The Neurogenic Component in Hypertension

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The magnitude of the blood pressure falls, in the horizontal posture, following intravenous hexamethonium, shows that an important part of the blood pressure elevation is neurogenically maintained in essential hypertension. When the blood pressure is first raised by angiotonin or by other pressor agents, the subsequent response to hexamethonium is much reduced. Similar responses are observed in normotensive and hypertensive subjects. This is due to the reaction of the regulating centers which compensate for the effect of the pressor agent by reducing the neurogenic component. The resulting decrease in the neurogenically maintained fraction of the blood pressure diminishes the response to hexamethonium. It is suggested that, in the course of time, long exposure to pressor stimuli induces the vasomotor centers to exercise their regulating function at a higher than normal level.

The pharmacology of hexamethonium salts was first studied by Paton and Zaimis. These workers reported that the substance acted predominantly at the autonomic ganglia, and were able to show that small concentrations of hexamethonium caused blocking of the ganglia. It was soon evident from clinical studies that the predominant action of hexamethonium in man is also to produce autonomic ganglionic block. Arnold and Rosenheim demonstrated that the substance caused a sharp fall of blood pressure and that postural hypotension occurred. Peripheral vasodilatation occurs, being greater in the legs than in the arms. The fall in blood pressure appears to depend on the interference by the drug with the capacity of the sympathetic nervous system to perform its normal circulatory reflex functions; thus, in the erect posture, the blood pressure falls because of the absence of sympathetic vasoconstriction, and a similar additional fall of blood pressure usually follows meals.

Reports on the effects of the drug on the cardiac output in man have been conflicting. Gilmore and associates, Freis and his coworkers, and Rakita and Sancetta reported that the cardiac output was usually little changed following the administration of hexamethonium and that the fall in blood pressure was due to a fall in the peripheral resistance. In a later report Freis and coworkers have reported that the cardiac output remains unchanged or rises in patients with malignant hypertension or heart failure, but in those with benign essential hypertension the cardiac output usually falls. Studies on the effect of the drug on cardiac output in dogs have likewise been conflicting, Moyer and his colleagues finding no fall in cardiac output whilst Crumpton and associates report that the fall of blood pressure induced by hexamethonium is accompanied by significant decrease in the cardiac output, with an increase in the calculated total peripheral resistance. All workers are agreed, however, that when the cardiac output falls, it does so as a result of pooling of blood in the extremities which follows the peripheral vasodilating action.

Arnold and Rosenheim showed that the fall of blood pressure after hexamethonium was usually larger in the hypertensive than in the normotensive subject; Conway and Barnett and Fraser have reached similar conclusions. It is now generally conceded that many hypertensive subjects have greater blood pressure falls than normotensives. This might seem to imply that the neurogenic component in hypertension is greater than in health, since the vasodilatation which causes the fall in blood pressure is predominantly due to the block of the sympathetic ganglia. Such a view may be an over-simplification, however, for the view has been expressed that, even if the

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A preliminary communication of the results of this paper were reported at the Second World Congress on Cardiology at Washington, D. C., September 16, 1954.
blood vessels were constricted primarily by the action of a chemical pressor substance, the effect of nervous stimulation would be thereby enhanced. If such an enhancement of the effects of nervous stimulation occurred, an exaggeration of the blood pressure fall would result from the removal of normal autonomic constrictor impulses. If the effect of the normal neurogenic component became increased in this manner as the result of the elevation of the blood pressure, it would seem likely that if the blood vessels were further constricted as a result of the action of a chemical pressor substance, the effect of the neurogenic component would be further enhanced.

It was decided to test this hypothesis experimentally in man by measuring the depressor action of hexamethonium in hypertensives and normotensives under standard conditions, and again after the artificial elevation of the blood pressure by various chemical pressor substances. In the present study we have observed the depressor action of hexamethonium under these conditions using angiotonin, noradrenaline or s-methyl isothiouria to elevate the blood pressure.

**METHODS**

Blood pressures were recorded by the auscultatory method in accordance with the recommendations of the joint Committee for the Standardization of Blood Pressure Readings of the American Heart Association and the British Cardiac Society, 1939. Observations were made both with the subjects recumbent and on a tilting table with the feet tilted down to 60 degrees. A needle was introduced into the median basilic vein and a slow infusion of 5 per cent glucose given. Intravenous injections were made by means of a three-way tap so that injections could be given without the patient's knowledge.

