Sympathetic Reactivity in Hypertension*

A Preliminary Investigation

By

E. Gellhorn**

(Received February 8, 1963)

During the past several years an extensive series of tests involving the use of Mecholyl and noradrenaline was performed on neuropsychiatric patients and normal controls. The quantitative evaluation of these tests led to two important findings: 1. that the sympathetic reactivity of neuropsychiatric patients as measured by the Mecholyl test shows significant deviations from that found in normal persons; 2. that this responsiveness diminishes with increasing age. Similar differences between the two clinical groups were found for the parasympathetic system on the basis of tests with noradrenaline [18, 19]. A small percentage of the non-mental and mental patients showed hypertension, the blood pressure being repeatedly higher than 150 mm. Hg. The results of the Mecholyl tests on these persons are briefly reported and discussed from the neurophysiological point of view although no further clinical studies on the type of hypertension were carried out.

As in our earlier work 10 mg. Mecholyl (methacholine chloride) was injected i. m. after the subject had rested adequately. Blood pressure and pulse rate were recorded continuously and the results were graphed, the areas measured, the quotient $\frac{\text{Area of decreased blood pressure}}{\text{Area of increased pulse rate}}$ determined and the duration of the effects and the slope of the curves evaluated ***.

Results

As in previous studies the Mecholyl tests were divided into three groups. Group I, characterized by a brief and small fall in blood pressure, a quick return of the blood pressure curve to the control level and also by overshooting, represents sympathetic hyperreactivity. Group II shows a moderate fall in pressure and a return of the blood pressure to the control

* Supported by a Grant from NIH MH 06552-01.

** *E. Gellhorn,* M. D., Ph. D., Professor Emeritus of Neurophysiology. Present address, 2 Fellowship Circle, Santa Barbara, California.

*** For further details of the procedures, see ref. 8.

level after about 7—9 min. which indicates moderate sympathetic responsiveness and is found in the majority of normal persons at all ages. Group III reacts to the drug with a large and prolonged fall in pressure followed by an incomplete or delayed return to the control level which signifies a hyporeactive sympathetic nervous system *. Correspondingly, the pulse acceleration induced by Mecholyl declines from Group I to Group III.

Table 1. *Reactivity to Mecholyl of Non-Hypertensives and Hypertensives of Similar Age (46 years and older)*

Mecholyl Group	*Number*	*%*	
A. Normotensive Neuropsychiatric Patients			
I	8	14	
II	27	49	Mean blood pressure 130.95
III	20	37	S. D. 11.95
B. Hypertensive Neuropsychiatric Patients			
I	4	21	
II	0	0	Mean blood pressure 163.1
III	15	79	S. D. 11.8
	$\chi^2 = 15.10$ $p < 0.01$		
C. Normotensive Control Group			
I	1	5	
II	13	69	Mean blood pressure 122.9
III	5	26	S. D. 11.25
D. Hypertensives (non-mental)			
I	5	20	
II	0	0	Mean blood pressure 164.0
III	20	80	
	$\chi^2 = 24.33$ $p < 0.01$		

Table I shows the distribution of the Mecholyl groups in unselected cases from a state hospital A, B) and also in non-mental cases (C, D). Since the sympathetic reactivity as measured by the Mecholyl test declines with increasing age the normal and hypertensive groups chosen for this study were of similar age. Nevertheless, striking differences appear: the percentage of Group III is greatly increased in the hypertensive groups regardless whether mental or non-mental cases were tested. Compared to the nor-

* See ref. 5 and 11 for the experimental foundations of this interpretation of the Mecholyl test.

motensive persons Group III was more than doubled in the hypertensive cases in the A, B and more than tripled in the C, D experiments. In a third experiment comprising only 13 hypertensive cases the reactivity to Mecholyl was compared in normo- and hypertensive cases regardless of age and a fourfold increase in the occurrence of Mecholyl Group III in the hypertensive patients was found again (Table II). These differences between the normo- and the hypertensive groups are statistically highly significant ($p < 0.01$).

