figure 1 do not persist, at 
least with the small doses used in this study. 
In the majority of our cases the large drop in 
foot resistance following the injection of tetra-
ethylammonium chloride observed before treat-
ment, is lessened after tolerance has developed; 
the mean drop in foot resistance being 56.5 
per cent before and 38.3 per cent during tol-
erance (table 1). The mean forearm resistance, 
though showing more scatter, is also converted 
from a 36.4 per cent drop to a 2.8 per cent rise 
during tolerance, which difference is close to 
statistical significance (p = 0.06). It must be 
stressed that the lessened decreases in resis-
tance are largely a result of the failure to 
produce a drop in blood pressure during "toler-
ance," while increases in blood flow still oc-
curred, although to a somewhat lesser degree. 
Similar changes were observed in the response 
of foot and forearm circulations to intravenous 
hexamethonium administration (table 2). The 
lessened drop of foot resistance (−59.0 per
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Fig. 2. Hemodynamic effects of intravenous injection of tetraethylammonium chloride and hexamethonium during tolerance to hexamethonium. Patient is the same as in figure 1, after five days of treatment with hexamethonium.

Table 1.—Responses of Blood Pressure and Extremital Circulation to Intravenous Tetraethylammonium Chloride before, during and after Tolerance to Ganglionic Blockade by Hexamethonium

<table>
<thead>
<tr>
<th>Test Dose mg</th>
<th>Mean Blood Pressure</th>
<th>% Change in Mean Blood Pressure</th>
<th>% Change in Foot Resistance</th>
<th>% Change in Forearm Resistance</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Before</td>
<td>During</td>
<td>After</td>
<td>Before</td>
</tr>
<tr>
<td>M. P. 300</td>
<td>168.5</td>
<td>150.0</td>
<td>155.7</td>
<td>-15.4</td>
</tr>
<tr>
<td>C. C. 300</td>
<td>165.5</td>
<td>154.0</td>
<td>188.5</td>
<td>-9.4</td>
</tr>
<tr>
<td>M. V. 300</td>
<td>178.0</td>
<td>178.0</td>
<td>160.5</td>
<td>-10.4</td>
</tr>
<tr>
<td>H. T. 300</td>
<td>169.5</td>
<td>141.5</td>
<td>149.0</td>
<td>-26.8</td>
</tr>
<tr>
<td>E. B. 300</td>
<td>197.0</td>
<td>141.5</td>
<td>201.0</td>
<td>-13.2</td>
</tr>
<tr>
<td>J. P. 250</td>
<td>151.0</td>
<td>162.0</td>
<td>167.0</td>
<td>-6.0</td>
</tr>
</tbody>
</table>

Mean blood pressure is calculated as systolic + diastolic / 2.

Resistance calculated as mean blood pressure / blood flow in ml./100 ml. of limb vol./min.

S.E., standard error of the mean.

Mean blood pressure is calculated as systolic + diastolic / 2.

Resistance calculated as mean blood pressure / blood flow in ml./100 ml. of limb vol./min.

cent to -21.8 per cent respectively) and especially the clear conversion to vasoconstriction in the forearm (from a mean of -53.4 per cent to +23.8 per cent, which is statistically significant) are also obvious. An interesting comparison is that between the blood pressure changes induced by these drugs and the resistance changes of the regional circulations studied. Although the mean hypotensive responses to both tetraethylammonium chloride and hexamethonium were approximately equal, the drop in forearm resistance induced by tetraethylammonium chloride in the pre-"tolerant" stage was much less than that in-
TABLE 2.—Responses of Blood Pressure and Extremital Circulation to Intravenous Hexamethonium before, during and after Tolerance to Ganglionic Blockade by Hexamethonium

<table>
<thead>
<tr>
<th>Test Dose mg.</th>
<th>Mean Resting Blood Pressure</th>
<th>% Change in Mean Blood Pressure</th>
<th>% Change in Foot Resistance</th>
<th>% Change in Forearm Resistance</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Before</td>
<td>During</td>
<td>After</td>
<td>Before</td>
</tr>
<tr>
<td>M. P.</td>
<td>15</td>
<td>168.5</td>
<td>150.0</td>
<td>—</td>
</tr>
<tr>
<td>C. C.</td>
<td>15</td>
<td>165.5</td>
<td>154.0</td>
<td>183.0</td>
</tr>
<tr>
<td>M. V.</td>
<td>36</td>
<td>160.0</td>
<td>178.0</td>
<td>165.0</td>
</tr>
<tr>
<td>H. T.</td>
<td>15</td>
<td>166.0</td>
<td>141.5</td>
<td>143.5</td>
</tr>
<tr>
<td>E. B.</td>
<td>15</td>
<td>183.0</td>
<td>141.5</td>
<td>182.0</td>
</tr>
<tr>
<td>J. P.</td>
<td>7.5</td>
<td>—</td>
<td>168.0</td>
<td>172.0</td>
</tr>
<tr>
<td>Mean S.E.</td>
<td>168.5</td>
<td>155.5</td>
<td>169.1</td>
<td>±3.8</td>
</tr>
</tbody>
</table>

