AN EVALUATION OF THE PROTECTIVE ACTION OF AUTONOMIC BLOCKING AGENTS IN PERIPHERAL CIRCULATORY STRESS

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Drugs which modify the activity of the autonomic nervous system serve an important function in both laboratory investigation and clinical practice. The introduction of hypotensive techniques in clinical anesthesia, as accomplished by autonomic blockade, has provided anesthesiologists with a substantial incentive to acquire a better working knowledge of these drugs, both as research tools and as therapeutic agents. To date the empiric clinical use of hypotensive anesthesia has apparently outdistanced its evaluation by systematic study (1). If this type of anesthesia is to be applied properly, more precise information relative to its desirable and undesirable properties is needed. The development of such critical appraisal is apparent from the increasing number of reports on various visceral functions as modified by hypotensive anesthesia (2, 3, 4). Specific influences of these drugs on basic vascular mechanisms, on which they have a profound effect, have not, however, been as numerous or as well documented.

Perhaps the most critical disturbance related to vascular mechanisms with which the anesthesiologist contends is the shock syndrome. It has been tentatively inferred that hypotensive anesthesia may serve to avert the onset of the deleterious effects of this syndrome on critical

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tissue functions. The objective characterization of this ameliorative effect would add considerably to the effective application of the method. Early reports on the clinical use of hypotensive techniques note that patients, in the early postoperative period, manifest relatively few of the shock syndrome sequelae as compared with similar patients operated on without the use of this method (5). Earlier investigations concerned with the shock syndrome per se have demonstrated in laboratory animals that certain autonomic blocking drugs and techniques exert a protective influence in terms of survival to stress (6, 7, 8). It seemed reasonable to infer, therefore, that a significant contribution of hypotensive anesthesia, in addition to the more obvious prevention of excessive blood loss, might be a specifically induced protection in terms of unfavorable homeostatic responses to extensive operative trauma and hemorrhage.

The principal vascular effect of the autonomic blockade used in hypotensive anesthesia has generally been accepted to consist of a decrease in peripheral resistance, with resultant hypotension and an unrestricted peripheral blood flow (9). Since the untoward and irreversible phenomena in shock have been attributed to metabolic disturbances generated by drastic curtailment of peripheral blood flow, it seemed reasonable to assume that the source of protection from such blockade might reside in the creation of an unrestricted blood flow in the periphery. This in turn would permit the maintenance of adequate tissue oxygenation and nutrition, and thereby avert the metabolic rearrangements in tissues thought to represent the critical disturbance progressively undermining homeostatic readjustments during shock.

Preliminary experiments in our laboratory with hexamethonium, to determine whether or not this drug exerted a protective effect in experimental shock, have indicated that despite the development of an unrestricted pattern of blood distribution no significant protection was afforded to the animal in terms of survival. A number of other blocking drugs yielded similar observations. These initial investigations concerning the protective mechanism of autonomic blockade, therefore, did not confirm that the source of protection resided in the vascular effects of such blockade on blood distribution and flow per se. There is no doubt that true protection as reported by others (6, 7, 8) and as observed in this laboratory, represents a real phenomenon, predictable and reproducible in nature. In relation to autonomic blockade, protection must be assumed to reside in one or more of the various other properties of these drugs over and above the direct vascular effects they have in common.

Autonomic blocking drugs as a group are not pure agents but have a variety of effects, significant among which are their ganglionic blocking, adrenolytic and anticholinergic properties (10). Fortunately, for purposes of study there is a sufficient number of these agents available
with predominantly ganglionic blocking, adrenolytic or anticholinergic properties. It seemed appropriate, as an initial investigation of autonomic blocking drugs, to determine which of their properties—ganglionic blocking, adrenolytic or anticholinergic—might provide a source of protection against shock.