For testing the depressor action of hexamethonium in the recumbent position, the initial dose was usually 25 mg.; subsequent doses of 15 mg. were given at two-minute intervals until two successive doses had produced no further fall in the blood pressure. When the subject was on the tilting table at 60 degrees the initial dose was 15 mg. and increments of 5 mg. were given at intervals of three or four minutes until faintness was noticed or until the systolic blood pressure fell below 70 mm. Hg.

The responses obtained by the methods described above were compared in some patients with the responses to similar doses during the administration of the humoral pressor substances noradrenaline, angiotonin or s-methyl isothiourea. In this test 5 units of angiotonin were given at two-minute intervals and the blood pressure was recorded at half-minute intervals. When the blood pressure had become stable, the dose of hexamethonium previously effective was again given intravenously. The injections of angiotonin at two-minute intervals were continued until such time as the period of maximal action of the hexamethonium, as judged from the previous test, might have been expected. When s-methyl isothiourea was used, the dose was 50 mg. at two-minute intervals. When noradrenaline was used it was administered by an intravenous drip of 5 per cent glucose containing 2 micrograms of noradrenaline per milliliter. The rate of the drip was adjusted to give a suitable rise of blood pressure.

**RESULTS**

(a) **Depressor Effect of Hexamethonium in Recumbent Hypertensive Patients**

Observations were made in 80 subjects with hypertension of various clinical types. The mean systolic blood pressure for the group was 233 mm. Hg (S. D. ± 23) and the mean diastolic pressure was 133 mm. Hg (S. D. ± 13). The mean fall in systolic pressure was 85 mm.
not be predicted on clinical grounds in any individual patient. There was no correlation between the grading of the fundi and the sensitivity to hexamethonium, and in particular patients with malignant hypertension seemed to exhibit average sensitivity to the drug. There was no important correlation between the age of the subject and the extent of the blood pressure fall. With numerous exceptions there was a slight tendency for the more elderly subjects to have larger falls of blood pressure.

The level to which the blood pressure fell after hexamethonium also varied widely, the mean systolic level being 148 mm. Hg (S. D. ± 21.5) and the mean diastolic level being 95 mm. Hg (S. D. ± 18). Figure 2 shows that there is an inverse relationship between the level of the blood pressure after hexamethonium (i.e. residual or floor pressure) and the extent of the blood pressure fall, those patients who had large falls of blood pressure having a low level after hexamethonium whilst those who had a high level after hexamethonium had only small falls of blood pressure. The coefficient of correlation between these two measurements was −0.521 (p < .001).

(b) Depressor Effect of Hexamethonium in Recumbent Normotensive Subjects

Observations were made in 22 subjects with normal blood pressures. The mean initial systolic pressure was 137 mm. Hg (S. D. ± 12) and the mean initial diastolic blood pressure was 82 mm. Hg (S. D. ± 7). The falls of blood

**Table 1.**—Falls of Blood Pressure Induced in Recumbent Hypertensives by Intravenous Hexamethonium, under Standard Conditions and During the Infusion of Angiotonin (5 Units Every 2 Minutes)

<table>
<thead>
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<th>B.P. after</th>
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<td>270/135</td>
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<td>15/0</td>
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</tr>
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</table>

| Result | Fall less | Fall less | Fall less | Fall less | Fall less | Fall less | Fall greater | Fall less |

**Fig. 2.** The relation between the “floor” or “residual” blood pressure after administration of a “maximal” intravenous dose of hexamethonium and the extent to which the blood pressure is reduced by hexamethonium. It is seen that both in normotensives and in hypertensives the patients with higher residual pressures tend to have the smaller blood pressure falls.

Hg (S. D. ± 24) and the mean fall in diastolic pressure was 37 mm. Hg (S. D. ± 16.5). The positive relationship between the size of the fall in systolic blood pressure and the initial systolic level is shown in figure 1. The coefficient of correlation between these two measurements was 0.557, which is highly significant (p < .001).

The extent of the blood pressure fall could
Intravenous hexamethonium, under Standard Conditions and during the Infusion of Noradrenaline (2 µg. per ml.)

