Pyretotherapy and Subcutaneous Hexamethonium in the Treatment of Severe and Malignant Hypertension

By Pablo Thomsen, M.D., Ramón Ortúzar, M.D., Fernando Goñi, M.D., Cristobal Espíndora-Luque, M.D., and León Vial, M.D.

The permanent lowering of arterial pressure in cases of malignant and severe hypertension is of paramount importance. A new treatment that combines subcutaneous administration of hexamethonium with fever therapy produced by intravenous injections of bacterial vaccine is described. Reduction of blood pressure to normal levels and improvement of eye grounds, electrocardiogram, heart condition and subjective symptoms were obtained. The basis for these effects could be the potentiation of the action of hexamethonium produced by the induced fever.

The seriousness of the picture of severe and malignant hypertension, the usually progressive nature of the resulting vascular alterations, and the meager results obtained in the majority of cases by the medical or surgical treatments that have been recommended warrant any therapeutic innovation which brings about a change for the better in this condition and promises a recession of the malignant features responsible for the sinister prognosis of such cases.

Pyretotherapy has been used for the past 30 years in the treatment of hypertensive retinopathy. The results obtained had been slightly different, but in general the reported cases have shown some improvement.1 2

In 1944, Taylor and Page,2 working on the hypothesis that certain renal extracts might contain hypotensive substances, injected such extracts and observed resulting pyretic crises together with marked hypotension and improvement of kidney function. The same authors reported their results with this method in experimental hypertension and later in hypertensive subjects, concluding that the results were encouraging in cases with preserved renal function, but varied with the pyretogenic substances employed.4 5 Other investigators,6-9 have obtained comparable results, but they have dismissed this form of treatment because of the difficulties and suffering experienced by the patients.

We have not found any description of the use of hexamethonium combined with pyretotherapy, and have proposed it in the hope that the combination of the two methods would enhance the effects produced by each method singly and permit reduction of dosage or frequency of administration, thus avoiding undesirable side effects of hexamethonium and some of the discomfort of pyretotherapy.

This article reports the results obtained with combination of pyretotherapy and hexamethonium in 12 cases of severe and malignant hypertension.

Method

The patients treated were regarded as cases of severe and malignant hypertension by reason of the presence of the following features: (1) Diastolic hypertension above 115 mm. Hg, not modified by 10 days bed rest, salt-free diet and administration of usual dosage of phenobarbital, (2) progressive impairment of general condition, necessitating definite and enforced limitation of activity and (3) vascular damage as evidenced by changes in the eye grounds (five cases showed the complete picture of hypertensive neuroretinopathy), increase in size of the heart, and electrocardiographic signs of left ventricular strain with or without signs of myocardial alteration or coronary insufficiency.

Renal function, as determined by nitrogen retention, specific gravity of urine, concentration test and urea clearance, was variable, but those patients showing marked renal insufficiency were excluded.

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The hexamethonium chloride used in this study was supplied through the courtesy of E. R. Squibb & Sons (as Bistrium) and Burroughs Wellcome & Company, Inc., Tuckahoe, N. Y. (as Hexameton).
because of the risk of the proposed treatment in such cases.

The pyretogenic substance was Neurovaccine Beta, a water-soluble bacterial suspension containing in 1 cc. 50 million Bacillus pyocyaneus, 52.5 million Staphylococcus aureus and 25 million Bacillus prodigiosus. As hypotenstive agents, injectable hexamethonium bromide and chloride were used. After termination of treatment, and with the hope of maintaining the favorable effects produced, therapy was continued with Apresoline and oral hexamethonium.

All patients were hospitalized. For the first 10 days, they were subjected to strict bed rest, salt-free diet, and the usual dosage of phenobarbital. Those patients who at the end of this time had a diastolic pressure below 115 mm. Hg were excluded.

Measurements of arterial pressure were for the most part taken by two persons only, 6 to 15 readings daily being made on each patient, the figure computed being the average of two determinations.