These data confirm work reported in the literature [2, 24] according to which the effectiveness of Mecholyl on the blood pressure is increased in hypertension. Before an interpretation of this fiinding is attempted further data need to be described. The records of the eleven cases of Mecholyl

Table 2. *Reactivity to Mecholyl (regardless of age)*

Mecholyl Group	*Number*	*%*
A Normotensives Psychiatric Patients		
I	119	33
II	177	48.5
III	67	18.5
B. Hypertensive Psychiatric Patients		
I	1	7.5
II	1	7.5
III	11	85

$\chi^2 = 33.38$
$p < 0.01$

Type III of the experiment listed in Table II were subjected to a quantitative analysis as in a former study [8]. Six parameters such as the area of fall in blood pressure, the area of increased pulse rate, the quotient $\frac{\text{Area of decreased blood pressure}}{\text{Area of increased pulse rate}}$ etc. were chosen and given numerical values according to the degree of sympathetic responsiveness. The sums of these parameters have been found to be reliable and reproducible indicators of sympathetic responsiveness as measured by the Mecholyl test. They varied between 6 for the strongest and 18 for the weakest sympathetic reaction. Table III shows that the hypertensive Group III shows similar means and range for the sums of the 6 parameters as has been found to be characteristic for Group III of normotensive patients: the difference was not statistically significant. The quotient $\frac{\text{Area of decreased blood pressure}}{\text{Area of increased pulse rate}}$ was even larger in the hypertensive than in the normotensive Group III and the difference between the two groups was significant. It follows that hypertensives belonging to the Mecholyl Group III show in this test all the signs

of sympathetic hyporeactivity which characterize this group in normotensives. If anything, the signs of sympathetic hyporeactivity are even stronger in the hypertensive than in the normotensive group as the "area quotient" referred above indicates. Bearing in mind that this group is two to four times as large in the hypertensives than in the normotensives the investigations seem to indicate a great preponderance of sympathetic hyporeactivity among hypertensives.

Before accepting this rather paradoxical finding it seems advisable to consider further the data presented in Tables I and II. It is surprising to see that Group II which is dominant in normals and in mental cases

Table 3. *Analysis of Eleven Cases of Hypertension of Mecholyl Type III*

A. Based on the "sums" of 6 parameters

Mecholyl Group	*N*	"Sums" *Means*	*Range*
II normotensive	177	11.9	10—15
III normotensive	67	15.1	11—18
III hypertensive	11	15.9	14—17

Statistical difference between	S. D.	S. E.	E	d. f.	p
II and III (normotensives)	1.28	0.40	10.0	186	0.01
III (normo-) and III (hypertensives)	1.42	0.47	1.70	76	0.1

B. Based on the quotient $\frac{\textit{area of decreased blood pressure}}{\textit{area of increased pulse rate}}$

Mecholyl Group	*N*	*Quotient M*
II normotensive	171	0.42
III normotensive	55	0.82
III hypertensive	11	1.33

Statistical difference between	S. D.	S. E.	t	d. f.	p
II and III (normotensives)	0.32	0.05	8.24	224	0.01
III (normo-) and III (hypertensives)	0.58	0.19	2.68	64	0.01

(although to a lesser extent in the latter) has virtually disappeared in the hypertensive group. Only one person out of 57 hypertensives belongs to Group II whereas in normotensives 48 to 74% belong to it (Table IV) *. On the other hand, the sympathetic hyperreactors (Mecholyl Group I) seem to have actually increased their numbers in hypertensives if we compare normo- and hypertensives of similar age. Do hypertensives consist of sympathetic hyper- and hyporeactors while the normal range of sympathetic reactivity is absent, and if so, what is the significance of this peculiar shift in autonomic reactivity?

* Only in the young neuropsychiatric patients is the percentage of the Group II les (29%, Table IV). However, the persons listed in Table I belong to the age group 46 years and older and even in the mixed age group (Table II B) the mean age of the patients was 48 years.