<table>
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<th>B.P. after</th>
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</tbody>
</table>

The results show that the mean fall in systolic pressure was much smaller in the normotensive subjects than in the hypertensive group, the mean fall in systolic pressure being 31 mm. Hg (S. D. ± 18) and the mean fall in diastolic pressure 15 mm. Hg (S. D. ± 11). As in the hypertensive group, there was a correlation between the size of the initial pressure and the fall of blood pressure, the coefficient of correlation being .618 (p < .001). In contrast to the results in the hypertensive patients there was a close correlation between the ages of the patients and the extent of the blood pressure fall, but since the elderly subjects tended to have rather higher casual pressures and lower residual pressures, both of which seemed to be associated with larger blood pressure falls, it is not possible to determine to which of these factors the increased fall in blood pressure can be related.

As in the hypertensives, there was an inverse relationship between the height of the residual blood pressure and the extent of the fall in blood pressure. The mean systolic level after hexamethonium was 106 mm. Hg (S. D. ± 14)

Table 3.—Falls of Blood Pressure Induced in Hypertensives while Tilted to 60 Degrees Feet Down by Intravenous Hexamethonium under Standard Conditions and During the Infusion of Angiotonin

<table>
<thead>
<tr>
<th>No.</th>
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<td>70/40</td>
<td>275/150</td>
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Table 4.—Falls of Blood Pressure Induced in Hypertensives while Tilted to 60 Degrees Feet Down by Intravenous Hexamethonium, under Standard Conditions or During the Infusion of S-methyl Iso-Thiourea

<table>
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<td>60/10</td>
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</table>

The results show that the mean fall in systolic pressure was much smaller in the normotensive subjects than in the hypertensive group, the mean fall in systolic pressure being 31 mm. Hg (S. D. ± 18) and the mean fall in diastolic pressure 15 mm. Hg (S. D. ± 11). As in the hypertensive group, there was a correlation between the size of the initial pressure and the fall of blood pressure, the coefficient of correlation being .618 (p < .001). In contrast to the results in the hypertensive patients there was a close correlation between the ages of the patients and the extent of the blood pressure fall, but since the elderly subjects tended to have rather higher casual pressures and lower residual pressures, both of which seemed to be associated with larger blood pressure falls, it is not possible to determine to which of these factors the increased fall in blood pressure can be related.

As in the hypertensives, there was an inverse relationship between the height of the residual blood pressure and the extent of the fall in blood pressure. The mean systolic level after hexamethonium was 106 mm. Hg (S. D. ± 14)
Table 5.—Falls of Blood Pressure Induced in Recumbent Normotensives by Intravenous Hexamethonium under Standard Conditions and During the Infusion of Angiotonin (5 Units every 2 Minutes)

<table>
<thead>
<tr>
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Fig. 3. The effect of experimental elevation of the blood pressure by a humoral agent upon the fall of blood pressure from the subsequent administration of hexamethonium. Blood pressure falls (horizontal posture) in a hypertensive patient following a large intravenous injection of hexamethonium. The upper two curves are systolic and the lower two diastolic pressures.

Fig. 4. The lengths of the lines down to the dots represent the falls of blood pressure from large intravenous doses of hexamethonium. The lengths of the lines down to the crosses represent the smaller falls of blood pressure from the same doses of hexamethonium when the blood pressure has been first raised to a higher level by intravenous injection of a pressor agent. Each line represents the mean of 10 to 12 experiments. The results obtained with angiotonin are marked "A", with noradrenaline "N-Ad", with s-methyl iso-thiorea "SM", "Horizontal" and "60 degree tilt" refer to the positions of the patients during the investigation. Results on hypertensives and normotensives are set out separately.
and the mean residual diastolic blood pressure was 67 mm. Hg (S. D. ± 11).

(c) Modification of the Depressor Effect of Hexamethonium by Pressor Substances in Hypertensive and Normotensive Subjects

In 60 patients the effects of hexamethonium under resting conditions were compared with the effects of the drug after the blood pressure had first been raised by the continued administration of angiotonin, s-methyl iso-thiourea or noradrenaline. The pressor substance was given first and the administration continued until a steady blood pressure had been obtained. The blood pressure was usually about 20 mm. Hg higher than the resting level. The effective dose of hexamethonium was then given. In all the tests the fall of blood pressure was much smaller after the administration of a pressor agent than under resting conditions. Similar results were obtained both with the patients recumbent and on a tilting table at 60 degrees with the legs down, although the falls of blood pressure were usually still greater in the tilted position than with the subject recumbent.