Treatment was begun by observing the response to injection of 10 to 20 mg. hexamethonium, and continued by administering 20 to 50 mg. one to four times in 24 hours. The size and frequency of the dose was determined by the influence on the blood pressure and the side effects produced. In some patients, total doses of 200 mg. of the ion were administered daily. At first the intravenous route was used, but, notwithstanding the recommendations of Freis, very marked declines of pressure occurred, for which reason the subcutaneous route was consistently used thereafter. Upon stabilization of the results thus obtained, pyretic injection was added for six days out of the week in doses increasing from 0.1 to 1 cc. to induce fever of over 102 F. In some patients, the febrile crises were spaced, insofar as maintenance of reduced blood pressure permitted, so that they occurred only two to three times per week. Aminopyrin was used to alleviate the distress attendant upon the thermal reaction, and when declines in arterial pressure were too marked, the foot of the bed was elevated, generally with satisfactory response. We did not resort to pressor amines in such cases because in patients with malignant hypertension, cardiac accidents may result. Moderate restriction of salt was maintained during the treatment.

**RESULTS**

Tables 1, 2 and 3 show the clinical features presented by our cases and the changes produced in the blood pressure, eye grounds, electrocardiogram, cardiac condition, subjective symptoms and general condition, and renal function.

**Arterial Pressure.** Aside from the drops in pressure directly related to administration of hexamethonium, there was an observable gradual decline in pressure measured under basal conditions, immediately after the patient awoke from sleep. After the first weeks of treatment, there were not even isolated recurrences of the high control figures, and the pressure curve tended to stabilize at figures around 170/90 (figs. 1 and 2).

The correlations found between administration of hexamethonium and pyretic injections are illustrated in figures 3 and 4.

**Eye Grounds.** The changes in the ocular fundi of the patients (cases 2, 4, 5, 11 and 12) with hypertensive neuroretinopathy (group IV), were favorably modified to an appreciable extent in all instances. There was no substantial change in the cases manifesting only sclerosis, nor in two patients in whom treatment was suspended prematurely. A striking feature was the marked diminution of hemorrhage when present. Vision improved consistently in those cases where it had been impaired.

**Electrocardiogram.** Of the 11 patients who received treatment of satisfactory duration, one had a normal electrocardiogram at the beginning of treatment. Of the other 10 patients, the abnormal electrocardiogram became normal in four (figs. 5, 6 and 7) except for persistence of left axis deviation; in three cases the height of the T wave in lead I increased more than 1 mm., and in three cases no change occurred.

**Cardiac Condition.** At the start of our studies
Table 2.—Clinical Data before Treatment

<table>
<thead>
<tr>
<th>Case No.</th>
<th>General Condition</th>
<th>Cerebral Involvement</th>
<th>Renal Involvement</th>
<th>Cardiac Involvement</th>
<th>ECG</th>
<th>Eye Grounds</th>
<th>Pressure</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>bad</td>
<td>Hemiparesis</td>
<td>0</td>
<td>Dysp.; card. asthma; L.V. Hyper.</td>
<td>L.V. straing</td>
<td>Marked sclerosis.</td>
<td>250/145</td>
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<tr>
<td>2</td>
<td>bad</td>
<td>0</td>
<td>Urea Cl. 24%; albumin.; cylindruria.</td>
<td>Dysp.; card. asthma; L.V. Hyper.</td>
<td>L.V. straing</td>
<td>Papilledema; hemor.; exudates; gen. constr.</td>
<td>230/130</td>
</tr>
<tr>
<td>3</td>
<td>poor</td>
<td>Pseudobulbar syndrome</td>
<td>0</td>
<td>Mild angina; L.V. Hyper.</td>
<td>L.V. straing</td>
<td>Marked gen. and focal constrict.; mod. sclerosis.</td>
<td>205/120</td>
</tr>
<tr>
<td>4</td>
<td>poor</td>
<td>Albumin.; cylindruria.</td>
<td>0</td>
<td>Gallop; mod. angina; L.V. Hyper.</td>
<td>L.V. straing</td>
<td>Sl. papilledema; hemor.; exudates; mod. sclerosis.</td>
<td>230/125</td>
</tr>
<tr>
<td>5</td>
<td>bad</td>
<td>Hypertens. encephalop.; diplopia</td>
<td>Urea Cl. 30%</td>
<td>L.V. Hyper.</td>
<td>L.V. straing</td>
<td>Papilledema; hemor.; exudates; marked constrict.</td>
<td>230/150</td>
</tr>
<tr>
<td>6</td>
<td>poor</td>
<td>0</td>
<td>0</td>
<td>L.V. Hyper.</td>
<td>L.V. straing</td>
<td>Marked constrict.; mod. sclerosis.</td>
<td>200/125</td>
</tr>
<tr>
<td>7</td>
<td>poor</td>
<td>0</td>
<td>Albumin.; cylindruria.</td>
<td>0</td>
<td>Normal</td>
<td>Sl. blurr. of the disk; mod. sclerosis.</td>
<td>195/125</td>
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<tr>
<td>8</td>
<td>poor</td>
<td>0</td>
<td>0</td>
<td>L.V. Hyper.</td>
<td>L.V. straing</td>
<td>Hemor.; exudates; mod. sclerosis.</td>
<td>220/120</td>
</tr>
<tr>
<td>9</td>
<td>bad</td>
<td>Hemiparesis</td>
<td>Urea Cl. 37%; albumin.; cylindruria.</td>
<td>L.V. Hyper.</td>
<td>L.V. straing</td>
<td>Hemor.; marked sclerosis.</td>
<td>230/130</td>
</tr>
<tr>
<td>10</td>
<td>poor</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>Normal</td>
<td>Mod. sclerosis.</td>
<td>205/115</td>
</tr>
<tr>
<td>11</td>
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<td>0</td>
<td>L.V. Hyper.</td>
<td>L.V. straing</td>
<td>Marked papilledema; exudates; marked sclerosis.</td>
<td>200/115</td>
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<tr>
<td>12</td>
<td>poor</td>
<td>0</td>
<td>0</td>
<td>L.V. Hyper.</td>
<td>L.V. straing</td>
<td>Papilledema; mod. sclerosis.</td>
<td>230/125</td>
</tr>
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</table>

