A Clinical Appraisal of Pentapyrrolidinium (M&B 2050) in Hypertensive Patients

By Edward D. Freis, M.D., Edward A. Partenope, M.D., Lawrence S. Lilienfield, M.D., and John C. Rose, M.D.

The new ganglionic blocking agent, pentapyrrolidinium or M&B 2050, appears to have several distinct advantages over hexamethonium in the treatment of severe hypertension. These advantages include longer duration of action, greater potency, less tolerance, less interference with intestinal motility, and, most important, a more uniform response from day to day on oral administration. However, critical adjustment of dosage is necessary and side effects are not infrequent, the most disturbing being postural faintness and impotence.

The advantages as well as the deficiencies of hexamethonium in the treatment of hypertensive patients have stimulated interest in the development of ganglionic blocking agents which will retain the desirable effects of hexamethonium and eliminate its undesirable qualities. By the very nature of its action it can be expected that any drug which acts by inhibiting transmission through autonomic ganglia will exhibit many of the side effects of such blockade. However, it seems possible that there may be differences in the predilection of various compounds for certain ganglia as compared with others; and also that other advantages might be gained, such as longer duration of action, lessened tolerance, greater and more predictable absorption from the gastrointestinal tract, which would decrease the hazards and inconveniences attendant upon hexamethonium administration.

Recently, a new ganglionic blocking agent, pentamethylene 1:5-bis-(1-methyl-pyrrolidinium bitartrate) (pentapyrrolidinium or M&B 2050) has been synthesized by Libman, Pain and Slack.3

Detailed pharmacologic studies in animals have been carried out by Wein and Mason.4 Preliminary clinical trials by Campbell and Maxwell suggested that the new drug was more potent, longer-acting, and produced a more predictable response on oral administration than hexamethonium.5 Smirk found that pentapyrrolidinium administered orally was more effective and better tolerated by hypertensive patients than was hexamethonium.6 The purpose of the present report is to describe the experiences in this clinic with this new agent in hypertensive patients. For the sake of clarity all dosage of both hexamethonium and M&B 2050 will be referred to in terms of the amount of ion. Hexamethonium was administered in the form of the chloride and M&B 2050 as the bitartrate salt.

Potency and Duration of Action of M&B 2050 as Compared with Hexamethonium

Four hospitalized hypertensive patients were given hexamethonium intravenously in an amount sufficient to produce a significant reduction of arterial pressure. Several days later pentapyrrolidinium was injected slowly intravenously until the fall of blood pressure was similar to that produced by the hexameth-
onium. These patients had received no prior therapy with either agent.

On the basis of these acute comparative studies M&B 2050 was approximately five (range four to seven) times more potent than hexamethonium (table 1). The average duration of action of M&B 2050 also was 42 per cent (range 40 to 46 per cent) longer than that of hexamethonium.

During an intravenous titration with hexamethonium the blood pressure falls rapidly when the effective dose has been reached. When M&B 2050 is administered intravenously, however, the reduction in the blood pressure proceeds more gradually over a period of 10 minutes or more following an effective dose. Thus, intravenous titration with M&B 2050 is more difficult than with hexamethonium since the effective dose may be exceeded. This could be avoided in some measure by injecting the drug quite slowly with the patient sitting on the side of the bed, since postural hypotension appears before supine hypotension.

**Relation between Effective Parenteral and Oral Dosages of M&B 2050**

Following intravenous titration 10 hypertensive patients were treated with M&B 2050 subcutaneously twice daily either in the hospital or, occasionally, in the home. If treatment was on an ambulatory basis, the blood pressure was recorded five times daily in the home. At the end of one week parenteral therapy was discontinued and the drug administered orally every eight hours. The dosages were increased every other day until the average daily blood pressure approximated that achieved during parenteral therapy.

The mean effective parenteral dose of M&B 2050 was 15 mg. per day, whereas the mean daily oral dose was 280 mg. Thus, the effective oral dose was approximately 20 times as great as the effective parenteral dose. This relationship between oral and parenteral dosage is similar to that previously observed with hexamethonium. It also agrees in general with urinary recoveries of M&B 2050 in animals, which indicated that less than 20 per cent of an orally administered dose is absorbed.