The marked initial reduction of foot resistance with both substances still occurred with tetraethylammonium chloride during "tolerance," while the hexamethonium effect was much weaker.

C. Studies Concerning the Mechanism of Tolerance

I. Adrenergic Factors. It has been shown that strong doses of tetraethylammonium chloride may release epinephrine from the adrenals by direct stimulation, and this property has been used as a diagnostic test in pheochromocytoma. We therefore investigated the possibility that, in our patients, rising amounts of circulating adrenergic substances might not only be responsible for maintaining the basal resting blood pressure during tolerance, but their acute release might explain the blood pressure rises occurring after tetraethylammonium chloride and hexamethonium, given intravenously in the "tolerant" state.

The areas of vasoconstriction, however, are different. In figure 3, obtained from patient E.B. during tolerance to hexamethonium, the blood pressure rise following 5 micrograms of norepinephrine equals that of 300 mg. of tetraethylammonium chloride. Norepinephrine, however, acts almost entirely on the foot circulation while tetraethylammonium chloride does not change appreciably the flow in either foot or forearm. The reflex bradycardia with norepinephrine is also missing with tetraethylammonium chloride. Repeated experiments on two of our patients (M.P. and J.P.) with the adrenergic blocking agent Dibenzyline brought further evidence that epinephrine is very probably not the cause of the recurrent hypertension during tolerance, since both patients did not show the sharp decline in blood pressure...
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### Table 3.—Hypotensive Action of Drugs before and after Development of "Tolerance" to Hexamethonium

<table>
<thead>
<tr>
<th>Patient</th>
<th>Drug</th>
<th>Blood Pressure (mm. Hg) Before &quot;Tolerance&quot;</th>
<th>Blood Pressure (mm. Hg) After &quot;Tolerance&quot;</th>
<th>Max. Response to Drug (mm. Hg) Before</th>
<th>Max. Response to Drug (mm. Hg) After</th>
<th>Max. Change after TEA Before</th>
<th>Max. Change after TEA After</th>
</tr>
</thead>
<tbody>
<tr>
<td>M. P.</td>
<td>Dibenzyline 1 mg./Kg. i.v.</td>
<td>198/114</td>
<td>193/107</td>
<td>-18/-8</td>
<td>0/+6</td>
<td>-30/-18</td>
<td>+21/+13</td>
</tr>
<tr>
<td>J. P.</td>
<td>Dibenzyline 1 mg./Kg. i.v.</td>
<td>193/120</td>
<td>180/124</td>
<td>-13/-22</td>
<td>+10/+4</td>
<td>-58/-38</td>
<td>-12/-2</td>
</tr>
<tr>
<td>G. F.</td>
<td>Regitine 10 mg. i.v.</td>
<td>185/120</td>
<td>182/118</td>
<td>-12/-14</td>
<td>-8/-4</td>
<td>-42/-17</td>
<td>0/+3</td>
</tr>
<tr>
<td>E. B.</td>
<td>Regitine 5 mg. i.v.</td>
<td>198/140</td>
<td>205/150</td>
<td>-8/-16</td>
<td>-9/-12</td>
<td>-44/-21</td>
<td>+24/+15</td>
</tr>
<tr>
<td>G. F.</td>
<td>SU 1194 250 mg. i.v.</td>
<td>196/134</td>
<td>190/114</td>
<td>-39/-24</td>
<td>-24/-10</td>
<td>-46/-16</td>
<td>-5/0</td>
</tr>
<tr>
<td>S. C.</td>
<td>SU 1194 150 mg. i.v.</td>
<td>240/120</td>
<td>204/115</td>
<td>-70/-8</td>
<td>0/-3</td>
<td>-82/-10</td>
<td>0/+2</td>
</tr>
<tr>
<td>S. C.</td>
<td>Histamine 0.025 mg. i.v.</td>
<td>202/122</td>
<td>212/122</td>
<td>-54/-22</td>
<td>-84/-44</td>
<td>-24/-16</td>
<td>0/+2</td>
</tr>
<tr>
<td>G. F.</td>
<td>Protoveratrine 0.1 mg. i.v.</td>
<td>200/126</td>
<td>188/120</td>
<td>-55/-35</td>
<td>-44/-24</td>
<td>-48/-17</td>
<td>-22/-4</td>
</tr>
</tbody>
</table>

