SOME OBSERVATIONS ON THE EFFECT OF ALPHA-METHYL-DOPA ON MODERATE AND SEVERE HYPERTENSION

By C. S. Toh and C. H. Lim

(Department of Clinical Medicine, University of Singapore)

INTRODUCTION

It is well established now that hypotensive drugs are capable of prolonging the life of severe hypertensives. A good number of drugs are available for this purpose. The ganglion-blocking agents, though potent, had many side effects which often made the treatment of the disease more unpleasant than the disease itself. However, for the severe hypertensives who face the constant danger of a crisis, the treatment was worthwhile in spite of the side effects. The Rauwolfia and Thiazide compounds with relatively few and mild side effects are widely used for the treatment of mild hypertension; whilst guanethidine has taken the chief place in the treatment of moderate and severe hypertension. The ideal hypotensive drug should possess the following qualities:

1. It should be able to lower the recumbent as well as the standing blood pressure.
2. Minimal side effects.
3. Tolerance should not develop to the drug.
4. Absorption should be good and uniform when given orally.

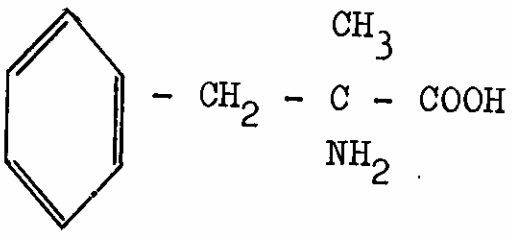
In the last three to four years alpha-methyl-dopa (Aldomet) has been tried with some success in a number of centres (L. Gillespie et al, 1962, R. O. H. Irvine et al, 1962, M. Hamilton, et al, 1963, A. Smirk, 1963).

The object of the present investigations are:—

1. To assess its hypotensive potency.
2. To evaluate its long-term use in the treatment of moderate and severe hypertension and
3. To note the side effects.

PHARMACOLOGY

Alpha-methyl-dopa (1-alpha-methyl-3, 4-dihydroxy-1-phenylalanine) has been known for many years to possess the property of inhibiting decarboxylation of L-aromatic amino-acids to their corresponding amine compounds. Thus it inhibits the decarboxylation of 3,4 hydroxyphenylalanine (dopa) to dopamine which is the precursor to the synthesis of nor-epinephrine and epinephrine.



Structural formula of alpha-methyl-dopa.

In 1960, Oates et al demonstrated the hypotensive properties of both DL and L forms of this drug.

Subsequently, it was found that only the L-isomer was the active compound. Work by Gillespie et al 1962 and Sjoerdsma et al, 1963, showed that the drug is incompletely absorbed from the gastrointestinal tract. It disappeared from plasma with a half life of 2 hours. Urinary excretion is rapid, but part of it is excreted in the faeces. It is excreted unchanged and as alpha-methyl-dopamine.

MATERIAL AND METHOD

Twenty patients were selected for the trial. They all had persistent diastolic pressures of 120 mm. Hg. or more in spite of three days' rest in hospital. Cases with high casual readings in outpatient but whose diastolic pressure

fell below 120 mm. Hg. on admission were omitted from the trial. The age distribution ranged from twenty five to fifty eight years. There were nineteen males and one female.

Two patients had malignant hypertension, eleven had moderate to severe hypertension with Grade 3 retinopathy (following the Keith-Wagner classification) and seven had either Grade 1 or 2 retinopathy. Of the twenty patients, eight had hypertension of proven renal origin. The other twelve patients probably had essential hypertension. The high proportion of cases with renal hypertension was picked up purely by chance during routine investigations.

TYPES OF CASES IN TRIAL

TABLE I

Retinopathy	Grade I & II	Grade III & IV
Essential Hypertension 12 cases	4	8
Renal Hypertension 8 „	3	5
Total: 20 cases	7	13

All patients were hospitalised initially. Routine investigations included haematological examination, blood urea, serum electrolytes, urine microscopy, urine concentration test, creatinine clearance, an electrocardiogram, chest X-ray, intravenous pyelogram, urinary mandelic acid estimation and retrograde aortogram in some cases. A normal diet was prescribed except in diabetics and those with cardiac failure. Blood pressure response to sodium amytal was studied in every patient on one day; otherwise no routine sedatives were used. Blood pressures were recorded lying and standing by standard methods at 8 a.m., 12 mid-day, 4 p.m. and 8 p.m. Baseline pressures were recorded for the first three days. In 3 patients response to intravenous infusion of alpha-methyl-dopa was studied. The remaining seventeen were given the oral preparations beginning with 250 mgm. eight-hourly. Generally, the dose was adjusted every two days, depending upon the response and side effects. In addition, Chlorothiazide, 0·5 G. was given to potentiate its action when side effects began to appear before the blood pressure was adequately lowered. Following discharge from hospital, patients were seen weekly at first, and forthightly subsequently. Blood urea estimations were done every three months and electrocardiogram was done every six months.

RESULTS

Using the criteria set out by Dollery et al (1960) we regarded a sustained fall of recumbent or standing pressure to 160/100 mm. Hg. or less as "good" response, and a fall of diastolic pressure of 20 mm. Hg. or more as "satisfactory" even though the blood pressure was still above 160/100 mm. Hg. Response of less than 20 mm. Hg. was considered to be "poor".

RESPONSE TO INTRAVENOUS INFUSION OF ALPHA-METHYL-DOPA.

The blood pressure in two patients fell significantly with 500 mgm. and 1,000 mgm. of the drug respectively. The third patient responded only slightly with 1,000 mgm. Blood pressure began to fall after two hours. The pressures were almost back to pre-therapy levels after 24 hours though not shown in the charts below. The recumbent as well as the standing pressure fell, though the postural drop was greater in all instances. Two patients were found to be very drowsy 2 to 3 hours after giving the drug, irrespective of the fall in pressure. The third patient developed fever during the infusion but it is not certain whether this reaction was due to pyrogens in the dextrose solution or the drug. Charts 1 to 9 illustrate the pattern of response to intravenous alpha-methyl-dopa.

