ALPHA-METHYLDOPA IN HYPERTENSION

B. GOLDBERG, M.D., M.R.C.P.; N. W. LEVIN, M.B., B.CH., F.C.P. (S.A.); A. RUBINSTEIN,* M.B., B.CH.; and L. COHEN, M.B., B.CH.

From the Renal Unit and Peripheral Vascular Clinics, Department of Medicine and Department of Surgery, Johannesburg General Hospital and University of the Witwatersrand, Johannesburg

The formation of adrenaline and noradrenaline in the body is dependent upon the prior decarboxylation of dihydroxyphenylalanine (dopa) to dihydroxyphenethylamine (dopamine) (Fig. 1). Alpha-methyldopa is a potent inhibitor of the decarboxylation of aromatic amino acids; it blocks this step in the metabolism of catecholamines both *in vitro* and *in vivo*.[12,17,18] The formation of serotonin which results from the decarboxylation of 5-hydroxytryptophan is similarly inhibited and both the serotonin content of brain tissue of mice and the catecholamine levels in the brain stem, heart and spleen of dogs are reduced by administration of the drug.[16,19] Since sympathetic vasoconstrictor activity is mediated by the release of noradrenaline at sympathetic nerve endings, a reduction in this activity by the inhibition of catecholamine synthesis might be expected to lower the blood pressure. Such an antihypertensive effect of α-methyldopa has been demonstrated by several workers.[1,4,5,7,8,10,11,13,15] Decarboxylase inhibition and blood-pressure lowering effect have been shown to reside in the laevo-isomer.

This paper records the results of treatment of a group of hypertensive patients with α-methyldopa ('aldomet').† The effects of a single intravenous injection of the drug on the blood pressure, renal haemodynamics, rate of urine flow and urinary electrolyte excretion are also reported.

CLINICAL STUDY

Fifteen patients with hypertension formed part of a pilot trial designed to investigate the antihypertensive action of α-methyldopa. They have been followed up for periods varying from 1 to 15 months. (Additional patients have been treated with the drug as part of their routine manage-

* Senior Research Bursar, CSIR, Department of Medicine.

† Aldomet was supplied for purposes of this trial by Dr. K. C. Mezey, of Merck, Sharp and Dohme Research Laboratories.

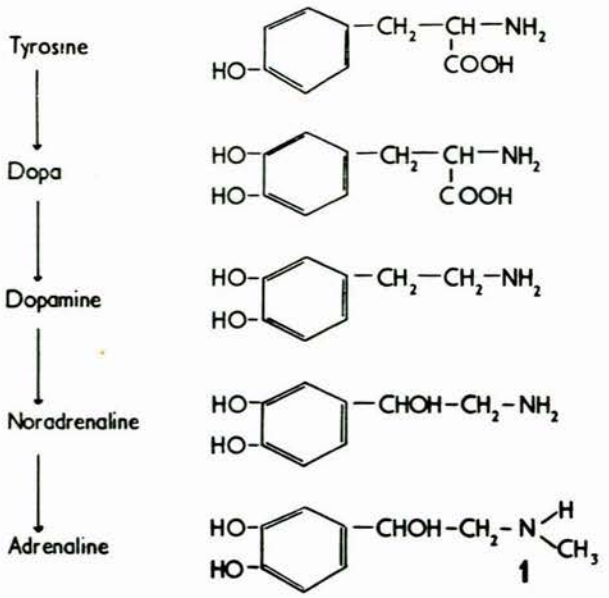

Fig. 1. The metabolic pathways for the synthesis of catecholamines from tyrosine.

ment, with results conforming to those in the 15 reported.)

There were 6 male and 9 female patients, their ages ranging from 38 to 67 years with an average of 51. All were known to have had hypertension for at least a year and 9 had received previous antihypertensive therapy. Six had chronic renal disease (4 pyelonephritis, 2 glomerulonephritis), while in the remainder no aetiological cause of the hypertension was found. Grade-3 or grade-4 fundi (Keith Wagener) were present in 4 patients, proteinuria in 7, and electrocardiographic abnormalities in 9. The mean blood pressure for the group before treatment was started was 205/125 mm.Hg and in every patient the diastolic blood pressure was greater than 105 mm. Apart from routine clinical examination, pre-treatment assessment included a 3-week control period during which the blood-pressure levels were established by serial readings taken with the patient lying and standing, and the following investigations: Complete blood count, erythrocyte sedimentation (ESR), blood urea, serum electrolytes, serum proteins, cephalin-cholesterol, thymol turbidity, alkaline phosphatase, serum bilirubin, serum glutamic oxalacetic transaminase, urine (including microscopic examination and culture), electrocardiography, X-ray examination of the heart, intravenous pyelography and, in selected cases, aortography and studies of divided renal function. During the treatment period patients were seen at weekly intervals and serial tests were repeated to determine any toxic effects of the drug on the haemopoietic system, liver and kidney.