Discussion

The conclusion that blood pressure and pulse rate responses to Mecholyl are determined by the reactivity of sympathetic centers is based on the following facts *. A fall in blood pressure through Mecholyl (or any other hypotension producing procedure) diminishes the discharges from the sino-aortic area and releases, thereby, the sympathetic centers. This release leads to increased vasoconstriction, acceleration of the heart rate and, reciprocally, to a diminished vagal activity. As a result, blood pressure and pulse rate rise. This effect parallels the wide variations in central sympathetic reactivity, particularly of the hypothalamus, induced by stimulation, lesions and drug action confined to its posterior division [9, 10, 21]. By increasing the hypothalamic sympathetic reactivity a response of Type II (consisting of a moderate, reversible fall in blood pressure) could be converted into Type I in which the fall in pressure was lessened and was followed by an over-

Table 4. *Frequency of Mecholyl Group II in Normotensives* *

Total number	*%*	*Age*	
45	69	less than 25	
38	74	26 to 45	Normals *
19	69	46 and older	
35	29	less than 25	
118	48	26 to 45	Neuropsychiatric cases *
55	49	46 and older	
363	48	all age groups	Neuropsychiatric cases **

* See ref. 18 and 19. ** See ref. 8.

shooting. On the other hand, when the central sympathetic reactivity was diminished (through a posterior hypothalamic lesion or the injection of minute amounts of barbiturate into this structure) the hypotensive action of Mecholyl was aggravated and became less reversible. That these findings are applicable to man is suggested by the following observations: 1. Electroshock and other forms of induced convulsions known to produce powerful sympathetic discharges [4, 11] intensify the sympathetic reaction to Mecholyl [5, 11]; 2. There is a parallelism between sympathetic reactivity indicated by the type of response to Mecholyl and the resistance to blackout unter the influence of centrifugal forces [1].

In the light of these findings it can hardly be doubted that Mecholyl responses to Type I, II, and III represent decreasing degrees of central sympathetic responsiveness.

The changes of blood pressure in experimental hypertension are explained either on the basis of increased central sympathetic activity and/or functional and anatomical changes in the kidney. In general, the experimental work to produce chronic hypertension has been more successful

* See ref. 5 for further details.

when the kidney function was altered (*Goldblatt* [12]) than when attempts were made to increase central sympathetic discharges through sino-aortic denervation. Nevertheless, there is a close relation between these two types of approach since section of the buffer nerves which leads to temporary or permanent hypertension causes ischemia of the kidneys as long as the sympathetic nerves innervating the kidneys and adrenals are intact [13 *]. It is, therefore, not improbable that increased sympathetic hypothalamic discharges play an important role in the causation of hypertension at least in its initial stage and that renal changes occur secondarily. This interpretation is supported by the following lines of evidence: 1. Emotional disturbances play an important role in the precipitation of hypertension [28]; 2. The sympathetic reactivity indicated by the response of the blood pressure to emotionally charged interviews is greater in hypertensives than in normotensive individuals [14]; 3. Hypertensive persons show not infrequently a generally increased sympathetic responsiveness [22]; 4. Sympathotonia has been reported to be predominant in the early phase of hypertension [16 a].

The gradual development of hypertension as the result of repeated emotional stresses presupposes some persistance of the autonomic processes evoked by these episodes. It is, therefore, of importance to mention that conditioning known to involve hypothalamic excitation [11] is accompanied by states of increased sympathetic excitation which, in the case of experimental neurosis may last for years [3]. Moreover, even minimal stimuli acting on the sympathetic division of the hypothalamus may greatly increase sympathetic discharges under conditions of repeated excitation and, thereby, predispose to the development of a state of central autonomic imbalance [6].

From the area of animal experimentation the following additional data may be mentioned: 1. Exposure of cats to barking dogs during several months leads to the development of hypertension and also to hypertrophy of the left ventricle [23]; 2. Experimental neurogenic hypertension is characterized by a greater fall in blood pressure on administration of sympathetic blocking agents such as TEA than is seen in control animals and similar results have been obtained in some cases of clinical hypertension [20]. These data suggest the presence of an increased sympathetic discharge in neurogenic hypertension. (See also [27].)