RESPONSE TO ORAL TREATMENT IN HOSPITAL

Of the twenty patients, 16 showed "good" response and 4 showed "satisfactory" response. The blood pressure response is shown in Chart 9. The initial blood pressure was taken as the average of 8 control readings and the mean control blood pressure was calculated by taking the diastolic pressure plus one third the pulse pressure. The final blood pressure was similarly worked out from the blood pressure readings in the last 2 days of their hospital stay. It can be seen that the fall in standing

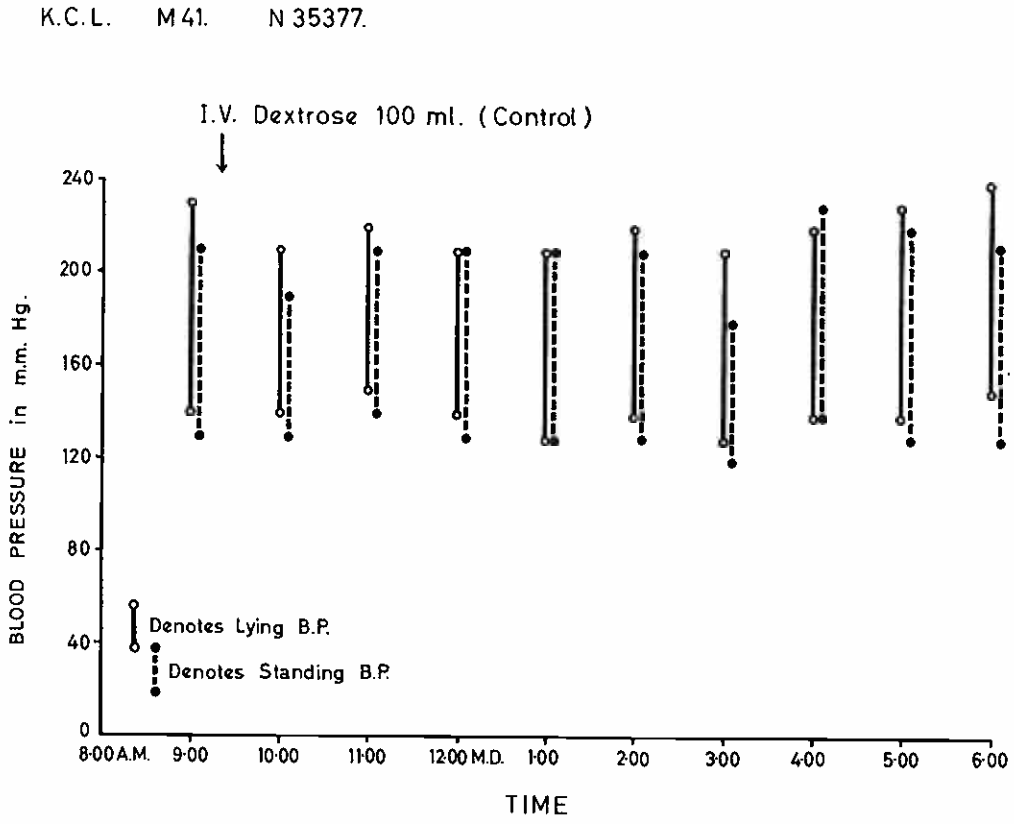


Chart 1.

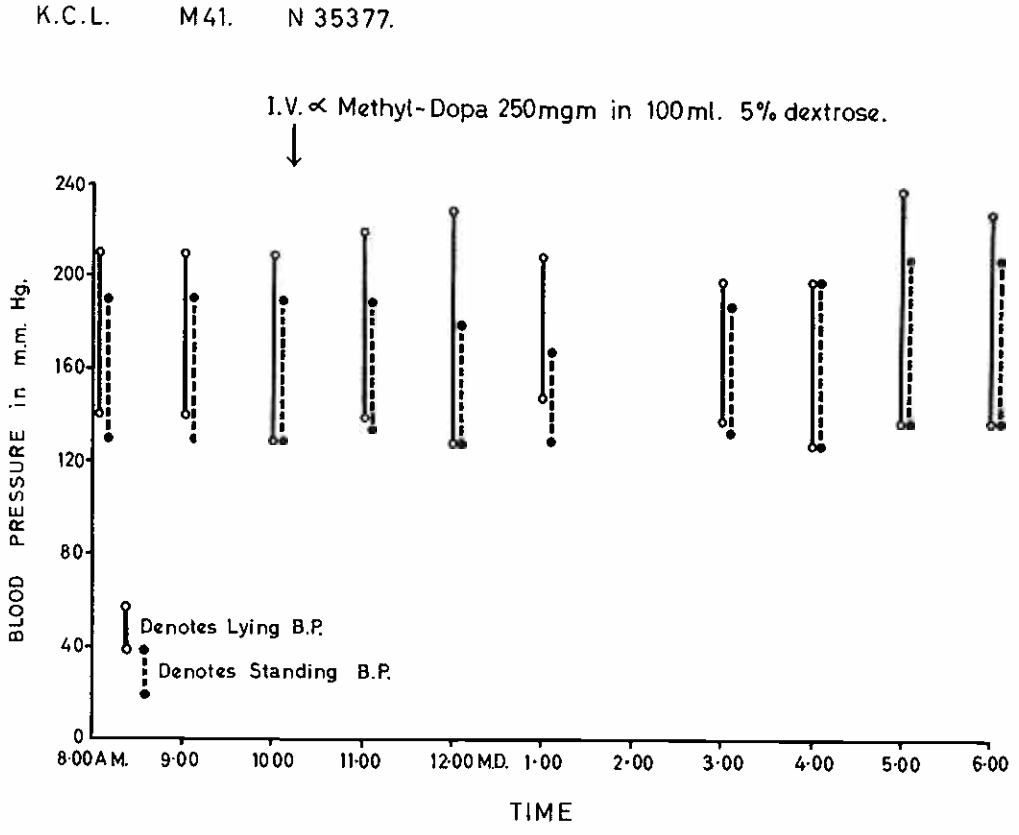


Chart 2.