Before-“Tolerance” blood pressures represent the usual readings. Responses to tetraethylammonium chloride before and after “tolerance” refer to the test performed nearest to the time of administration of the drug in question and usually within 12 hours. Dose of tetraethylammonium chloride given intravenously was variable but the same for any one patient.

**Fig. 4.** Nontolerant patient. Hemodynamic effects of tetraethylammonium chloride before and after Dibenzyline infusion.
usually associated with this drug when hypertension is due to adrenergic substances (table 3). Moreover, the acute rise in pressure after tetraethylammonium chloride is also not due to epinephrine release, since it cannot be prevented by prior infusion with Dibenzyline (fig. 4). Similar results were obtained with the less specific adrenergic blocking agent, Regitine, an imidazoline derivative, tried repeatedly in two other patients (table 3). With this agent, the blood pressure decreases following tolerance were considerably reduced more or less in parallel with reductions in the response to tetraethylammonium chloride. These experiments suggest that epinephrine is not present in increased amounts in the blood in the tolerant state.

II. Vascular Reactivity. Direct vasodilators, such as histamine, were still active during the refractory state, indicating that reactivity of the vascular wall is not diminished during tolerance (table 3).

III. Adrenocortical Mechanisms. Although direct measurements of the output of 17-ketosteroids were not done, three of our patients, who became completely or partially tolerant to hexamethonium treatment, showed either no decrease or a mild rise in total circulating eosinophils during their treatment; body weight of our patients also showed a downward trend, as they were on a low sodium diet.

Discussion

I. Explanation of the Conversion of the Acute Depressor Effect of Tetraethylammonium Chloride to a Pressor One

The pressor action of tetraethylammonium chloride has been ascribed to adrenaline release, but its persistence in our experiments after Dibenzyline makes this explanation unlikely.

Another possibility would be the activation of pressor pathways not blocked by tetraethylammonium chloride, such as the ones described by Freyburger and co-workers in the dog. The afferent limb of this reflex arc might rise from aortic and carotid chemoreceptors which can be stimulated by tetraethylammonium chloride and hexamethonium under partial blockade. Such chemoreceptor stimulation would then increase blood pressure through channels which might not be vulnerable to ganglionic blocking agents.

A final possibility, which we favor, is that tetraethylammonium chloride is directly vasoconstrictor, in the concentration momentarily reached following an initial injection. A number of authors have reported acute vasoconstrictor effects of tetraethylammonium chloride on local vascular beds. We believe that when sympathetic vasomotor tone is inhibited, the vasodilator and depressor component of the action of tetraethylammonium chloride is absent, while the vasoconstrictor effect remains and hence the blood pressure rises. If sympathetic tone is suppressed, the drug becomes pressor as after multiple injections in the dog, after corticotropin (ACTH) administration, and after total sympathectomy in man. Such an action would explain the initial blood pressure rises that frequently precede the depressor phase when tetraethylammonium chloride is rapidly injected intravenously. The pressor effect of hexamethonium in our experiments may possibly have the same explanation, although it is said not to have a local vasoconstrictor action in animals. The irregularity and delay in appearance of pressor effects in the tolerant state makes this clinical observation less certain than those involving tetraethylammonium chloride. We believe that the vasoconstrictor effects are not the indirect result of ganglionic blockade (e.g. differential blockade of vasodilators) in a tolerant patient, but are more likely a side effect peculiar to tetraethylammonium chloride itself, like paresthesias and other signs of excitation of peripheral structures which do not occur with other acutely acting ganglioplegic drugs.

II. Explanation of the Mechanism of “Tolerance” to Hexamethonium

It seems certain that establishment of “tolerance” to ganglionic blocking agents is not, as in the case of many other drugs, due to increased efficiency of inactivation, since they are not destroyed or inactivated in the body. Renal excretion is probably not intensified.
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Furthermore, during hexamethonium treatment, "tolerance" to parasympathetic blocking effects on the pupil, gut or salivary secretion does not appear, according to the observations of Morrison. The development of "tolerance" to adrenergic blocking drugs has also been reported with Dibenzyline.