Table 3.—Results of Treatment

<table>
<thead>
<tr>
<th>Case No.</th>
<th>Pressure</th>
<th>Renal Involv.</th>
<th>Eye Grounds</th>
<th>Vision</th>
<th>ECG</th>
<th>Heart Involv.</th>
<th>General Condition</th>
<th>Headache Dizziness</th>
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<tbody>
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<td>1</td>
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<td>0</td>
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<td>+</td>
<td>+</td>
<td>++</td>
<td>++</td>
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<tr>
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<td>++</td>
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<tr>
<td>3</td>
<td>170/105</td>
<td>0</td>
<td>+</td>
<td>0</td>
<td>+++</td>
<td>+</td>
<td>+</td>
<td>+++</td>
</tr>
<tr>
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<td>170/90</td>
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<td>+++</td>
<td>0</td>
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<td>+</td>
<td>++</td>
<td>+++</td>
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<tr>
<td>5</td>
<td>175/100</td>
<td>0</td>
<td>+++</td>
<td>+++</td>
<td>0</td>
<td>+++</td>
<td>0</td>
<td>+++</td>
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<tr>
<td>6</td>
<td>145/85</td>
<td>0</td>
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<td>+</td>
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<td>+</td>
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<td>+</td>
</tr>
<tr>
<td>7</td>
<td>140/90</td>
<td>+</td>
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<tr>
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<td>170/100</td>
<td>0</td>
<td>+++</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>+</td>
<td>+++</td>
</tr>
</tbody>
</table>

The results of the treatment have been evaluated according to the following convention: +++ marked improvement; ++ moderate improvement; + slight improvement; 0 no change; - worse.
definite cardiac insufficiency was present in three patients. There was complete recovery in two, and substantial improvement in one. In one additional patient an anginal syndrome disappeared. There was no appreciable reduction of cardiac size in any instance.

Subjective Symptoms and General Condition. The symptoms due to hypertension disappeared in all but one patient. The general condition improved in seven cases, was unchanged in two, and deteriorated in three owing to intolerance to treatment and vomiting in one case, intercurrent gastrointestinal hemorrhage in another, and arthralgia and general prostration in the third. There was considerable loss of weight in one patient.

Kidney Function. Renal function did not change substantially, but in three patients there were frequent and transitory elevations of blood urea, related to persistent vomiting which necessitated temporary suspension of treatment. In two cases, a pre-existing albuminuria disappeared.

Complications. Acute hypotension, with prolonged syncope necessitating suspension of treatment, was observed in one case. Marked lowering of pressure, which responded to elevation of the feet, was observed on numerous occasions in many patients. Anginal pain appeared in some of these patients during the hypotensive phase, in one instance with electrocardiographic manifestations.

Transitory nitrogen retention, with oliguria as stated previously, was observed in three cases where there was vomiting due to intolerance of the treatment.