This report is a preliminary evaluation of a group of autonomic blocking drugs in terms of their known activities to determine (1) whether they were protective, and (2) in which of their predominant properties the protection, when present, resided. Two general approaches were utilized. The first was statistical in nature, based on the survival of animals pretreated with autonomic blocking agents and then subjected to lethal drum trauma. The second approach was a more critical evaluation of selected agents in terms of direct visceral observation of the peripheral vascular bed following stress induced by hemorrhage. Observations on control animals not subjected to stress

<table>
<thead>
<tr>
<th>Drug</th>
<th>Ganglionic Blocking</th>
<th>Adrenolytic</th>
<th>Anticholinergic</th>
<th>Antihistaminic</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hexamethonium</td>
<td>+++</td>
<td>0</td>
<td>+</td>
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<td>+++</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
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<td>+++</td>
<td>+</td>
<td>+</td>
</tr>
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<td>01503 (Lilly)</td>
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</tr>
<tr>
<td>Yohimbin®</td>
<td>+</td>
<td>+++</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Atropine</td>
<td>+++ (?)</td>
<td>0</td>
<td>+++</td>
<td>0</td>
</tr>
<tr>
<td>Bantidine</td>
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<td>0</td>
<td>++</td>
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</tr>
<tr>
<td>Probanthine</td>
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<td>0</td>
<td>+++</td>
<td>0</td>
</tr>
<tr>
<td>SC 3581 (Searle)</td>
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<td>0</td>
<td>++</td>
<td>0</td>
</tr>
<tr>
<td>Histadyl®</td>
<td>0</td>
<td>+</td>
<td>+</td>
<td>+++</td>
</tr>
<tr>
<td>Benadryl®</td>
<td>0</td>
<td>+</td>
<td>+</td>
<td>+++</td>
</tr>
</tbody>
</table>

* Compiled from various published and unpublished sources.

were also made. In the drum trauma experiments, the following drugs were used (table 1): A. Ganglionic Blocking Agents—hexamethonium chloride, SC 2159 (Searle); B. Adrenolytic Agents—dibenzylene®, 01503 (Lilly), yohimbin®; C. Anticholinergic Agents—atropine, bantidine, probanthine, SC 3581 (Searle), histadyl® and benadryl.

Methods

I. Statistical. Rats of a given age, sex and weight (40–50 days, female, 125–150 Gm.) were selected for Noble-Collip drum experiments. These showed a predictable mortality to drum trauma. The several agents under investigation were administered from ten to twenty minutes before the onset of drumming, the rats receiving no other medication. Following the trauma, the animals were returned to their cages and a record was made of their survival up to twenty-four hours. Ani-
mals still alive at this point were recorded as survivals. The range of drum trauma selected was severe, 675 revolutions, which regularly produced a 70 to 85 per cent mortality in untreated controls. Protection was not considered as valid unless survival equal to or greater than 50 per cent was encountered, since normal variability in untreated controls, using groups of 10 to 12 animals, ranged from 10 to 30 per cent. In most experimental runs a parallel set of unmedicated controls was set up for each drug to rule out seasonal variability or other environmental factors. Each drug was administered intravenously in doses previously shown to have: blocking action (in terms of blood pressure response) to acetylcholine for anticholinergic drugs; a reversal of response to atropine (in terms of blood pressure) for adrenergic blocking drugs; a reduction of blood pressure of at least 60 mm. of mercury for ganglionic blocking drugs, or a blocking action to a standard hypotensive dose of histamine (2.5 gamma per 100 Gm. of body weight) for the two antihistaminic drugs. Inasmuch as the pharmacologic effects of these drugs became evident and persisted for variable time intervals, it was also necessary to ascertain in each instance that the drug remained active at least throughout the period of drum trauma. Since the periods of effectiveness of the agents under study were shown to be from one to three hours, the drum experiments could validly be carried out during the interval of most effective drug activity.