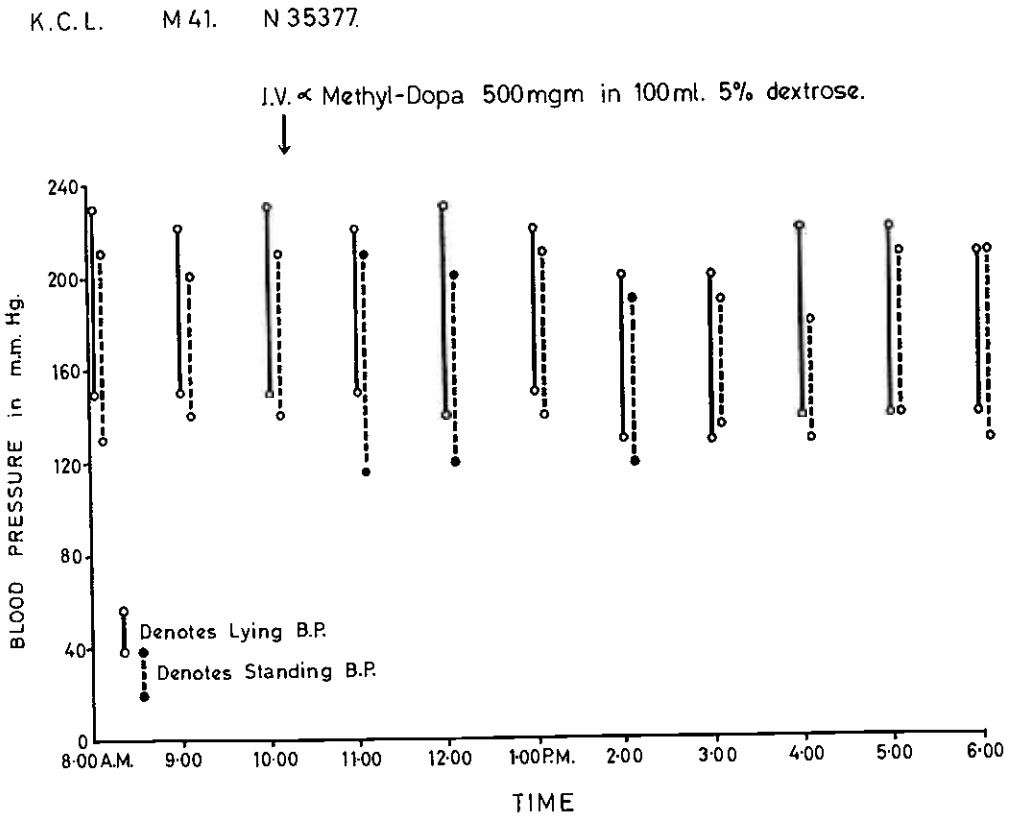


Chart 3.

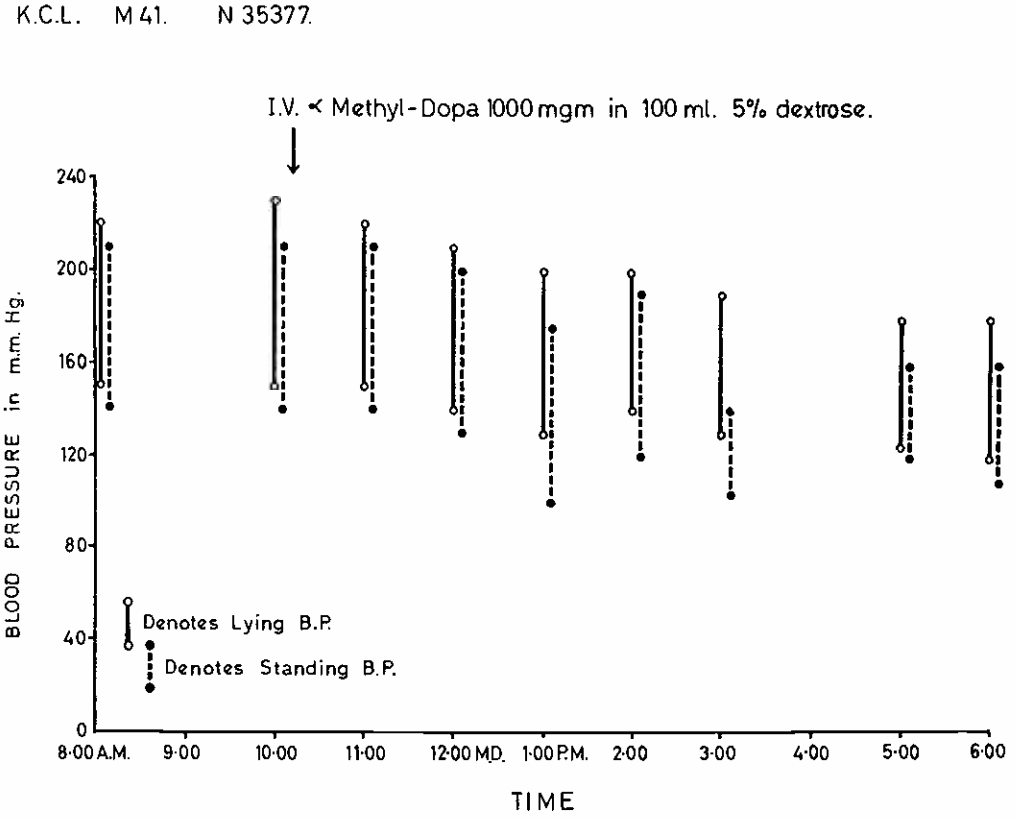


Chart 4.