Marked arthralgia, myalgia and prostration accompanied the induced fever in the majority of cases, and accounts for resistance of patients to prolonged treatment. Aminopyrin definitely lessened the severity of the symptoms. Constipation, meteorism, vesical paresis and changes in accommodation, all signs related to the effect of hexamethonium on the autonomic nervous system, were observed in nearly all patients in varying degrees.

Discussion

There is now sufficient evidence to support the hypothesis that the high level of diastolic pressure maintained in small arteries and arterioles is the chief, if not the only, cause of malignant hypertension.10-12

The view that the extent of hypertension is the major known factor determining malignancy brings us to the conclusion (1) that
FIG. 3. Case 4. All pressures recorded in supine position. 1-2-53 slight hypotensive response to 50 mg. hexamethonium ion; during the previous weeks the patient had received progressive doses of hexamethonium that were effective at that time. 1-3-53 pyrogen and five hours later 50 mg. hexamethonium ion with marked hypotensive effect. 1-5-53 effect on blood pressure of pyrogen alone. 1-6-53 mild action of hexamethonium. 1-7-53 pyrogen and 50 mg. hexamethonium ion 10 hours later with a slight response, but the summation of the hypotensive effects of fever and of hexamethonium resulted in a low level of pressure. 1-9-53 pyrogen and 50 mg. hexamethonium ion three hours later, a marked and sustained reduction of blood pressure is obtained. This represents potentiation of hexamethonium by pyrogen. 1-10-53 slight effect of hexamethonium. 1-12-53 50 mg. of hexamethonium ion one hour after pyrogen; also a potentiation of hexamethonium.

FIG. 4. Case 8. All pressures recorded in supine position. 12-11-52, development of tolerance and poor response to hexamethonium. 12-12-52, no pressure change with pyrogen. 12-13-52, pyrogen plus hexamethonium three hours later. Prolonged and accentuated hypotension. 12-14-52, increased response to hexamethonium.
**Fig. 5.** Case 3. A, 1-9-52, before treatment. Marked hypertensive pattern with slight left axis deviation. B, 8-29-52 after five weeks of treatment. Marked improvement.

**Fig. 6.** Case 5. A, 8-19-52, before treatment. Left ventricular strain. B, 9-17-52, after two weeks of treatment. T wave less inverted in lead I, higher in leads V3 and V4, and positive in lead V5. C, 10-28-52, after eight weeks treatment. Further improvement, disappearance of S-T depressions, T wave isoelectric in lead I, T wave positive in precordial leads.

**Fig. 7.** Case 11. A, 10-24-52, before treatment. Well marked left ventricular strain pattern. B, 12-7-52, after five weeks of treatment. Marked improvement; T wave positive in standard and precordial leads.
malignant hypertension may appear in any type of severe hypertension which is accompanied by sustained high diastolic pressures, and (2) that if the arterial pressure is reduced sufficiently before there is major renal impairment, recession of the syndrome to a benign form of hypertension may be possible. This would be what we might call a “reversible phase of malignant hypertension.”

The correctness of the former statement has been demonstrated by the description of cases with the clinical and histological features of malignant hypertension in which the elevation of blood pressure was due to chronic pyelonephritis, periarteritis nodosa, pheochromocytoma, Cushing’s syndrome, chronic lead poisoning and chronic nephritis. Pickering has pointed out that the only form of hypertension known in which hypertensive neuroretinopathy, progressive renal insufficiency and arteriolonecrosis have not been observed is aortic coarctation.

That sustained reduction of arterial pressure will eliminate malignant features appears from the observations of Smithwick, Hammertrom and Beechgaard and Pickering.

From these observations it may be inferred that when the malignant phase appears in any type of arterial hypertension, it is imperative to seek to reduce the blood pressure in order to prolong the life of the patient. When the original hypertension is so-called “essential hypertension,” hope may be entertained of securing regression to the benign form, with its far more favorable prognosis, especially if pressure within acceptable limits can be maintained. The treatment we have used in our patients apparently produced these results, having not only systematically reduced the pressure but also favorably altered the aspect of the eye ground in those patients who had hypertensive neuroretinopathy.

Kidney function, on the other hand, in those patients in whom it had seriously deteriorated, underwent no change. Indeed these patients sometimes showed an increase in nitrogen retention, such increase being associated in the majority of cases with gastrointestinal disturbances, diarrhea or vomiting, accompanied by oliguria. On other less frequent occasions, rise in uremia was linked with excessive and sustained declines of pressure.