II. Direct Observations on Vascular Bed. In these experiments, hemorrhage was induced in a small series of rats pretreated with selected agents from each of the three major categories used in the drum series. The bleeding procedure used had been standardized, using a bleed-out reservoir to produce an irreversible state of shock. This was accomplished by removing sufficient blood through an arterial cannula to lower the systolic blood pressure to 60 to 70 mm. of mercury for a period of one hour, and followed by further hemorrhage sufficient to lower the blood pressure to 40 to 45 mm. of mercury for an additional two to two and one-half hours. Irreversibility was established by returning all the removed blood after a standardized period of spontaneous take-up from the bleed-out reservoir. The use of a reservoir for spontaneous take-up or bleed-out was necessary to adjust and maintain the blood pressure at predetermined levels for desired time intervals. In this type of bleeding, experience has shown that the situation is experimentally more valid if the removed blood is not reinjured until after some 35 to 40 per cent of the blood loss is spontaneously taken up from the reservoir by the animal. This procedure was followed. Throughout these experiments, microscopic observations were carried out on the blood vessels of the meso-appendix, according to a previously published method (11). Control studies were similarly made following hemorrhage in the absence of any drug therapy and also to establish the specific effects of various drugs on the peripheral circulation of the meso-appendix.
**Observations**

I. The results of the Noble-Collip drum trauma experiments are summarized in table 2. In effect, these data represent a screening procedure to determine survival with each drug. Severe trauma, as indicated by the high control LD of 70 to 85 per cent, increases the validity of the experimental results when relatively small groups of animals are used for evaluating each drug. This was shown by the consistent results in repeated runs of similar small groups of animals with several of the drugs examined, but not included in table 2 because the animals were not identically treated in terms of drug dosage. As contrasted

<table>
<thead>
<tr>
<th>TABLE 2</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Effect of Autonomic Blocking Drugs on Survival after Noble-Collip Drum Trauma</strong></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>Dose mg./100 Gm.</th>
<th>No. of Rats</th>
<th>No. Died</th>
<th>No. Alive**</th>
<th>Per Cent Alive</th>
</tr>
</thead>
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<td><strong>Controls (saline)</strong></td>
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<td>46</td>
<td>6</td>
<td>12</td>
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<td></td>
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<td>1.0</td>
<td>22</td>
<td>16</td>
<td>6</td>
<td>27</td>
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<tr>
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<td>10</td>
<td>1</td>
<td>9</td>
<td>90</td>
</tr>
<tr>
<td><strong>Adrenolytic:</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dihexylamine e</td>
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<td>10</td>
<td>2</td>
<td>8</td>
<td>80</td>
</tr>
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<td>01503</td>
<td>0.01</td>
<td>12</td>
<td>9</td>
<td>3</td>
<td>25</td>
</tr>
<tr>
<td>Yohimbine x</td>
<td>0.5</td>
<td>12</td>
<td>9</td>
<td>3</td>
<td>25</td>
</tr>
<tr>
<td><strong>Anticholinergic:</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Atropine</td>
<td>2.0</td>
<td>12</td>
<td>6</td>
<td>6</td>
<td>50</td>
</tr>
<tr>
<td>Banthine</td>
<td>0.25</td>
<td>18</td>
<td>14</td>
<td>4</td>
<td>22</td>
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<tr>
<td>Probanthine</td>
<td>0.06</td>
<td>12</td>
<td>12</td>
<td>0</td>
<td>0.0</td>
</tr>
<tr>
<td>SC 3581</td>
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<td>10</td>
<td>6</td>
<td>4</td>
<td>40</td>
</tr>
<tr>
<td><strong>Antihistaminic:</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Histadyl x</td>
<td>0.3</td>
<td>12</td>
<td>12</td>
<td>0</td>
<td>0.0</td>
</tr>
<tr>
<td>Benadryl x</td>
<td>0.5</td>
<td>12</td>
<td>9</td>
<td>3</td>
<td>25</td>
</tr>
</tbody>
</table>

* 675 revolutions; body weight 125–150 Gm.
** Figures based on number of rats alive 24 hours after drumming.