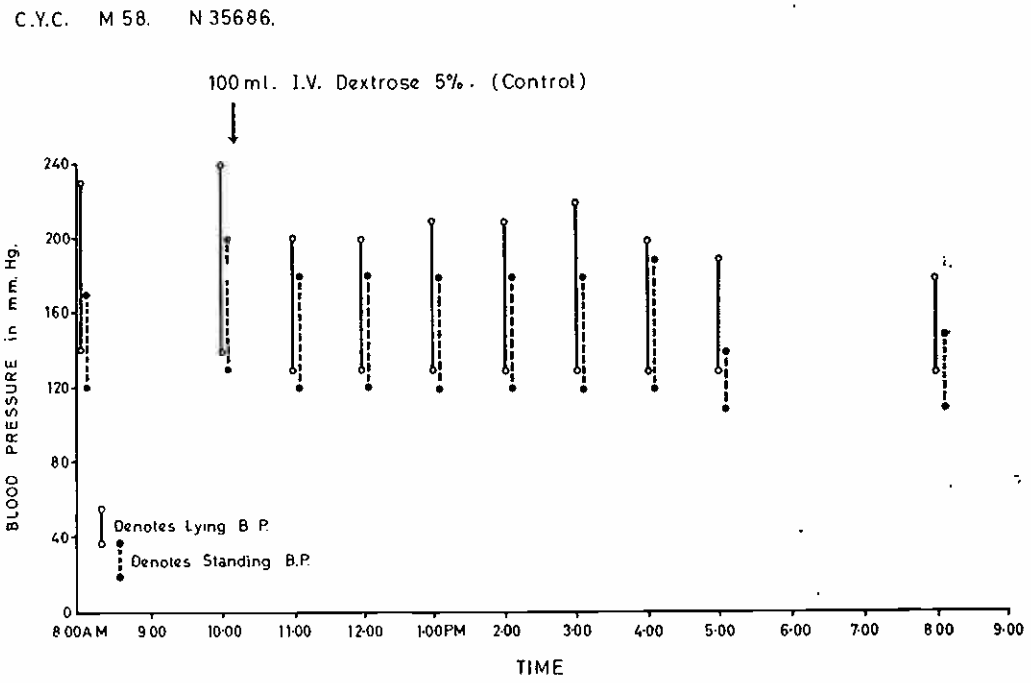


Chart 5.

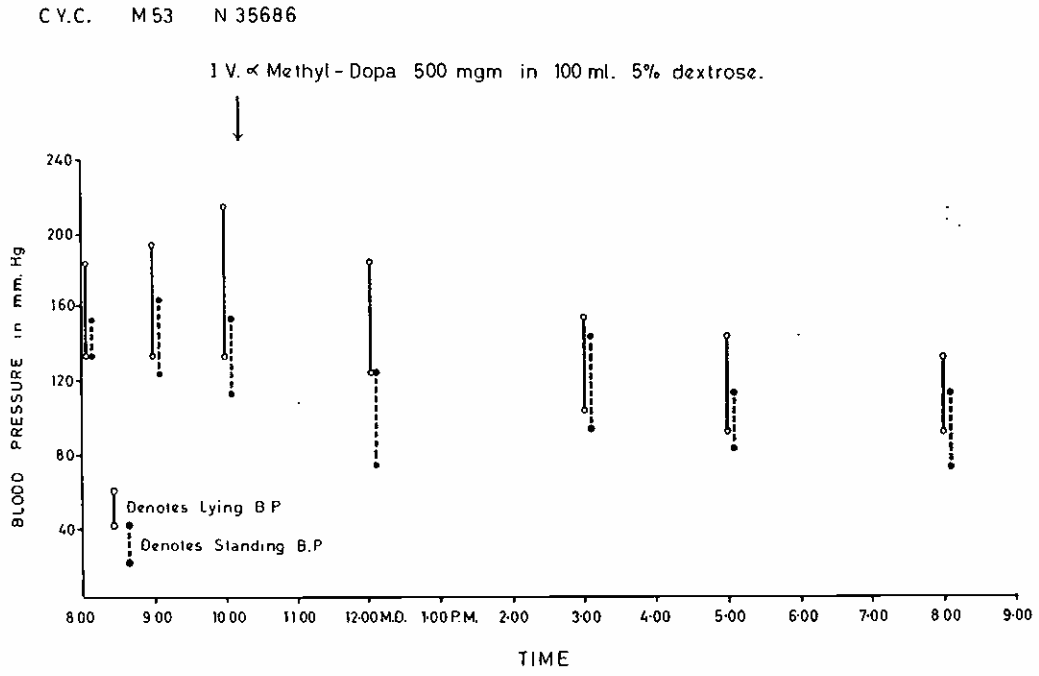


Chart 6.

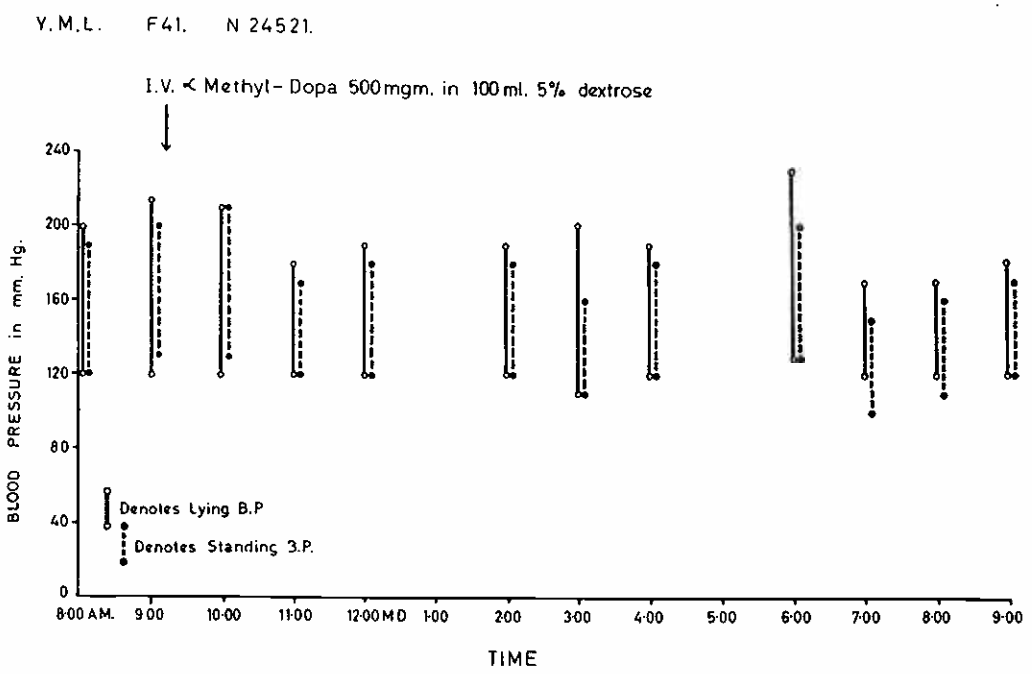


Chart 7.