It is clear from our observations that, although the initial level of the blood pressure had been raised by the pressor agent, the falls of blood pressure produced by hexamethonium were then smaller than under resting conditions. Detailed results of some of the individual experiments are shown in tables 1 to 5 and typical falls of blood pressure are shown in figures 3 and 4.

DISCUSSION

Our results have confirmed the work of others, that the falls of blood pressure after ganglionic blockade are usually much greater in hypertensive subjects than in those with normal blood pressures. It is of interest that patients with hypertension due to renal disease and to postpregnancy toxemia often have falls of blood pressure as large as those in subjects with essential hypertension. Indeed, there does not seem to be any correlation between the clinical manifestations of the hypertension and the response to ganglionic blockade. In particular, the fundal changes do not offer a guide as to the likelihood of greater or smaller blood pressure falls with hexamethonium.

We shall point out later that there appears to be some doubt about the mechanism of action of hexamethonium, and in particular about its action on the cardiac output. It is evident, however, that hexamethonium acts by the removal of a neurogenically maintained fraction of the blood pressure and from our results it is evident that the neurogenically maintained fraction is greater in the average patient with hypertension than it is in health.

It has been shown that when in hypertension or health, a humoral vasoconstrictor, such as angiotonin, is administered, the subsequent administration of a ganglion blocking agent induces much smaller blood pressure falls. It seems likely that the reaction of the blood pressure control mechanisms to the administration of a pressor agent is to decrease the neurogenic component. Under such circumstances, when there is less of the neurogenic component to be removed, it is found, as might reasonably be expected, that smaller blood pressure falls follow ganglionic blockade.

There has never been any real doubt that the homeostatic mechanisms continue to operate in patients with hypertension. The present study has indicated that there is a reciprocal relationship between the neurogenic and nonneurogenic components in maintaining a raised blood pressure level. It seems that the neurogenic component fluctuates with changing circumstances so that nonneurogenic changes in the level of the blood pressure are to some extent buffered by the neurogenic changes. Thus, without very much change in the level of the blood pressure, there may be considerable fluctuation in the proportion of the neurogenic and nonneurogenic components. For example, after ganglionic blockade, when there is no compensatory adjustment by neurogenic means, the assumption of the erect posture leads to an important decrease in the level of the blood pressure measured in the arm. It seems that normally as the effect of the nonneurogenic component decreases with assumption of the erect posture, the effect of the neurogenic component increases, so that normally there is little change in blood pressure.
with change of posture. There is, however, a considerable change of proportion in the effects of the neurogenic and nonneurogenic components with change of posture. It is clear that in the vertical posture, not only does the effect attributable to the neurogenic fraction increase, but the effect of the nonneurogenic fraction decreases. Because of this, both in normotensives and in hypertensives, hexamethonium causes greater falls of blood pressure in the erect posture for more neurogenic impulses are concerned in the maintenance of the blood pressure level in this posture.

Our findings are inconsistent with the view so commonly expressed that stimuli applied when the blood pressure is high are likely to induce changes which are larger because they are in proportion to the degree of blood pressure elevation. On the contrary, we find that in one and the same patient, the blood pressure fall from hexamethonium is decreased if the blood pressure is first raised by a pressor agent. In other words, the constriction of the blood vessels by a humoral agent reduces and does not exaggerate the neurogenic vasoconstriction. It seems from our observations, therefore, that falls of blood pressure occurring with hexamethonium are not exaggerated by the fact that the starting level of the blood pressure is high, so that the observed increase in the blood pressure fall in hypertensives may be taken to indicate an increase in the neurogenic component, and the observed increase in the level after ganglionic blockade may be taken to indicate an increase in the nonneurogenic component.