Results

Of the 15 patients, 12 showed a fall in blood pressure to normotensive levels, in 2 there was no antihypertensive effect with doses of 3·0 and 4·0 G. per day respectively, and one was removed from the trial because of lack of cooperation.

Of the 12 patients showing the fall in blood pressure, one stopped taking the drug because of side-effects. Two others, in whom the diastolic blood pressure decreased by about 20 mm.Hg in the standing position but was still more than 100 mm. after 1 - 2 months of treatment, were subsequently changed to other antihypertensive drugs. (One of these showed a better hypotensive response to hydralazine and chlorothiazide, while the other has not been as well controlled with hydralazine, guanethidine and a thiazide diuretic.) In the remaining 9 patients the diastolic blood pressure was reduced to less than 100

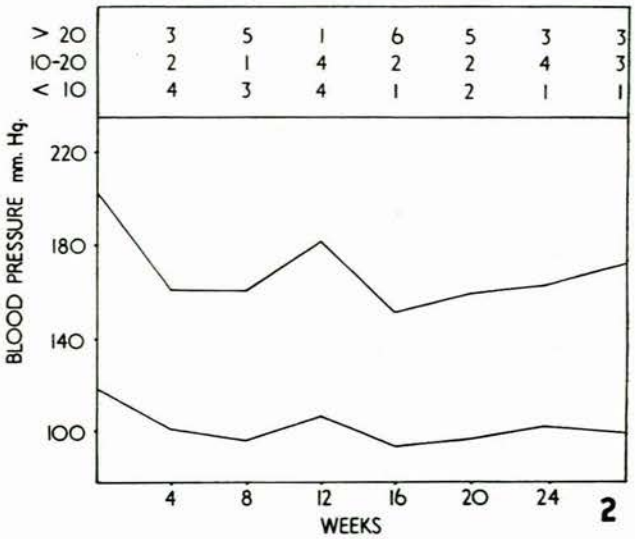

Fig. 2. The mean lying blood pressure in the 9 patients who responded well to treatment, before and at 4-weekly intervals during treatment. The pre-treatment blood pressure is the average of 54 readings in the 9 patients taken over a 3-week control period. The figures in the top compartment of the diagram represent the number of patients in whom the diastolic pressure was reduced, respectively, by more than 20, 10 - 20, and less than 10 mm.Hg.

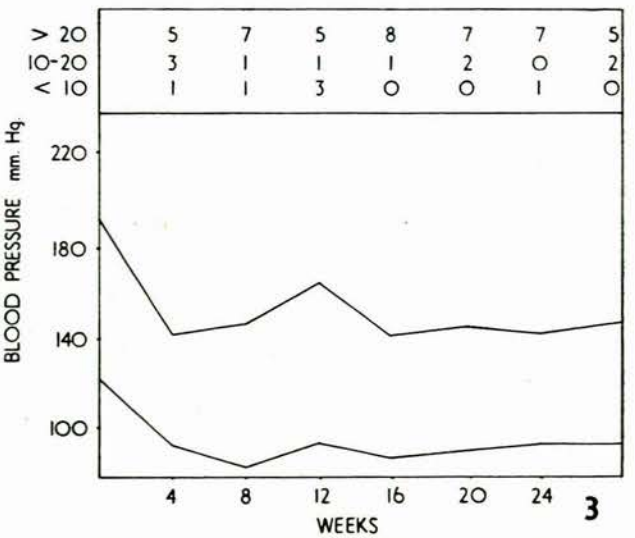

Fig. 3. The average standing blood pressures before and during treatment. See legend to *Fig. 2.*

mm.Hg in the standing position and their response is considered good. The average effective daily dose was 1·75 G. in 2, 3 or 4 divided doses, ranging from 0·5 G. to 3·75 G. per day. The effect on the blood pressure in the 9 patients, who were treated for 6 or more months, is shown in Figs. 2 and 3. Blood pressure in the standing position was lower than in the lying but in all a significant reduction in the lying position was found. The postural effect was more pronounced in those patients in whom the pre-treatment blood pressure was greater; although those with severe hypertension as well as those with a more moderate degree responded, the moderate cases were the more easily and better controlled. A good response of the blood pressure to treatment is shown in Fig. 4.