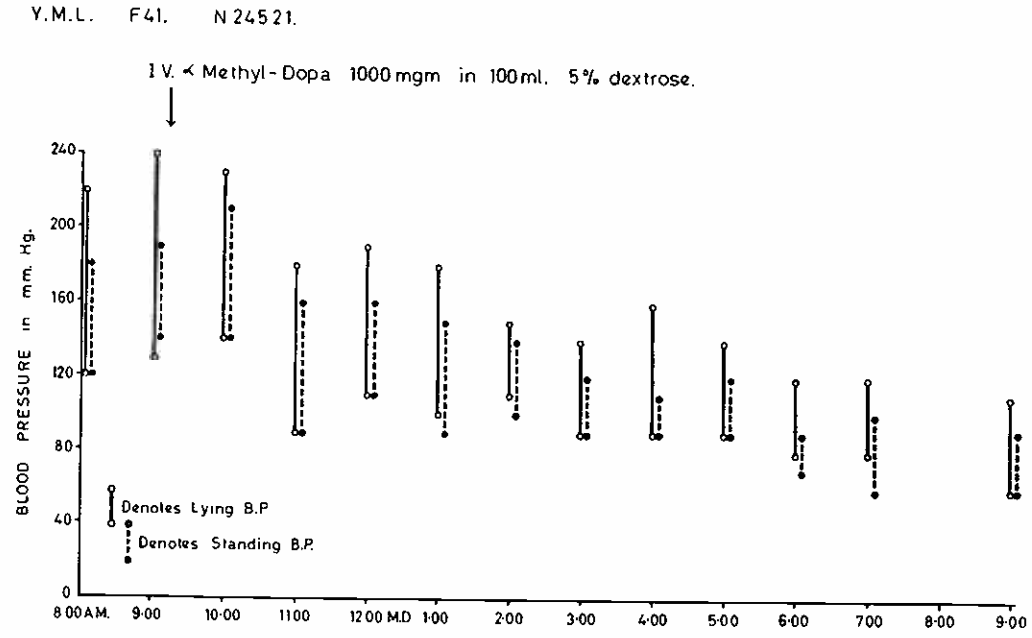


Chart 8.

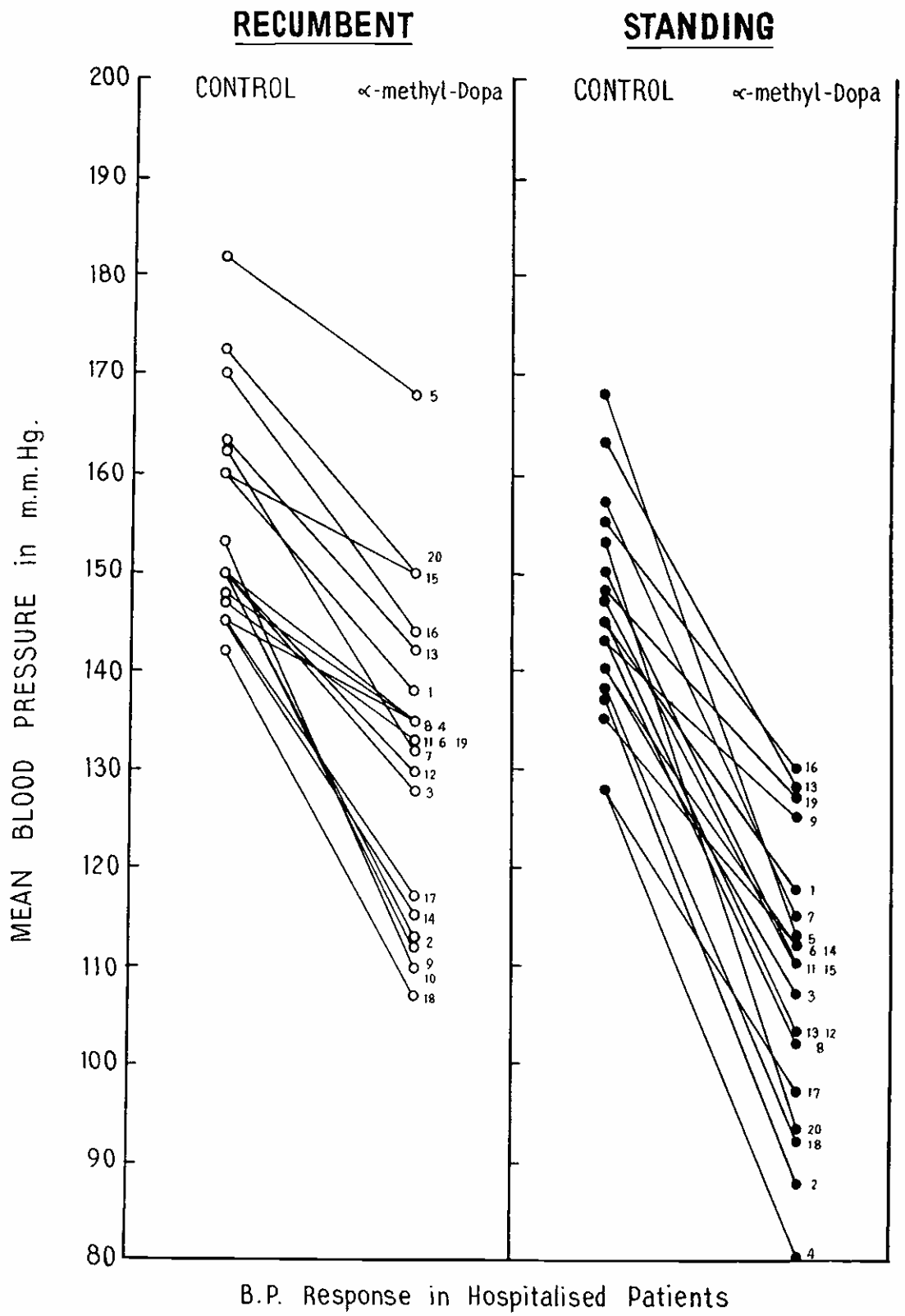

RECUMBENT
STANDING
CONTROL
∝-methyl-Dopa
CONTROL
∝-methyl-Dopa
MEAN BLOOD PRESSURE in m.m.Hg.
200
190
180
170
160
150
140
130
120
110
100
90
80
B.P. Response in Hospitalised Patients

Chart 9.