One would, therefore, expect that hypertensives would show predominantly a Mecholyl response of Type I indicating sympathetic hyperreactivity but our results and those of other investigators show that the Type III is chiefly presented — in our cases in about 80%. This finding raises the question whether conditions exist in which in spite of increased central sympathetic activity the Mecholyl response of Type III prevails. The neurogenic hypertension resulting from a denervation of the sino-aortic area is, indeed, such a condition. Since the lowering of the sino-aortic pressure is the chief factor by which the blood pressure is restored following the administration of Mecholyl it is not surprising that this process is ineffective

* Moreover, it was shown recently that angiotensin increases the pressure response of noradrenaline releasing drugs [17 a].

and delayed in sino-aortic denervated animals [7]. Important studies of *McCubbin* and *Page* [17] have shown in renal hypertensive dogs that the baroreceptor activity is greatly diminished at normal blood pressure levels. Apparently, in this form of experimental hypertension these receptors have been reset at a higher level. If applicable to clinical hypertension this resetting would, indeed, account for the appearance of Type III in the Mecholyl test in the majority of the hypertensive patients without compelling us to abandon the concept of simultaneously increased central sympathetic discharges! The greater fall in blood pressure in hypertensives when subjected to a tilting in the "head up"-position [25] is likewise interpretable on this basis. The weakening of the carotid sinus reflexes would also lessen the homeostatic control against blood pressure raising agents, thus accounting for the greater pressor effect of injected noradrenaline in hypertensives than in normotensives [29]. Two further studies lend support to this interpretation. In one, degenerative changes in the baroreceptors have been described in human hypertension [15]; in the other, physiological experiments present evidence that it is the continued increased pressure in the carotid sinus which leads to a diminished activity and to a resetting of the baroreceptors [16].

It seems, therefore, reasonable to suggest that the occurrence of Mecholyl Type III in the great majority of hypertensives is due to the weakening of the baroreceptor reflexes which results from the persistance of an increased blood pressure over long periods of time. The relative high percentage of sympathetic hyperreactors (Mecholyl Type I) in this group may be due to the fact that they represent cases of lesser severity or duration. Further clinical studies, particularly repeated Mecholyl tests on the same persons over several years, are necessary to substantiate, modify, or reject this interpretation.

It should, however, not be forgotten that another possibility exists for the explanation of the predominance of Mecholyl Type III in chronic hypertension. It is conceivable that prolonged hypothalamic sympathetic discharges may ultimately lead to a state of *diminished central sympathetic activity*. Such changes have been produced in the experimental animal by lesions in the posterior hypothalamus and similar procedures. The application of some of the findings in this work may aid in the further analysis of the hypertension problem. It is, therefore, of interest to mention that with the reduction of sympathetic central reactivity the parasympathetic responsiveness was found to be increased as indicated by the increased slowing of the heart rate on injection of noradrenaline [9]. The intravenous injection of this drug and the quantitative determination of its action on blood pressure and heart rate as in earlier studies [8, 18, 19] is recommended in order to decide whether the Mecholyl reaction of Type III, so characteristic for hypertension, results solely from the relative failure of the baroreceptor reflexes or whether a decline in central sympathetic reactivity associated with a reciprocally increased parasympathetic responsiveness is also involved. It should be emphasized that in view of the enormous influence which the baroreceptors exert on the blood pressure, a reduction in hypo-

thalamic sympathetic excitability if combined with a resetting of the buffer mechanism would still be associated with a high blood pressure! If these changes would occur in chronic hypertension a Mecholyl Type III would be expected. It would be the result of the discussed changes in central (hypothalamic) *and* peripheral (baroreceptor) structures. This interpretation would be compatible with the tilting experiments described above and the finding that the noradrenaline concentration in the blood is increased in normotensives but not in hypertensives under these conditions [12a].

Another line of approach to investigate the autonomic basis of clinical hypertension, the determination of the concentration of noradrenaline in blood and urine has not yet produced consistent results. Increased [26] as well as decreased rates [29] of excretion have been reported in hypertension. Perhaps different stages in the disease process account for this discrepancy in correspondence with our suggestion that the response to Mecholyl shifts from Type I to Type III with the progression and duration of the disease.