It might be argued that the acute administration of angiotonin or other pressor substances leads to a different response than that which would occur with the continued presence of these agents. Our observations on the depressor action of hexamethonium, however, also lead us to the conclusion that the nonneurogenic and neurogenic components vary in a reciprocal manner; for although there is a correlation between the height of the blood pressure and the response to hexamethonium, we have also found that a high residual blood pressure tends to be associated with a smaller neurogenic component, both in hypertension and in health. Thus, both in our acute experiments with pressor substances and in chronic hypertension the elevation of the blood pressure by nonneurogenic means seems to lead to a decrease, rather than an increase, in the neurogenic fraction.

The further interpretation of our results is made difficult by the fact that the mechanism of the blood pressure fall resulting from ganglionic blockade with hexamethonium is in dispute. Some workers maintain that it is due almost entirely to a reduction in the peripheral resistance with little change in the cardiac output. Others have found, however, that the cardiac output often falls. It is generally conceded that if the cardiac output falls it does so as a result of peripheral vasoconstriction leading to pooling of blood in the extremities. If the fall in cardiac output is assumed to be the cause of the blood pressure fall after ganglionic blockade it would be to be expected that the blood pressure fall would be proportional to the initial level of the blood pressure, for by Poiseuille's law a reduction in the cardiac output would ordinarily lead to a larger fall in blood pressure if the peripheral resistance were high than if it were low. It would be expected, therefore, that a fall in cardiac output would lead to a larger fall of blood pressure in the hypertensive subject whether the arteriolar constriction was primarily neurogenic or primarily humoral. In our experiments, however, an increase in the amount of circulating pressor substance led to a reduction of the depressor action of hexamethonium. If indeed the action of hexamethonium is to reduce the cardiac output, then we have to explain why this action is antagonized by the humoral pressor substances which we have used. The best explanation would seem to be that an important part of the action of the humoral pressor substances used is exerted on the vessels whose dilatation leads to a fall in cardiac output. Thus, it might be that an important part of the action of angiotonin or similar substances is exerted on the veins, so that to a great extent neurogenic venous tone can be replaced by humoral venous tone. If this is so the presence of humoral pressor substances might prevent or reduce the amount of
venous pooling which usually follows gangli- 
onic blockade. Such a conclusion might account 
for the observations of Freis and coworkers\(^8\) 
that in some patients with malignant hyper-
tension or hypertensive heart failure, hexa-
methonium causes no fall in cardiac output; 
whereas in subjects with essential hyperten-
sion the cardiac output falls. In any case, whether 
these pressor substances act on arteries or 
veins or both, their effects are to antagonize 
the effects of ganglionic blockade and to do- 
minish the neurogenically maintained fraction 
of the blood pressure.

Our experiments are consistent with the 
already strong evidence that in established 
hypertension the vasomotor centres continue 
to regulate blood pressure levels both in an 
upward and in a downward direction. Our experi-
ments with angiotonin and hexamethonium 
suggest that the effects of pressor stimuli are 
still opposed by homeostatic decreases of sym-
pathetic tone and factors tending to reduce the 
blood pressure, such as the erect posture, or 
falls of cardiac output, are countered by in-
creases of sympathetic tone. It may be worth 
considering the possibility, admittedly specu-
lative, that rises of blood pressure imposed by 
a variety of primary causes, some perhaps 
physiological, and others pathological, lead in 
the course of time to a displacement of the 
centre’s activity so that, while continuing to 
regulate, it does so mainly in a higher range. 
Some explanation is needed for the fact that 
in almost all kinds of continued hypertension 
the vasomotor centre remains active and op-
poses both pressor and depressor stimuli. Evi-
dence for the view that this change in the level 
of response of the vasomotor centre may have 
resulted from long exposure to the effects of 
raised blood pressure is the fact that this 
change in the vasomotor centre appears to 
occur in all forms of hypertension, even of the 
most varied aetiology. Without an explanation 
of this sort it is difficult to explain such changes 
occurring in nephritis, pregnancy toxemia, es-
ential hypertension, pyelonephritis, and other 
less common causes of high blood pressure in 
man.

If the evidence for increased vascular re-
activity in hypertension cited by Doyle and 
Black\(^41\) be confirmed, it becomes evident that 
both normal and pathological vasopressor in-
fluences will have a greater effect upon the 
blood pressure in hypertension than in health 
and will demand correspondingly greater at-
ttempts at homeostasis. The vasomotor centres 
have functions concerned with postural ad-
justments and distribution of blood which 
demand bidirectional adjustments. Unless an 
alteration in the homeostatic level of the blood 
pressure control centres occurred it seems 
likely that an increase in vascular reactivity 
would imply that only unidirectional (down-
ward) control could be exercised.