Pentapyrrolidinium given orally differed from hexamethonium administered orally in one important respect. The onset of action was far more predictable than with hexamethonium, beginning approximately one hour after an effective dose. There also was less variation from day to day in the response to a given dose of M&B 2050 than had previously been experienced with the response to hexamethonium. However, as will be discussed later, many extraneous factors influenced the response to M&B 2050 so that the extent of blood pressure reduction was not completely uniform from one day to another. The improvement in predictability of response after M&B 2050 as compared with hexamethonium was one of degree, therefore, rather than being an absolute qualitative difference.

**Tolerance to M&B 2050**

During one week of therapy with M&B 2050, administered subcutaneously twice daily to 10 hypertensive patients, there was no evidence of development of tolerance. In five of these listed in table 2 at the end of the week the mean effective dose of M&B 2050 was 0.5 times less (range −1.8 to +1.6 times) than the initial titrating dose. Five of these patients previously

### Table 1.—Comparison of Single Intravenous Doses of Hexamethonium (C6) and Pentapyrrolidinium (M&B 2050) in Previously Untreated Hypertensive Patients

<table>
<thead>
<tr>
<th>Patient</th>
<th>Blood Pressure</th>
<th>Reduction of Blood Pressure</th>
<th>Change in Heart Rate Beats Min.</th>
<th>Dose, mg. of Ion</th>
<th>Duration of Effect in Hours</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>mm Hg</td>
<td>mm Hg</td>
<td>After M&amp;B</td>
<td>C6</td>
<td>M&amp;B 2050</td>
</tr>
<tr>
<td>C. B.</td>
<td>195/120</td>
<td>28/22</td>
<td>48/35</td>
<td>0</td>
<td>-4</td>
</tr>
<tr>
<td>R. C.</td>
<td>220/145</td>
<td>65/30</td>
<td>72/38</td>
<td>+16</td>
<td>+18</td>
</tr>
<tr>
<td>A. S.</td>
<td>215/115</td>
<td>68/27</td>
<td>92/28</td>
<td>-4</td>
<td>-4</td>
</tr>
<tr>
<td>P. D.</td>
<td>185/135</td>
<td>60/20</td>
<td>50/30</td>
<td>+18</td>
<td>+16</td>
</tr>
</tbody>
</table>
had been under continuous therapy with hexamethonium for periods of 6 to 19 months. Review of their records showed that at the end of the first week of therapy with hexamethonium given subcutaneously, dosages had been raised progressively to a mean dose which was 1.9 times (range 1.5 to 2.5 times) the initial titrating dose. Thus, during this short period of observation the degree of tolerance induced by M&B 2050 administered subcutaneously was far less than that experienced previously with hexamethonium.

If oral administration was begun without any preceding period of parenteral therapy, there frequently was a transient hypotensive response lasting one to several days and occurring at a level considerably below the final effective maintenance dose. Following this, the increase in tolerance to the drug was very slight. For example, in 15 patients treated with oral M&B 2050 alone for periods varying from three to six weeks, the mean effective dose at the beginning of therapy was 232 mg. (range 45 to 518 mg.) per day; while at the end of the above period the average effective dosage was 275 mg. (range 135 to 562 mg.) per day.

**Cross Tolerance Between M&B 2050 and Hexamethonium**

The degree of cross tolerance existing between M&B 2050 and hexamethonium seemed to be very small. This was estimated in five patients who had been treated continuously with hexamethonium, subcutaneously administered for periods of six months to two years (table 2). When comparison is made between the initial effective dose of hexamethonium obtained by intravenous dosage (prior to any previous therapy with ganglionic blocking agents) and the initial effective titrating dose of M&B 2050 (after prolonged therapy with hexamethonium) the data indicate that M&B 2050 was approximately 2.5 times more active (range 0 to 4 times) than hexamethonium. Thus, in these hexamethonium-treated patients, the relative potency of M&B 2050 was only half as great as in patients previously untreated with ganglionic blocking agents.