In those patients in whom pyretotherapy was discontinued but hexamethonium alone or in combination with Apresoline continued, the pressure has remained at satisfactory levels and the subsequent course so far has been that which is characteristic of benign essential hypertension. In the patients in whom therapy with oral hexamethonium and Apresoline was not continued for lack of drugs, a return to the initial arterial pressure values was observed.

Taylor and Page, in their series of 20 patients treated by pyretotherapy alone, found marked improvement of electrocardiogram in 11 patients and moderate improvements in the remaining 9. White and his co-workers, discussing the results obtained in operations by Smithwick, noted an increase of more than 1 mm. in the height of the T wave in lead I in 47 per cent of the patients. Doyle found improvement of the electrocardiograms of 76 per cent of the patients treated by Smirk with hexamethonium. The improvement appeared to be proportional to the degree of control of arterial pressure gained by the treatment. Our series is smaller, but generally accords with the results of Doyle.

The first parenteral administration of hexamethonium produced sudden and prolonged drops of pressure. Subsequent doses, even if larger, had less effect, and the daily pressure curve was highly irregular during this period. In some cases, the maximum doses administered were ultimately without effect. Upon institution of pyretotherapy, hexamethonium regained its effectiveness, and the blood pressure levels present after the effect of the drug had worn off, were below those preceding pyretic injection. Thus a gradually descending curve was established, permitting wider spacing of febrile crises while sustaining their immediate favorable effects.

It was also possible to show that the sensitization to hexamethonium resulting from pyretic injection begins minutes after injection and remains marked for as long as seven hours, and, at times, continues into the following day. Induction of fever is not necessary to secure lowering of pressure and potentialization of the
effects of hexamethonium, satisfactory results being obtained when fever is suppressed with antipyretics. Add to this the fact that the potentiating effect of the pyretic injection on the action of hexamethonium manifests itself almost immediately upon injection, prior to appearance of fever, and we may assume that it is not the temperature rise in itself that produces the results obtained, but that these results are due to other mechanisms having to do with the injection of foreign protein. The term "pyretotherapy" would then be inappropriate, and we might more correctly speak of intravenous bacterial proteinotherapy.

It may well be asked whether the results obtained in our cases were effected exclusively through the drop in pressure produced by the combined therapy, or whether fever also acted through some other mechanism. Selye21 feels that pyrogenics are definitely powerful "stressors" which might, at least in part, act to correct a generalized modified alarm syndrome.

Again, the increase in renal circulation produced by the fever might be a beneficial factor in the correction of hypertension.

**Summary and Conclusions**

(1) So-called "pyretotherapy" by bacterial vaccines, used alone, is capable of producing major declines of pressure in patients with severe and malignant hypertension, but very frequent injections are required and poorly tolerated by the majority of patients.

(2) Injectable hexamethonium induces hypotension in many patients with severe and malignant hypertension, but habituation to the drug sets in rapidly and necessitates increase of dosage to values producing intolerable effects.

(3) Combination of hexamethonium and pyretotherapy has been shown to be capable of markedly reducing pressure levels in patients with severe and malignant hypertension, at the same time improving eye ground and vision, electrocardiogram, cardiac condition and subjective symptomatology.

(4) This combination has made it possible (a) to space the pyretic injections so as to render prolonged treatment more tolerable, and (b) to reduce the daily dose of hexamethonium to values that do not cause major side-effects.

(5) The source of this advantage would appear to lie in an increased sensitivity to hexamethonium produced by the pyretic injection.

(6) These results are not linked with the temperature rise, since they occur before the latter has appeared, persist after it has disappeared, and are present when fever is prevented with antipyretics.

(7) This treatment appears to be advisable in patients with severe and malignant hypertension resistant to hexamethonium or other therapeutic means now employed. In our experience it has also been useful in cases resistant to combination of hexamethonium and Apresoline.

(8) The treatment requires hospitalization of patients and continuous medical supervision.

**Acknowledgment**

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**Summario in Interlingua**

In casos de sever e maligne hypertension le reduction permanente del pression arterial es de importancia cardinal. Es desribite un nove trattamento que combina le administration subcutanea de hexamethonium con un therapia a febre producete per le injection intravenose de vaccino bacterial. Esseva obteinte le reduction del pression sanguine a nivello normal e le melioration del fundo del oculos, del electrocardiagma, del condition del corde, e del symptomas subjective. Il es possibile que le base de iste effectos es a cerar in un potentia- tion del action de hexamethonium per le febre resultante del injection bacterial.

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