with the LD of 70 to 85 per cent in the controls, an arbitrary survival rate of 50 per cent or greater was established for the drug treated rats. Each control animal was given a volume of normal saline solution intravenously equivalent to the volume of saline solution in which the drug was administered to the experimental animals. Protection against drum shock was afforded by only three agents: (1) SC 2159, a ganglionic blocking drug, (2) dibenzylamine*, a predominantly adrenolytic drug, and (3) atropine, a predominantly anticholinergic drug. These showed survival rates of 90, 80 and 50 per cent, respectively. Protection did not appear to be related to the particular predominant autonomic blocking property of each of these three drugs.
II. In the hemorrhagic shock experiments, initial observations were made to determine the alterations in particular facets of peripheral vascular behavior induced by some of these drugs (table 3). With the exception of atropine, all of these agents produced changes in the peripheral bed in the direction of blunting the normal compensatory readjustment mechanisms, with a consequent plethoric or increased over-all blood flow through the tissues. This type of attenuated response is directly comparable to the changes seen during preganglionic, sympathetic epidural nerve block with procaine (12). Atropine, on the other hand, yielded virtually diametrically opposite vascular changes, resulting in a restricted type of capillary blow flow. The specific effects produced by these agents in the normal vascular bed are, of themselves, of particular interest. In the periphery, the regulation of the activity of the arteries and arterioles is predominantly a function of the sympathetic nervous system (13). Activity of the metarterioles and precapillaries, which have no anatomic nervous in-

### TABLE 3

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose*</th>
<th>Epinephrine Response</th>
<th>Artery (100 u)</th>
<th>Arteriole (35 u)</th>
<th>Metarteriole (29 u)</th>
<th>Vasomotion</th>
<th>Blood Flow</th>
</tr>
</thead>
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<tr>
<td>Hexamethonium</td>
<td>0.1</td>
<td>2x</td>
<td>dilate</td>
<td>dilate</td>
<td>no effect</td>
<td>no effect</td>
<td>plethoric</td>
</tr>
<tr>
<td>SC 2159</td>
<td>0.25</td>
<td>5x</td>
<td>dilate</td>
<td>dilate</td>
<td>no effect</td>
<td>slow increase</td>
<td>plethoric</td>
</tr>
<tr>
<td>Dibencyline®</td>
<td>0.02</td>
<td>4x</td>
<td>dilate</td>
<td>dilate</td>
<td>no effect</td>
<td>slow increase</td>
<td>plethoric</td>
</tr>
<tr>
<td>Yohimbin®</td>
<td>0.5</td>
<td>0.5x</td>
<td>no effect</td>
<td>no effect</td>
<td>no effect</td>
<td>increase</td>
<td>restrict</td>
</tr>
<tr>
<td>Atropine</td>
<td>2.0</td>
<td>6x</td>
<td>constrict</td>
<td>constrict</td>
<td>no effect</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* Mg./100 Gm.

nervation, is regulated principally by local metabolic factors and humoral agents of specific visceral origin. Ordinarily, in the normal circulation the interlocking of this dual neurohumoral regulatory mechanism operates to maintain peripheral homeostasis in accord with both systemic and local requirements. Most of the drugs studied alter the activity of peripheral circulatory mechanisms under control of both neurogenic and humoral activity. The obvious implications might be either that the drugs alter both regulatory systems or that the regulatory factors themselves are not as discrete in their function as heretofore alleged, or more probably, that the drugs act on a cellular metabolic level in the smooth muscle itself.

Having established the pattern of changes produced by different drugs in the normal animal, a small number of rats were subjected to hemorrhagic shock following the administration of hexamethonium, SC 2159, dibencyline® and atropine in the same same dosages used for the drum experiments. Typical protocols of these experiments are included
as figures 1 through 4. It is important to note that the data refer to
vascular behavior in the visceral mesenteric circulation of the rat.
Other vascular beds, such as exist in the skeletal areas, may not show
identical responses under comparable experimental situations.