However, when comparison was made in these same patients between the initial titration dose of M&B 2050 and the dosage of hexamethonium required after prolonged therapy with the latter drug, the mean relative potency of M&B 2050 was 13.5 times (range 5 to 35 times) that of hexamethonium. It would appear, therefore, that the degree of cross tolerance between the two drugs is so slight that for practical clinical purposes one may consider that tolerance to hexamethonium does not induce significant tolerance to M&B 2050.

**Factors Potentiating the Hypotensive Response to M&B 2050**

Since the majority of the patients under treatment with M&B 2050 recorded their blood pressures at home, it was possible to study in some detail the various extraneous factors which influenced the blood pressure. These were as follows:

*Postural Effects.* (1) When the patient was up and about a smaller dosage usually was necessary to lower the blood pressure than when he was supine. Hence, a larger dose usually was required at bedtime. (2) Severe postural hypotension with faintness occurred more frequently after the morning dose than at other times. (3) Some of the patients noticed increased nocturia accompanied by decreased urinary frequency during the day.

*Additive Effects of Other Vasodilating Influences.* (1) The ingestion of alcohol frequently was followed by marked potentiation of the hypotensive action of M&B 2050. The amount

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**Table 2.—Effect of Hexamethonium and Pentapyrrolidinium in the Same Patients Showing Development of Tolerance to Each and Degree of Cross Tolerance**

<table>
<thead>
<tr>
<th>Patient</th>
<th>Hexamethonium Ion, Effective Dose (mg.)</th>
<th>Pentapyrrolidinium Ion, Effective Dose (mg.)</th>
</tr>
</thead>
<tbody>
<tr>
<td>A. S.</td>
<td>Initial 8, After 1 wk. 12, After 6 to 18 mos. of treatment 20</td>
<td>Initial 2, After 1 wk. 1.5</td>
</tr>
<tr>
<td>H. B.</td>
<td>Initial 30, After 1 wk. 75, After 6 to 18 mos. of treatment 100</td>
<td>Initial 11, After 1 wk. 10</td>
</tr>
<tr>
<td>C. P.</td>
<td>Initial 2, After 1 wk. 4, After 6 to 18 mos. of treatment 75</td>
<td>Initial 1.8, After 1 wk. 3</td>
</tr>
<tr>
<td>O. H.</td>
<td>Initial 30, After 1 wk. 45, After 6 to 18 mos. of treatment 90</td>
<td>Initial 11, After 1 wk. 11</td>
</tr>
<tr>
<td>J. C.</td>
<td>Initial 50, After 1 wk. 100, After 6 to 18 mos. of treatment 120</td>
<td>Initial 20, After 1 wk. 11</td>
</tr>
</tbody>
</table>
of alcohol need not be large since one or two “cocktails” was sufficient to induce significant additional reductions of blood pressure. (2) The ingestion of a large meal at times acted as a potentiating factor. (3) Vigorous exercise such as pushing a lawn mower was followed at times by an additional fall of blood pressure. This was in contrast to the untreated individual whose blood pressure usually increases with exercise. (4) During the hot summer weather the dosage of M&B 2050 frequently had to be reduced because of marked hypotension. The incidence of postural faintness or frank syncopal attacks increased at the onset of a period of unusually hot weather.

Salt Depletion. (1) When patients were placed on diets rigidly restricted in sodium the hypotensive effect of M&B 2050 was exaggerated. Such individuals became unusually susceptible to postural hypotension, while the margin widened between the level of blood pressure in the erect position as compared with the supine position. For this reason it seemed advantageous to permit a moderate salt intake in all of the noncardiac patients. In this way dosages could be raised to the point of influencing the supine pressure without inducing postural syncope. (2) Mercurial diuretics were administered at times to the cardiac patients in order to control the signs of congestive heart failure although the necessity for using them usually decreased greatly after the institution of hypotensive therapy. It was noted that as the edema accumulated the dosages of M&B 2050 became progressively less effective. However, immediately following the mercurial-induced diuresis marked reductions of blood pressure occurred. For this reason it was necessary in some instances to reduce the dosage of M&B 2050 for a day or two following the mercurial injection. (3) The potentiating action of hot weather described above may have been due in part to excessive salt loss.