TABLE II

BLOOD PRESSURE RESPONSE ACCORDING TO AETIOLOGICAL GROUPING AND RETINOPATHY

Renal Hypertensives	**Result**	Grade 1 & 2 **Retinopathy**	Grade 3 & 4 **Retinopathy**
8 Cases	(Poor	-	-
	(Satisfactory	-	2
	(Good	2	4
Essential Hypertensives			
12 Cases	(Poor	-	-
	(Satisfactory	-	2
	(Good	5	5

TABLE III

BLOOD PRESSURE RESPONSE ACCORDING TO INITIAL BLOOD UREA LEVEL

	Result			
Blood Urea Level	**Poor**	**Satisfactory**	**Good**	**Total**
< 45 mgm. %	-	2	10	12
> 45 mgm. %	-	2	6	8

pressure was greater than the fall in the lying pressure in practically every case. In a few instances, the postural drop was considerable. A good number of these patients received 0·5 G. of Chlorothiazide in addition to alpha-methyl-dopa. Further details about response with regard to aetiological grouping, severity of retinopathy and initial blood urea levels are shown in Tables II and III.

There do not appear to be significant differences in response between the group with essential hypertension and the group with renal hypertension; nor any significant difference with regard to retinopathy and blood urea levels. However, the size of the groups are small and no definite conclusion can be drawn.

RESULTS OF LONG-TERM TREATMENT

18 patients were followed up for one to eighteen months. Of the remaining two, one failed to turn up for treatment, and the other died at home; he had congestive cardiac failure before treatment and did not continue medication at home. Ten out of the eighteen showed good response, one satisfactory response and seven poor response. Those showing consistently poor response were taken off from the trial; hence their follow-up periods are shorter. Of the nine patients followed up for 12 months or more, eight remained well controlled and in good health. The results with regard to retinopathy and initial blood urea levels are shown in Tables IV and V. It would appear from Table 4 that those with a slightly raised blood urea fared as well as those with normal blood urea levels. The results in Table V would suggest that those with severe retinopathy fared better, though statistical significance is not reached. A summary of the data and results of each case are shown in Table VI.

TABLE IV

BLOOD PRESSURE RESPONSE
ACCORDING TO INITIAL BLOOD UREA LEVELS

Blood Urea Level	Result: Poor	Satisfactory	Good	Total
< 45 mgm. %	5	0	7	12
> 45 mgm. %	2	1	3	6

TABLE V

BLOOD PRESSURE RESPONSE ACCORDING
TO RETINOPATHY

B.P. Response	Grade 1 & 2 Retinopathy	Grade 3 & 4 Retinopathy	Total
Poor	5	2	7
Satisfactory	-	1	1
Good	2	8	10

Again, the initial blood urea level seemed to make little difference to the final results. However, it must be noted that none of the patients had initial blood urea levels of greater than 80 mgm. %. The response of patients with severe azotemia may well be different. Five patients showed an actual fall in blood urea (greater than 10 mgm. %) following successful therapy. In two patients, the blood urea rose, one terminating in irreversible renal failure. This patient also developed tolerance to the drug as the pressure went up. On the face of the data in Table V, it would seem that those with Grade 3 and 4 retinopathy fared better than those with milder retinopathy. The dose of x-methyl-dopa required varied from 0·5 G. daily to 3·0 G. daily. 16 patients had follow-up electrocardiograms done. Nine cases showed distinct electrocardiographic improvement. The tracing became normal in 4 instances. Of the remaining 5, two showed significant improvement in left ventricular hypertrophy pattern, and three showed improvement in the left atrial hypertension with no noticeable change in the left ventricular hypertrophy pattern. Table VI sums up the cases and the results of long-term treatment.

SIDE-EFFECTS AND TOLERANCE

The side effects observed included drowsiness, weakness, insomnia at night, postural giddiness and dryness of mouth. Drowsiness was seen in most instances, but rarely persisted beyond the first five days. Two of the patients complained of insomnia though they felt drowsy in the day. Profound weakness was complained of by 4 patients. Three of them refused to continue with the drug and were consequently withdrawn from the trial.

The symptom of muscular weakness did not seem to bear any relationship to the fall in blood pressure. Postural giddiness appeared troublesome in cases 2, 15 and 20. One patient complained of intractable diarrhoea which did not respond to the usual measures and had to be taken out of the trial. Two noted mild dryness of mouth. One patient noticed increased pigmentation at the back of his neck while taking the drug soon after discharge. One patient suffered the first attack of gout after being on the drug and 0·5 G. Chlorothiazide for some months; he was not azotaemic. Weight increase was not noticed probably because most of the patients were receiving

TABLE VI

A Summary of the Data and Results of Long-Term Treatment of all the Patients.