Summary

In agreement with earlier studies reported in the literature it is found that the majority (about 80%) of hypertensives react to Mecholyl with a marked, prolonged and only partially reversible fall in blood pressure. This type of response seen in experimental subjects, mental patients, and experimental animals in which the central sympathetic reactivity is low, occurs also when the baroreceptors of the sino-aortic area have been eliminated. Since in experimental hypertension a weakening of the baroreceptor discharges and a resetting at a higher level occur it is suggested that the preponderance of Mecholyl Type III in hypertensives results from this diminution in baroreceptor function. It is further suggested that the virtual absence of the most common response to Mecholyl, the Type II, is due to the fact that hypertensives are sympathetic hyperreactors who respond to Mecholyl before failure of the baroreceptors with Type I and after failure with Type III. Studies on the Mecholyl test in an adequate number of recent and old cases are recommended to clarify this question. *Finally, the possibility that the Mecholyl test III in chronic hypertension is due to a lessened central sympathetic reactivity is discussed.*

Zusammenfassung

In Übereinstimmung mit der Literatur fand sich, daß die Majorität von Personen mit Hypertonie auf die Injektion von Mecholyl mit einer erheblichen, langdauernden Blutdrucksenkung reagiert. Diese Reaktion zeigt dieselben Merkmale, die sich mit der Mecholyl-Probe an Mensch und Tier finden, wenn diese an Fällen ausgeführt wird, in denen die zentrale sympathische Erregbarkeit gering ist, entweder spontan oder als das Ergebnis experimenteller Eingriffe. Ähnliche Resultate werden im Tierexperiment nach Beseitigung der Rezeptoren der Blutdruckzügler erhalten. Da die Annahme einer verminderten sympathischen Erregbarkeit in klinischer oder experimentaller Hypertonie vielen Tatsachen widerspricht, ist es mehr wahrscheinlich, daß die Mecholyl-Reaktion der Hypertonie auf eine Verminderung der Aktivität der Rezeptoren der Blutdruckzügler und ihr „Resetting" auf eine höhere Blutdrucklage zurückzuführen ist. Es ist außerdem anzunehmen, daß das Fehlen der beim Normalen häufigsten Gruppe (Mecholyl Typ II) dadurch bedingt ist, daß Hypertoniker in den Frühstadien zum Typ I gehören (sympathisch überreaktiv) und in dem Spätstadium aus den oben

besprochenen Gründen den Typ III aufweisen. Die Richtigkeit dieser Deutung muß noch durch ausgedehnte Studien an alten und jungen Fällen von Hypertonie und den Veränderungen der Mecholyl-Reaktion bei diesen während jahrelanger Beobachtungen bewiesen werden. *Die Möglichkeit, daß der Mecholyl-Test (Typ III) bei chronischer Hypertonie von einer verminderten zentralen sympathischen Erregbarkeit abhängig ist, wird erörtert.*

Résumé

D'accord avec la littérature il fut constaté, que la majorité de personnes hypertoniques réagissent après une injection de la Mécholyle avec une assez durable diminution de la pression sanguine. Cette réaction montre les mêmes caractères qui se trouvent chez l'homme et l'animal avec le test de la Mécholyle, si celle-ci est appliquée en cas d'excitation soit spontanée soit comme résultat d'actions expérimentales. De résultats analogues sont obtenus expérimentalement chez l'animal après élimination des barorécepteurs. Comme la supposition d'une excitation modérée en cas d'hypertonies cliniques et expérimentales est contraire à beaucoup de faits, il est très probable que la réaction mécholylénique de la hypertonie est due à une diminution de l'activité des barorécepteurs et leur montée sur un plus haut degré de la pression sanguine. On peut de plus admettre que la manque du groupe le plus fréquent chez l'individu normal (Mécholyle type II) est la suite du fait que les personnes hypertoniques dans la phase initiale appartiennent au type I (hyperactivité sympathique) et dans les phases tardives montrent le type III d'accord avec les motifs mentionnés plus haut. Le fait de cette interprétation doit être vérifié par des études approfondies en cas récents et chroniques d'hypertonie et les changements de la réaction mécholylénique chez ces cas pendant des longues années. *La possibilité que le test mécholylénique (type III) soit le résultat d'une diminution centrale sympathique en cas d'hypertonies chroniques est discutée.*