Of the 4 patients with grade-3 or -4 fundi, 2 in whom the blood pressure responded showed improvement in eyegrounds to grade 2. In 2 of the 7 proteinuric patients, the pre-existing proteinuria disappeared. Over the period of treatment no significant electrocardiographic changes were noted.

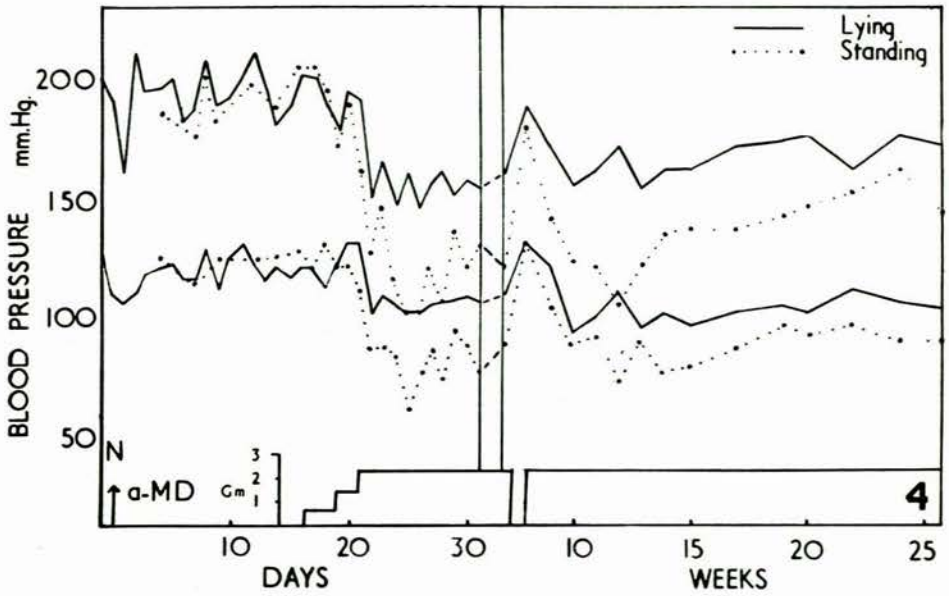

Fig. 4. Male aged 43. The response in a patient admitted to hospital with severe headaches. N=25 mg. Nepresol given intramuscularly. aMD=α-methyldopa.