Therapeutic Results

Twenty-seven patients were treated with M&B 2050 orally as the sole medication for periods varying from two to six months. All could be classified as having severe, “fixed” hypertension. Twelve had grade IV hypertension with papilledema or had shown evidence of papilledema in the recent past (21 of the total group had received previous therapy with other drugs), nine had grade III and six had grade II hypertension.

Dosages of the drug were administered as close to every eight hours as possible, the first dose being taken immediately after arising in the morning. Because of its long duration of action, the dosages of M&B 2050 should be widely spaced in order to avoid the additive effect of one dose overlapping on another.

Following the initial period of adjustment the mean daily effective dose was 300 mg. (range 135 to 630 mg.) of the ion. This was divided as follows: the average morning requirement was 95 mg., the afternoon dose 86 mg., and the mean bedtime dose was 122 mg. The larger dosage at night was well tolerated and usually was required to lower the blood pressure while the patient was in the supine position.

The results are based on the means of many home and clinic readings taken with the patient in the sitting position (table 3). Recordings taken with the patient in the supine position were somewhat higher, and those taken in the erect position were somewhat lower. The control value in each case was the level of blood pressure taken prior to any therapy after 48 hours or more of rest in bed in the hospital.

The average pretreatment blood pressure for the entire group was 230/135 (range 180/110 to 260/160) mm. Hg; the mean post-treatment

<table>
<thead>
<tr>
<th>Reduction of Blood Pressure</th>
<th>No.</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Systolic</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>60 mm. Hg or more</td>
<td>15</td>
<td>55</td>
</tr>
<tr>
<td>40 mm. Hg or more</td>
<td>22</td>
<td>81</td>
</tr>
<tr>
<td>20 mm. Hg or more</td>
<td>26</td>
<td>96</td>
</tr>
<tr>
<td>Less than 20 mm. Hg</td>
<td>1</td>
<td>4</td>
</tr>
<tr>
<td><strong>Diastolic</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>30 mm. Hg or more</td>
<td>14</td>
<td>52</td>
</tr>
<tr>
<td>20 mm. Hg or more</td>
<td>23</td>
<td>85</td>
</tr>
<tr>
<td>15 mm. Hg or more</td>
<td>24</td>
<td>89</td>
</tr>
<tr>
<td>Less than 15 mm. Hg</td>
<td>3</td>
<td>11</td>
</tr>
</tbody>
</table>
blood pressure was 170/110 (range 130/95 to 210/130) mm. Hg. Slightly more than 50 per cent of the patients exhibited a reduction of 60 mm. Hg or more in systolic pressure and of 30 mm. Hg or more in the diastolic pressure. Twenty-two, or 81 per cent, showed systolic reductions of 40 mm. Hg or more and 23, or 85 per cent exhibited diastolic reductions of 20 mm. Hg or more.

The hypotensive response to M&B 2050 was somewhat more predictable than the response to hexamethonium and once a maintenance dosage level had been established, the necessity for constantly modifying it was not nearly as great. Nevertheless, variability produced by the extraneous additive factors previously discussed or by unknown causes was sufficient to be an ever-present potential source of inconvenience and even hazard to many patients.

For example, patient C. P., a 42 year old, white, male teacher with "malignant" hypertension in therapeutic remission was taking 3 doses per day of 100, 150 and 350 mg. of M&B 2050 in the morning, afternoon and at bedtime, respectively. On arising in the morning his blood pressure usually was 190/110 mm. Hg; this fell after the morning dose to 140/95 mm. Hg. It then rose gradually to 190/120 mm. Hg at 2 p.m. but fell again after the 2 p.m. dose to 160/110 mm. Hg. During the evening the blood pressure rose gradually to 190/120 mm. Hg. Two hours after his morning dose on a hot July day he walked up a steep hill to the hospital for his regular office visit. When he appeared in the clinic he was pale and on the verge of syncope. His blood pressure sitting in a chair was 90/75 mm. Hg. Immediately after lying down the pressure rose to 165/115 mm. Hg, and after resting supine for an hour the patient was able to go about his usual day's activities.