These protocols indicate that protection in hemorrhagic shock is
afforded by the same drugs that protected against traumatic shock,
namely, SC 2159, dibenzyl ine®, and atropine. Microscopic observation
of the blood vessels during hemorrhage in control animals presented a
sequence of events epitomized by a period of compensatory hyperreact-
ivity of all peripheral mechanisms. This was characterized by intense
constriction of the arteries and arterioles, increased response to topi-
cally applied epinephrine, augmented vasomotion of the metarterioles
and precapillaries, with a resultant ischemic capillary blood flow. To-
ward the end of the experiment, this compensatory period was gradu-
ally replaced by a decompensatory period of hyporeactivity of the
mechanisms of the peripheral circulation. Ultimately the arteries and
arterioles underwent dilatation, epinephrine response fell and vaso-
motion disappeared. Blood flow was sluggish to the point of stagna-
tion and was no longer restricted in relation to capillary in-flow. At
this point all of the removed blood was reinfused. Despite the im-
provement in blood pressure, the mesenteric circulation did not recover
appreciably and merely became congested by the increased blood vol-
ume. These animals remained in shock and died after variable brief
periods.

With both dibenzyl ine® and SC 2159 the circulation during the early
period of hemorrhagic shock, like the controls, showed hyperreactivity
of the peripheral mechanisms. An important variation, however, was
the quantitative difference in these responses. Arterial and arteriolar
constriction was not as intense, and vasomotion not as augmented.
Over-all blood flow was excellent. In the subsequent period of pro-
tracted drastic hypotension, as contrasted with the controls, peripheral
vascular responses did not become hyporeactive. Arteries and arteri-
oles did not become atonic, epinephrine reactivity did not fall signifi-
cantly, and vasomotion did not disappear. Over-all blood flow re-
mained satisfactory, being continuous, undirectional and without stag-
nation.

Early with hexamethonium the terminal bed closely resembled that
noted after SC 2159 and dibenzyl ine. During the later period of drastic
hypotension, individual rats and small changes in dosage gave variable
results—some degree of protection and actual deleterious effects. In
terms of the vascular bed as a functional entity, the responses observed
during stress were comparable to those noted with dibenzyl ine and SC
2159. Blood flow generally was favorable in character. In no instance,
however, was actual protection, equal to that noted with the other pro-
tective drugs, obtained. The animal given hexamethonium, following
Graded Hemorrhage - Normal (Control) Rat

Rat - weight 123 g
Anes. - Pentobarb. (3.5 mg/100 g)
Maximum blood loss = 4.0%

Blood Pressure (mm Hg)

Blood Loss (% body wt.)

Time in hours

Fig. 1. Control, no medication.

Graded Hemorrhage - SC 2159 (0.25 mg/100 g)

Rat - weight 120 g
Anes. - Pentobarb. (3.5 mg/100 g)
Maximum blood loss = 4.03%

Blood Pressure (mm Hg)

Blood Loss (% body wt.)

Time in hours

Fig. 3. SC 2159, 0.25 mg./100 Gm.
Blood pressure records of rats subjected to graded hemorrhage with self-infusion reservoir connected to carotid artery. Drugs, as indicated were administered before bleeding. Microscopic observations in vascular bed of exposed meso-appendix were made throughout.
hemorrhage, resembles the animal subjected to thoracolumbar sympathectomy in showing an adequate peripheral blood flow through the mesentery until maximal blood loss is achieved. At this point up-take from the reservoir begins almost immediately.

With the large dose of atropine that can be used in the rat, and enhanced compensatory vasoconstriction and hyperreactivity were observed. Depression of vascular reactivity was not noted at any time. Vasomotion was not as prominent as in the controls. Nonetheless, venous return from the tissues during drastic hypotension was unusually effective, being comparable to that noted with dibenzyline or sympathectomy. These animals, following reinfusion of lost blood, recovered with remarkable rapidity.