References

1. *Cohen, S. I.,* and *A. J. Silverman,* J. Psychosomat. Res. *3* (1959), 185. — 2. *Engle, D. E.,* and *M. W. Binger,* Amer. J. Med. Sc. *198* (1939), 609. — 3. *Gantt, W. H.,* Ann. N. Y. Acad. Sc. *56* (1953), 143. — 4. *Gellhorn, E.,* Physiological Foundations of Neurology and Psychiatry, Minneapolis, University of Minnesota Press, 1953. — 5. *Gellhorn, E.,* Autonomic Imbalance and the Hypothalamus, Minneapolis, University of Minnesota Press, 1957. — 6. *Gellhorn, E.,* Acta neuroveget., Wien, *20* (1959), 181. — 7. *Gellhorn, E.,* Arch. internat. pharmacodyn. thérap. *122* (1959), 221. — 8. *Gellhorn, E.,* and *A. D. Miller,* Arch. Gen. Psychiatr. *4* (1961), 371. — 9. *Gellhorn, E., H. Nakao* and *E. S. Redgate,* J. Physiol. *131* (1956), 402. — 10. *Gellhorn, E.,* and *E. S. Redgate,* Arch. internat. pharmacodyn. thérap. *102* (1955), 162. — 11. *Gellhorn, E.,* and *G. N. Loofbourrow,* Emotions and Emotional Disorders, P. B. Hoeber, New York, 1963. — 12. *Goldblatt, H., J. Lynch, R. F. Hanzal* and *W. W. Summerville,* J. Exper. Med. *59* (1934), 347. — 12 a. *Hickler, R. B., J. T. Hamlin* and *R. E. Wells,* jr., Circulation *20* (1959), 422. — 13. *Grimson, K.,* Proc. Soc. Exper. Biol. Med., N. Y., *44* (1940), 219. — 14. *Hardyck, C., M. T. Singer* and *R. E. Harris,* Arch. Gen. Psychiatr. *7* (1962), 15. — 15. *Hilgenberg, F.,* Acta neuroveget., Wien, *19* (1958), 1. — 16. *Kezdi, P.,* Circulation Res. *11* (1962), 145. — 16 a. *Losse, H., M. Kretschmer, G. Kuban* and *K. Bottger,* Acta neuroveget., Wien, *13* (1956), 374. — 17. *McCubbin, J. W., J. H. Green* and *I. H. Page,* Circulation Res. *4* (1956), 205. — 17 a. *McCubbin, J. W.,* and *I. H. Page,* Science *139* (1962), 210. — 18. *Nelson, R.,* and

E. Gellhorn, Psychosomat. Med. *19* (1957), 486. — 19. *Nelson, R.,* and *E. Gellhorn,* J. Psychosomat. Res. *3* (1958), 12. — 20. *Page, I. H.,* and *J. W. McCubbin,* Amer. J. Physiol. *168* (1952), 208. — 21. *Redgate, E. S.,* and *E. Gellhorn,* Arch. internat. pharmacodyn. thérap. *102* (1955), 179. — 22. *Schneider, R. A.,* and *V. M. Zangari,* Psychosomat. Med. *13* (1951), 289. — 23. *Schunk, J.,* Zschr. klin. Med. *152* (1954), 251. — 24. *Sloane, R. B.,* and *D. J. Lewis, J.* Psychosomat. Res. *1* (1956), 273. — 25. *Sundin, T.,* Acta med. Scand., Suppl. 336 (1958), 1. — 26. *Euler, U. S. von,* Scandinav. J. Clin. Labor. Invest. *4* (1952), 254. — 27. *Wilhelmj, C. M.,* and *H. H. McCarthy,* Exper. Med. *19* (1961), 339. — 28. *Wolf, S., P. S. Cardon, E. M. Shepard* and *H. G. Wolff,* Life Stress and Essential Hypertension, Williams and Wilkins, Baltimore, 1955. — 29. *Yoshinaga, K., T. Sato* and *N. Ishida,* Tohoku J. Exper. Med. *72* (1960), 301.

Anschrift des Verfassers: Prof. Dr. *E. Gellhorn,* 2 Fellowship Circle, Santa Barbara, California (USA).