**SIDE EFFECTS**

The so-called side effects of M&B 2050 were similar to those experienced with hexamethonium; all could be accounted for on the basis of ganglionic blockade. The most prominent of these were postural faintness, dry mouth and loss of visual accommodation (table 4). These side effects were most pronounced when the blood pressure was the lowest. Many of the patients required reading glasses with positive lenses for occupations requiring accommodation for near vision and tinted glasses to wear in bright sunlight because of the failure of pupillary constriction.

In contrast to the lack of constipation in patients treated with parenteral M&B 2050, oral ingestion of the drug was accompanied by some degree of constipation in many instances (table 4). It was not as severe as that observed in patients taking hexamethonium and in most instances responded to oral neostigmine in doses of 15 to 45 mg. In a few instances irritant cathartics also were necessary. Paralytic ileus and severe obstipation did not occur. One of the patients who suffered severe bouts of acute gastric dilatation when taking parenteral hexamethonium suffered a similar attack on oral M&B 2050.

Imotence was a frequent and troublesome side effect in the male. In general the middle aged and elderly patients suffered complete impotence during the entire period of treatment whereas most of the younger patients were only partially incapacitated. The urethane of b-methylcholine (Urecholine), 10 mg. under the tongue every hour for three hours preceding sexual intercourse, seemed to benefit some of the patients, but it is impossible to say whether the effect of Urecholine was real or psychogenic.

A few patients complained of chilly sensations in a cold environment probably due to failure of reflex vasoconstriction in the skin. This required that they dress warmly during

**Table 4.—Incidence of Side Effects Produced by Pentapyrrolidinium in 27 Hypertensive Patients**

<table>
<thead>
<tr>
<th>Side Effect</th>
<th>No.</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Impaired visual accommodation</td>
<td>14</td>
<td>52</td>
</tr>
<tr>
<td>Dry mouth</td>
<td>12</td>
<td>40</td>
</tr>
<tr>
<td>Constipation of any degree</td>
<td>11</td>
<td>40</td>
</tr>
<tr>
<td>Not controlled by neostigmine</td>
<td>4</td>
<td>15</td>
</tr>
<tr>
<td>Enemas required</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Postural faintness</td>
<td>8</td>
<td>30</td>
</tr>
<tr>
<td>Postural syncope</td>
<td>1</td>
<td>4</td>
</tr>
<tr>
<td>Impotence</td>
<td>8</td>
<td>30</td>
</tr>
</tbody>
</table>
cooler weather in order to conserve body heat. None of the patients taking M&B 2050 suffered from inability to empty the urinary bladder; one of these patients had been unable to take hexamethonium because of this side effect.

Certain side reactions, particularly dryness of the mouth and frequent postural faintness, were most prominent during the early stages of treatment but tended to diminish as treatment progressed, whereas other side effects such as impotence remained unchanged during the entire period of treatment.

**DISCUSSION**

The purposes of this study were twofold: to determine, first, whether M&B 2050 possessed therapeutic advantages over hexamethonium and, second, whether it could be given safely and effectively by the oral route of administration. Our findings in general are in agreement with those of Smirk. In regard to the first question M&B 2050 appeared to be superior to hexamethonium in several respects:

1. The degree of tolerance induced by M&B 2050 definitely was less than that observed with hexamethonium. The negligible degree of cross tolerance was of theoretic as well as of practical importance. The reason for the development of “tolerance” to the hypotensive effects of hexamethonium has not been clear. It was unknown whether this represented a true drug tolerance or whether, despite continued ganglionic blockade, some other hypertensive mechanism operating humorally, or in some other way not dependent upon transmission of impulses through automatic ganglia, had been activated to restore the hypertension. The fact that after the development of tolerance to hexamethonium the patients remained sensitive to relatively small doses of M&B 2050 suggests strongly that the resistance to hexamethonium represented true drug tolerance. From the practical point of view the lesser degree of tolerance experienced with M&B 2050 permitted management of the patient with less frequent need for dosage readjustment.