Case	Sex/Age	Diagnosis	Chief Symptoms	Fundi	Blood Pressure Initial	Blood Pressure Final	Blood Urea (Mgm. %) Initial	Blood Urea (Mgm. %) Final	E. C. G.	Dose/Duration	Rusults
1.	M/46	Hypert. left Vent. Failure	Blurring of vision	Grade 3	(R) 210/135 (S) 185/125	185/125 130/ 90	30	36	LV3+	A=2·25G C=0·5 G 5 months	Good
2.	M/37	Hypert. Heart Disease	Headache Giddiness	Grade 2	(R) 180/135 (S) 160/125	220/150 200/140	30	200	LV4+	A=1·5 G C=0·5 G 3 months	Poor
3.	M/57	Nephrolithiasis Pyelonephritis Hypert. Left Vent. Failure	Blurring of vision	Grade 4	(R) 200/125 (S) 180/120	140/ 95 115/ 80	30	34	LV2+	A=1·0 G C=0·5 G 18 months	Good
4.	M/44	Diab. Mellitus Pyelonephritis Hypert. Left Vent. Failure	Dyspnoea Blurring of vision Headache Giddiness Weakness	Grade 2	(R) 190/120 (S) 155/115	135/105 105/85	30	33	LV1+ LA+	A=1·5 G 18 months	Good
5.	M/42	Bilateral Calculi Hypert. Heart Dis.	Blurring of vision. Frequency	Grade 3	(R) 245/150 (S) 225/140	255/135 215/135	51	29	LV4+	A=1·5 G C=0·5 G 3 months	Poor
6.	M/55	Diab. Mellitus Pyelonephritis Hypert. Heart Failure	Dyspnoea Anorexia Vomiting	Grade 3	(R) 205/120 (S) 185/110	175/105 120/80	75	35	LV3+	A=2·25G C=0·5 G 18 months	Good
7.	M/44	Renal calculi Pyelonephritis Hypert. Ht. Dis.	Headache Haematuria	Grade 3	(R) 205/140 (S) 190/140	145/105 130/100	68	35	LV3+ LA+	A=1·5 G C=0·5 G 18 months	Good
8.	M/45	Hypertension Cervical Spondylosis	Weakness of legs.	Grade 3	(R) 185/130 (S) 170/130	165/120 115/95	88	61	LV1+	A=1·0 G C=0·5 G 17 months	Good
9.	F/56	Hypertensive Heart Disease Old Hemiparesis	Blurring of vision	Grade 2 Retinal Artery Thrombosis	(R) 210/120 (S) 190/120	- -	67	-	LV3+	-	Absconded
10.	M/32	Essential Hypertension	Headache Giddiness	Grade 1	(R) 190/120 (S) 185/125	160/110 145/110	51	18	LV2+	A=0.75G 17 months	Poor

TABLE VI (contd.)

Case	Sex/Age	Diagnosis	Chief Symptoms	Fundi	Blood Pressure Initial	Blood Pressure Final	Blood Urea (Mgm. %) Initial	Blood Urea (Mgm. %) Final	E. C. G.	Dose/Duration	Rusults
11.	M/36	Hypert. Heart Disease	Headache Giddiness	Grade 3	(R) 190/125 (S) 185/120	200/120 160/120	25	-	LV_2+	A=1·5 G C=0·5 G 1 month	Poor
12.	M/51	Malignant Hypert. Cirrhosis	Cirrhosis	Grade 4	(R) 190/130 (S) 170/125	220/130 195/130	41	31	LV_4+	A=3·0 G C=0·5 G 5 months	Poor
13.	M/54	Hypert. Heart Failure	Headache	Grade 3	(R) 220/135 (S) 200/135	- -	36	-	LV_2+	-	Absconded died at home
14.	M/33	Renal Artery Stenosis	Angina Giddiness Headache	Grade 2	(R) 185/130 (S) 170/120	135/95 125/95	15	27	LV_3+ Ischaemic changes	A=0·75G C=0·5 G 13 months	Good
15.	M/41	Hypertensive Heart Failure	Dyspnoea Oedema Anorexia	Grade 3	(R) 220/150 (S) 210/135	190/120 170/120	70	60	LA+ LV_3+	A=3·0 G C=0·5 G 12 months	Satis-factory
16.	M/58	Hypertensive Heart Disease	Headache Giddiness Blurring of vision	Grade 3	(R) 230/140 (S) 205/130	165/105 130/95	25	31	LV_1+ Ischaemic changes	A=1·5 G C=0.5 G 12 months	Good
17.	M/35	Hypertensive Heart Disease	Headache Dyspnoea Palpitation	Grade 2	(R) 195/120 (S) 155/115	135/105 140/105	27	33	LV_2+	A=0·75G C=0·5 G 9 months	Poor
18.	M/25	Hypertension Nephritis	Blurring of vision	Grade 3	(R) 175/125 (S) 165/125	135/95 115/90	27	28	LV_1+	A=0·5 G 9 months	Good
19.	F/41	Hypertensive Heart Disease Pyelonephritis	Headache Giddiness	Grade 3	(R) 230/130 (S) 195/125	160/105 140/95	65	76	LV_3+	A=1·5 G C=0·5 G 5 months	Good
20.	M/52	Essential Hypertension	Headache Blurring of vision	Grade 2	(R) 210/135 (S) 200/130	260/150 260/150	25	-	LA+ LV_2+ Ischaemic changes	A=1·5 G C=0·5 G 3 months	Poor

(R) = Recumbent; (S) = Standing.

chlorothiazide as well. Tolerance developed in 5 out of the 7 cases who showed poor results. It is possible that the pressures could have been brought down further in some of these patients if much bigger doses of Aldomet were used but at the risk of producing weakness. In some instances, it did not seem to make much difference whether the dose taken was 1.5 G. daily or 3.0 G. daily. In general, most patients required a bigger dose after discharge from hospital.

DISCUSSION

Initially, the hypotensive action of alpha-methyl-dopa was considered to be due to the inhibition of decarboxylation of dihydroxphenylamine (dopa) with resultant fall in norepinephrine production. But Sjoerdsma et al in 1963 showed that the urinary vanyll mandelic acid excretion was unchanged with alpha-methyl-dopa, hence decarboxylase inhibition of endogenous synthesis of nor-epinephrine could not be adequate. Furthermore, analogues with decarboxylase inhibition property did not lower blood pressure. They concluded that the hypotensive effects are mediated by amine-metabolites of the drug following its decarboxylation and suggested that norepinephrine depletion at tissue level was probably the final denominator.

The response to intravenous infusion of alpha-methyl-dopa was found to be good in two and satisfactory in the third patient in our series. Dollery (1962) found satisfactory result in only one out of three cases using a fairly large dose of 1·5 G. Haemodynamic studies by Wilson in 1961 with intravenous alpha-methyl-dopa (0·7 G. per metre square) showed significant fall in both the recumbent and standing blood pressure in 5 patients. The mean pulmonary artery pressure fell and the oxygen consumption was reduced. He thought that the acute fall in blood pressure was due chiefly to the fall in cardiac output. In general, it can be said that results with intravenous alpha-methyl-dopa are not as consistently reliable as with intravenous guanethidine sulphate.