**Discussion**

This preliminary study was designed primarily to yield information pertinent to the vascular effects of various pharmacologic agents used with increasing frequency during clinical anesthesia. It was also anticipated that these data might indicate which, if any, of these agents were especially advantageous to patients and thus provide an additional means of evaluating hypotensive anesthetic techniques. The method employed, that is, the introduction of a stress situation by trauma or hemorrhage, served as a means of emphasizing the important pharmacologic influences of these various agents. Stress, of itself, results in a clear-cut predictable and reproducible sequence of changes in the terminal vascular bed. These changes are referable to compensatory or decompensatory activity of vascular mechanisms, such as vasoconstriction, epinephrine reactivity and vasomotion. Changes in the known sequence and intensity of such activity in the peripheral circulation, as introduced by a particular drug, would then indicate which of the specific mechanisms were altered by the drug. It was thought that this method would provide a logical approach toward identifying the particular vascular mechanisms concerned with increased and decreased protection against stress. It would also identify particular drugs which had the capacity to generate protection.

The data on drum shock indicate that no single known pharmacologic property is responsible for protection imparted by given agents. It is equally evident that the decrease in peripheral resistance and the plethoric circulation consequent to autonomic blockade is not, of itself, protective. True protection was afforded by the administration of dibenzyline, SC 2159 and atropine. Comparison of these protective drugs, on their pharmacologic characteristics, reveals no specific similarity on the basis of their predominant properties of anticholinergic, adrenolytic or ganglionic blocking activity. The lack of any specific protective property is underscored also by the similarity of the predominant activities of these protective drugs with other agents which do
not afford protection. Protection as a discrete entity must involve some combination of these properties or other suggested effects at a cellular metabolic level.

Various mechanisms reported as protecting against different types of stress, such as radiation, infection, hemorrhage and trauma, appear to have as a common denominator exposure to sublethal stress situations. For instance, protection in drum trauma is afforded by repeated exposure to bouts of graduated, sublethal drumming (14). Protection against fatal radiation injury is possible by exposure to hypoxia (15) or preingestion of amino acids, such as cysteine or methionine (16), both of which have free sulfhydryl groupings. (Ferritin, a specific vasodepressor material, present in irreversible shock, also contains free sulfhydryl groups in its biologically active form (17).) It is equally interesting to note that protective drugs, such as dibenzyline and atropine, are now being shown to have sulfhydryl binding properties as well as a diversity of metabolic effects at a cellular level (18). These metabolic effects, in considering sources of protection, may be more critical than their more gross autonomic blocking activities.

It would be difficult to compare experience with hexamethonium and other autonomic blocking agents used clinically in human beings with the present type of animal experiment. In man, scrupulous attention to the maintenance of normal blood volume is emphasized. Need for such stems from the clinical experience of rapid deterioration of the patient’s condition unless blood volume is sustained (1). By contrast, the animal experiments involve a significant decrease in blood volume as an important stress factor. Under such conditions no biological protection is afforded by hexamethonium other than that perhaps attributable to conservation of blood volume as the direct mechanical result of hypotension. This is not a true pharmacologic protection but a technical means of decreasing the magnitude of the important contributory factor during the subsequent course of the syndrome. In animals, the usual irreversible sequelae of hypotension develop despite the presence of hexamethonium. On the other hand, dibenzyline and SC 2159 have a true pharmacologic protective action in the presence of a markedly diminished blood volume. Since this cannot be attributed to the more favorable perfusion of tissues also produced by nonprotective autonomic blocking drugs, it must be related to other factors presumably at a cellular level.

Summary

By means of pretreating animals subjected to lethal drum and hemorrhagic stress with various autonomic blocking drugs, data were obtained concerning the protective actions of these drugs against stress. It was shown that some of these agents were, and some were not, protective. The source of their protection did not reside in any one of the predominant pharmacologic effects of these agents, namely, their
ganglionic blocking, adrenolytic or anticholinergic characteristics. Protection also was not a function of the increased blood flow in tissues, created by autonomic blockade. It was suggested that true pharmacologic protection in stress was probably a function of a combination of the properties of protective drugs including the changes they induce at a cellular metabolic level.

REFERENCES

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