2. When compared with hexamethonium, the duration of action of pentapyrroolidinium was longer than that of hexamethonium and permitted less frequent administration.

3. The response following oral administration of M&B 2050 was more predictable than that observed after hexamethonium. The effective dosage range was not as wide and the variations of blood pressure response on a given dose from day to day not as great. The greater predictability of response may have been related at least in part to the lesser effect of M&B 2050 on intestinal motility than that produced by hexamethonium. The degree of constipation and stasis in the gastrointestinal tract produced by oral M&B 2050 could be controlled usually by simple measures such as the administration of oral neostigmine. As a result accumulation of the drug in the gut seldom occurred. In the case of oral hexamethonium such accumulation of the drug may be followed by absorption of large dosages over a long period of time leading to severe and persistent hypotensive reactions. Although syncopal attacks occurred after M&B 2050, the prolonged collapse reactions often accompanied by ileus were not seen as they had been with hexamethonium.

Nevertheless, oral therapy with M&B 2050 left much to be desired. Some of the patients were controlled, with minimal side effects, but in the majority critical dosage adjustment was required, slight excesses producing hypotensive reactions and slight under-dosage failing to induce a significant hypotensive response. In addition, in order to lower the blood pressure, it usually was necessary to elevate dosage to a point where side effects were frequent particularly during the early weeks of adjustment.

During the treatment period it was observed frequently that vasodilator influences such as heat, alcohol, exercise and food, which ordinarily would have no effect on blood pressure, produced a significant hypotensive effect in the patient treated with M&B 2050. Under normal conditions such vasodilator influences are opposed immediately by homeostatic vasoconstrictor responses mediated over the sympathetic nervous system. These reflexes produce vasoconstriction in other vascular areas thereby preventing any appreciable fall in total peripheral vascular resistance. However, M&B
by producing ganglionic blockade, prevents these homeostatic adjustments. Therefore vasodilation in one vascular area will be unopposed by vasoconstriction in other regions, and, if the dilated area is large, the systemic blood pressure will fall. These considerations provide a rational basis for combining the ganglionic blocking agents with other vasodilating drugs. The effects of combining pentapyrrolidinium with other hypotensive agents will be discussed in a succeeding paper.10

**Summary and Conclusions**

1. Comparisons were made between the effects of hexamethonium and pentapyrrolidinium (M&B 2050) in hypertensive patients. The following differences were noted: (a) M&B 2050 was approximately five times more potent than hexamethonium. (b) The duration of the hypotensive effect was 40 per cent longer. (c) Less tolerance occurred after M&B 2050. Cross tolerance between this drug and hexamethonium was very slight. (d) Less constipation was produced by M&B 2050 and there was no interference with emptying of the urinary bladder. The constipation could be controlled with oral neostigmine and/or irritant cathartics. (e) On oral administration a more predictable hypotensive response was obtained.

2. The other side effects of ganglionic blockade were similar to those observed with hexamethonium.

3. Various extraneous factors such as postural changes, ingestion of alcohol or a heavy meal, exercise, hot weather and salt depletion intensified the hypotensive effect of M&B 2050.

4. Unlike hexamethonium it was possible to lower the blood pressure significantly in the majority of patients with oral administration of M&B 2050 without producing prolonged collapse reactions or paralytic ileus. However, critical adjustment of dosage was necessary and side effects were not infrequent, the most disturbing being postural faintness and impotence. For these reasons M&B 2050 seems to be of greatest value in those cases of severe hypertension which cannot be controlled by simpler measures.

**Sumario Español**

El nuevo agente bloqueador ganglionar, pentapyrrolidinium o M&B 2050 aparenta tener ciertas ventajas distintivas sobre el hexamethonium en el tratamiento de la hipertensión severa. Estas ventajas incluyen una acción más prolongada, mayor potencia, menor tolerancia, menos interferencia con la movilidad intestinal y mas importante aún, una respuesta mas uniforme de día en día a la administración oral. Sin embargo, un ajuste crítico de la posología fue necesario y los efectos no deseados no fueron infrecuentes, el más alarmante siendo el desfallecimiento postural y la impotencia.

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