Investigations by Cannon et al (1962) showed that alpha-methyl-dopa had no effect on sodium and potassium balance. But in hypertensive patients a low sodium diet made the subject more sensitive to the drug. They also found that the inulin clearance was unchanged in 4 and reduced in 3 out of 7 patients. The paramino-hippuric clearance was unchanged.

The ability of alpha-methyl-dopa to lower blood pressure is undisputed. Both the recumbent and standing pressures are lowered; this is a distinct advantage over the other hypotensive drugs. In our series of 20 cases, 16 had good response and 4 had satisfactory response in hospital. All of them required no more than 3·0 G. of the drug daily with or without 0·5 G. Chlorothiazide. However, the long term results were less satisfactory; 7 out of 18 patients showed poor response. 5 of them developed tolerance to the drug; the other 2 were receiving relatively small doses and might have fared better if the doses were raised. This development of tolerance is contrary to the observation of Hamilton (1963) who did not find any case of tolerance in 69 cases. It would seem impossible to predict which patient would or would not respond favourably to the drug.

Those with severe retinopathy did just as well as those with mild retinopathy, in fact slightly better in this series. There was no difference in behaviour between the renal hypertensives and the essential hypertensives, nor any difference between those with slightly raised blood urea levels and those with normal blood urea levels. However, 2 patients not in this series with blood urea levels of greater than 100 mgm. % were found to be very sensitive to the drug. Their blood pressures fell to below normal with only 0·75 G. of the drug daily; the blood urea levels rose concomitant with the fall in pressure. Their blood pressure was subsequently controlled with 0·5 G. daily. This observation of undue sensitivity of azotemic patients confirms the statement of Cannon et al (1962).

Electrocardiographic improvement in the left ventricular overload pattern is the ultimate evidence of adequate control of hypertension. But in long standing cases with left ventricular hypertrophy and ischaemic changes the control of hypertension is not always accompanied by electrocardiographic improvement. 9 out of 16 cases with follow-up E.C.G. showed distinct improvement.

The side-effects encountered are well-known. Insomnia during the first few days would tend to make outpatient treatment initially less

satisfactory unless the patient can rest at home. Mental depression and aberration were not seen as noted by Gillespie (1962) and Smirk (1963). It is likely that with mentally unstable patients prone to depression, this complication may well develop. Muscular weakness was troublesome in a few patients, but its frequency seemed less than with guanethidine among the patients here. Postural hypotension does occur but is generally not very severe. Gout developed in one case, however whether it was precipitated by Chlorothiazide or methyl dopa is not certain. This complication was reported only in Hamilton's series (1963).

The dose of alpha-methyl-dopa required to lower the blood pressure is not as critical as with guanethidine or the ganglion-blocking agents. Those who failed to respond to 1·5 G. per day sometimes did not respond to bigger doses like 3·0 G. daily.

SUMMARY

In a series of 20 patients with moderate or severe hypertension, alpha-methyl-dopa was found to produce significant lowering of blood pressure in hospital, and continued response in slightly less than two-thirds of the cases. Those with severe retinopathy responded as well as those with mild retinopathy. It was not possible to predict which patient would show a good response. Both recumbent and standing pressures were lowered though the postural drop was more marked.

Maximal dose of the drug used was 3·0 G. daily. Chlorothiazide was found to have a pontentiating effect on alpha-methyl-dopa and was used in most cases.

Tolerance developed in almost a quarter of the cases. Most patients require a slightly large dose of the drug following discharge.

Side-effects included transient drowsiness, insomnia at night, mild dryness of mouth, postural giddiness, muscular weakness and diarrhoea. Except for the feeling of weakness, the other symptoms were rarely troublesome.

Only in one case was the uraemia aggravated following the use of the drug.

Electrocardiographic improvement was observed in more than half of the cases.

ACKNOWLEDGEMENT

We wish to thank Merck, Sharpe and Dohme for their generous supply of the drug for our trial. We are much indebted to Professor E. S. Monteiro, Dr. O. T. Khoo and Dr. A. L. Gwee for the opportunity to include their patients in the trial.

REFERENCES

1. R.I.S. Bayliss, E.A. Harvey-Smith, (1963): "Methyl Dopa in the treatment of Hypertension", Lancet, Vol. 1, 763.
2. Cannon, P.J., Whitlock, R.J., Morris, R.C., Angers, M. and Laragh, J.H. (1962): "Effect of Alpha-MethylDopa in severe and malignant hypertension", J.A.M.A., Vol. 179, No. 9, 673.
3. Dollery, C.T. and Harrington, M. (1962): "Methyl Dopa in Hypertension. Clinical and Pharmacological Studies", Lancet, Vol. 1, 759.
4. Jr. Gillespie, L., Oates, J.A., Crout, J.R., Sjoerdsma, A. (1962): "Clinical and Chemical Studies with Alpha-Methyl-Dopa in Patients with Hypertension", Circulation, 25, 281.
5. Hamilton, M. and Kopelman, H. (1963): "Treatment of Severe Hypertension with Methyl-Dopa", B.M.J. Vol. 1, 151.
6. Irvine, R.O.H., O'Brien, K.O. and North, J.O.K. (1962): "Alpha-Methyl-Dopa in the Treatment of Hypertension", Lancet, Vol. 1, 300.
7. Oates, J.A., Gillespie, L.J., Udenfriend, S. and Sjoerdsma, A. (1960): "Decarboxylase Inhibitor and Blood Pressure Reduction by Alpha-Methyl-3-4 dihydroxy-DL-phenylalamine", Science, 131, 1890.
8. Sjoerdsma, A., Vendsahi, A., and Engelman, K. (1963): "Studies on the Metabolism and Mechanism of Action of Methyl-Dopa", Circulation, 28,492.
9. Smirk, Sir H. (1963): "Hypotensive Action of Methyl-Dopa", B.M.J., Vol. 1, 146.