In our experiments "tolerance" has been demonstrated not to be associated with total cessation of sympathetic activity, since foot vasodilatation still followed acute injections of ganglionic blocking agents. In the muscular areas and possibly elsewhere, sympathetic vasmotor tone is apparently considerably reduced; if we can judge by forearm blood flow measurements before and during "tolerance," such reduction is not associated with an increase in resting blood flow in the "tolerant" patient. Hence some compensating mechanism has restored the vasoconstriction. Humoral substances such as epinephrine and norepinephrine have been excluded by the failure to note a fall in blood pressure following infusion of Dibenzyline in the tolerant patient (table 3). Adrenocortical activity might compensate although eosinophil counts do not give evidence of increased glucocorticoid excretion during "tolerance." The "cerebral pressor substance" of Taylor and Page might play a role or the natural tendency of the vasculature to resume its "normal" contracted state might explain the restoration of normal muscle flow in the absence of sympathetic tone.

The situation would then resemble that in the totally sympathectomized hypertensive whose blood pressure is restored to high levels by unknown, probably intrinsic, compensations and who then fails to respond with a drop in blood pressure to ganglionic blocking agents. The chemically sympathectomized patient is still responsive to other vasodilators such as histamine and protoveratrine according to our observations, and it may be that with these other drugs, the refractory state may be overcome. In any event the failure of ganglionic blocking drugs to lower supine blood pressure, failures of sympathectomy and local denervations probably have their root in the nature of the compensatory mechanisms involved. It is to be hoped that further study of these reactions will lead to a better understanding of the role of sympathetic tone in hypertensive disease.

Conclusions

1. In man under chronic partial ganglionic blockade with hexamethonium, the usually depressor effects of intravenous tetraethylammonium and hexamethonium chloride in the supine position decrease and later become pressor.

2. During such a blockade, the resting foot and forearm blood flows, as studied in six cases, are not appreciably higher than the control values; the test injections elicit definite but less prominent increases in foot blood flow, indicating persistence of sympathetic tone to this area; the forearm blood flow response is considerably reduced, and increases in forearm flow are frequently observed, especially with hexamethonium.

3. Reasons are given for suggesting that the pressor action of tetraethylammonium chloride is a result of its direct vasoconstrictor action in the absence of a concomitant depressor effect.

4. Evidence is presented for exclusion of increases of sympathoadrenal and cortical hormones as the mechanism of tolerance, and other possibilities are discussed.

5. Cross tolerance developed between the various quaternary and tertiary-N ganglionic blocking agents studied (tetraethylammonium chloride, hexamethonium, pendiomide, SU-1194) and extended to a minor degree also to the adrenergic blocking agents Regitine and Dibenzyline.

SUMARIO ESPAÑOL

1. En el hombre sujeto a un bloqueo ganglionar crónico parcial con hexamethonium, los efectos usualmente depresores del cloruro de tetraetilamonio intravenoso y hexamethonium en la posición recostada disminuyen y luego se tornan en presores.

2. Durante tal bloqueo, la circulación del pie descansado y el antebrazo, según estudios en seis casos, no son apreciablemente más altos que los valores controles; las inyecciones de prueba produjeron aumentos definitivos pero menos prominentes en la circulación del pie,
indicando persistencia de tono simpático a esta área; la repuesta de la circulación del antebrazo estuvo considerablemente reducida y aumentos en el antebrazo fueron frecuentemente observados, especialmente con hexamethonium.

3. Se dan razones sugiriendo que la acción presora del cloruro de tetraetilamonio es un resultado directo de su acción vasoconstrictora en la ausencia de un efecto depresor concomitante.

4. Se presenta evidencia para excluir aumentos de hormonas simpatoadrenales y corticales como un mecanismo de tolerancia y otras posibilidades se discuten.

5. Tolerancia cruzada se desarrolló entre los varios agentes cuaternarios y terciarios-N bloqueadores gangliónicos estudiados (cloruro de tetraetiloamón, hexamethonium, penidio-mide, Su-1194) y se extendió en grado menor también a los agentes bloqueadores adrenérgicos Regitine y Dibenzyline.

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5 Donatas, A. S.: unpublished observations.


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Circulation. 1954;10:887-895
doi: 10.1161/01.CIR.10.6.887

Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0009-7322. Online ISSN: 1524-4539

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