**Summary**

1. Blood pressure falls in the horizontal 
posture were induced by large intravenous 
doses of hexamethonium.

2. In normotensives as well as hypertensives 
the blood pressure falls are greater when the 
initial blood pressure level is high than when 
it is low. The blood pressure falls are much 
greater in hypertensive than in normotensive 
subjects.

3. In normotensives and hypertensives it is 
found that those patients with high floor (re-
sidual) blood pressures (after the hexameth-
onium) have smaller blood pressure falls than 
patients with low floor blood pressures.

4. In normotensives and in hypertensives 
elevation of the blood pressure by the admin-
istration of angiotonin, noradrenaline or \(s\)- 
methyl iso-thiourea leads to a decrease in the 
extent of the blood pressure fall which may be 
obtained by the intravenous administration of 
hexamethonium.

5. The above evidence makes it unlikely that 
the enhanced response to hexamethonium ob-
served in most of our hypertensive patients 
could be merely the result of an increase in the 
blood pressure brought about by circulating 
pressor agents. The results, while in no way 
excluding the participation of humoral factors, 
are more consistent with the hypothesis that, 
in most hypertensives, the blood pressure ele-
vation is predominantly the result either of an 
increase in the nervous stimulation of blood 
vessels or in an increase in the reactivity of 
blood vessels to nervous stimulation.
6. It is pointed out that in health and in hypertension an alteration in the neurogenically maintained fraction of the blood pressure is the principal means by which blood pressure levels are regulated.

7. The prompt response of the homeostatic mechanisms to assumption of the erect posture consists of an increase in the neurogenically maintained fraction of the blood pressure, to compensate for the gravitational decrease in the effect (at arm level) of the nonneurogenically maintained fraction. Likewise, in normotension and hypertension the response of the homeostatic mechanism to the horizontal posture or to the administration of a pressor drug consists in a compensatory decrease of the neurogenically maintained fraction of the blood pressure.

8. The smaller blood pressure fall from hexamethonium when the subject is in the horizontal posture and the decrease in the extent of the fall when the hexamethonium is given after administration of a pressor substance are both explained in terms of decrease in the amount of neurogenically maintained vascular tone which is available to be removed when the hexamethonium is administered.

9. It is not settled to what extent decrease in neurogenic vascular tone (by hexamethonium) affects the peripheral resistance by its action on arterioles, or the cardiac output by its action on veins and capillaries.

10. It seems likely that continued exposure to blood pressure elevation from a variety of primary causes may lead to upward displacement of the activity of the vasomotor centre, so that while continuing to regulate it does so mainly in a higher range.

**Summario in Interlingua**

Le magnitude del reduction del pression sanguine, le qual se manifesta in positura horizontal post le administration intravenose de hexamethonium, monstra que un importante parte del elevation del pression sanguine in patientes con hypertension essential es mantenite neurogenicamente. Quando le pression sanguine es inicialmente altitate per angiotonina o altere agentes pressorial, le subsequite responsa a hexamethonium es grande-mente reduceite. Simile responsas es observate in individuos normo- e hypertensive. Isto es cause per le reduction del centros regulatori que compensa le effecto del agentes pressorial per reducir le componenta neurogenic. Le resultante reduction del neurogenicamente mantenite fraction del pression sanguine reduce le responsa a hexamethonium. Nos avantia le hypothesa que in le curso del tempore un prolongate exposition a stimulus pressorial induce le centros vasomotor a exercer lor function regulatori a un nivello superior al nivello normal.

**Acknowledgment**

We are much indebted to Dr. O. M. Helmer of Eli Lilly & Co., Indianapolis, Indiana, for his kindness in supplying us with angiotonin. Valuable secretarial assistance from Miss N. Richardson is acknowledged. This work was supported by the Life Insurance Medical Research Fund of Australia and New Zealand.

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The Neurogenic Component in Hypertension
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Circulation. 1955;12:543-552
doi: 10.1161/01.CIR.12.4.543
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

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circ.ahajournals.org/content/12/4/543

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