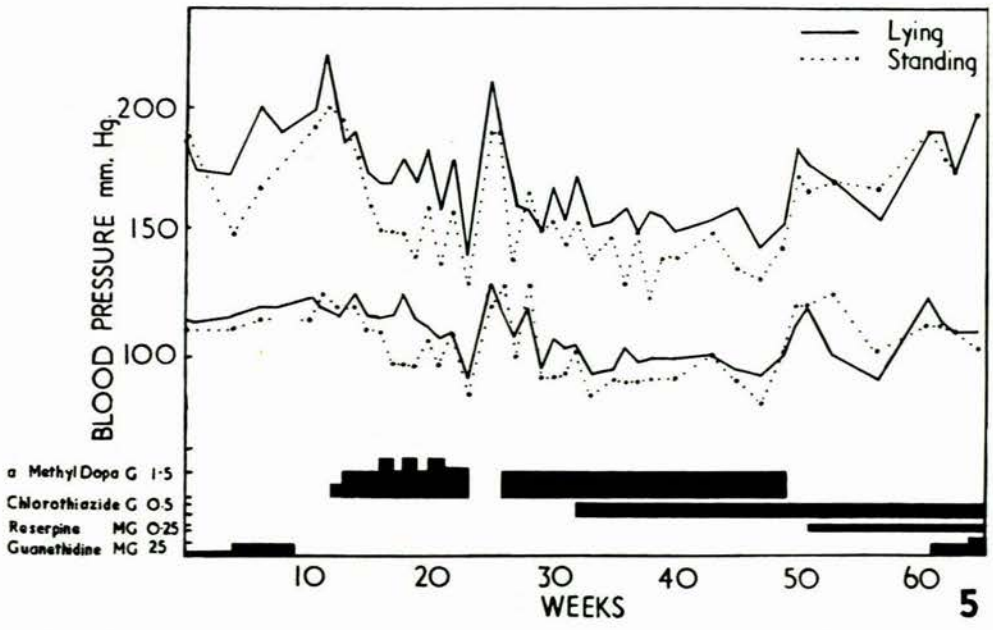

Fig. 5. Female aged 48. The additive effect of a thiazide diuretic is shown. Increasing the dose of α-methyldopa to more than 1·5 G. per day produced unpleasant drowsiness although better blood-pressure control. On 1·5 G. per day and a thiazide diuretic good control was obtained without side-effects.

In 5 of the 9 patients a thiazide diuretic was combined with α-methyldopa and appeared to enhance its efficacy. In Fig. 5 this effect is shown in a patient who could not tolerate the drowsiness produced by increasing the dose of α-methyldopa to more than 1·5 G. per day.

Two patients died. One, with advanced renal failure and pre-existing oedema, in whom there was no lowering of blood pressure, died from uraemia 1 month after stopping treatment. The other, also with advanced renal disease, developed oedema and cardiac failure in spite of a good antihypertensive effect. On discontinuing the drug cardiac failure persisted; renal failure advanced and death took place in uraemia about 2 months later. One patient, with associated obliterative arterial disease of the legs, suffered a myocardial infarction while on treatment. On starting the drug again 6 weeks later there was no deleterious effect.

Side-effects. The side-effects that occurred were usually mild and did not interfere with continuation of treatment except in one patient, who developed nightmares. The

blood pressure in this patient had been reduced to normotensive levels. Nightmares and restlessness were observed in another patient subsequently treated, but this was temporary. Ten patients complained of drowsiness on starting medication. In most of them this disappeared within a week and was never troublesome or of a degree sufficient to interfere with normal activities. The drowsiness was not related to the dose of the drug nor to the antihypertensive effect. It varied from patient to patient, some being affected by a dose of 1·0 G. per day and others unaffected by doses up to 4·0 G. per day. Mild dizziness on standing was experienced by 8 patients but this was never severe. Six patients complained of dryness of the mouth and 1 of pains in the legs, which disappeared in spite of continued therapy. There were no instances of gastro-intestinal disturbances; nor, in the initial series of patients, of mental depression, but one patient, who has been treated subsequently, became mildly depressed.

Toxic effects. Toxicity of the drug was assessed by serial blood studies in patients on long-term treatment. No haematological abnormalities were observed, and no derangement was seen in the liver-function tests done. Worsening of renal function was observed in 2 patients. These already had grossly advanced renal disease before starting treatment, the blood urea in both being greater than 175 mg.%. The progression of the uraemia did not appear to be affected by administration of the drug and continued after it was stopped. In the rest of the patients, some with lesser degrees of renal insufficiency, worsening of renal function was not observed. No drug rashes, fever or jaundice occurred in the pilot trial.

ACUTE STUDIES

In 7 patients on 10 occasions from 250 mg. to 1,500 mg. of α-methyldopa was given as a single intravenous injection and the blood pressure recorded in the supine and standing positions for 6 hours or more. In one patient a significant reduction in the blood pressure occurred in both positions after a dose of 1,500 mg. The effect was apparent after 3 hours and persisted for 24 hours (Fig. 6). In 2 other patients doses of 500 mg. and 750 mg. respectively resulted in smaller decreases of blood pressure in both positions. In the remainder the changes observed were negligible.

In 5 patients (4 supine, 1 sitting) the blood pressure, clearance of inulin and para-aminohippurate (PAH), rate of urine flow, and urinary excretion of sodium, potassium and chloride, were measured before and for about 6 hours after the intravenous administration of α-methyldopa in doses of 500 mg. to 1,500 mg. All the patients were prehydrated and plasma levels of inulin and PAH were kept constant by a continuous intravenous infusion. Urine was collected through an indwelling bladder catheter with bladder washouts, and the state of hydration was maintained by oral replacement of fluid at intervals of 30 minutes in an amount equal to the urine flow.

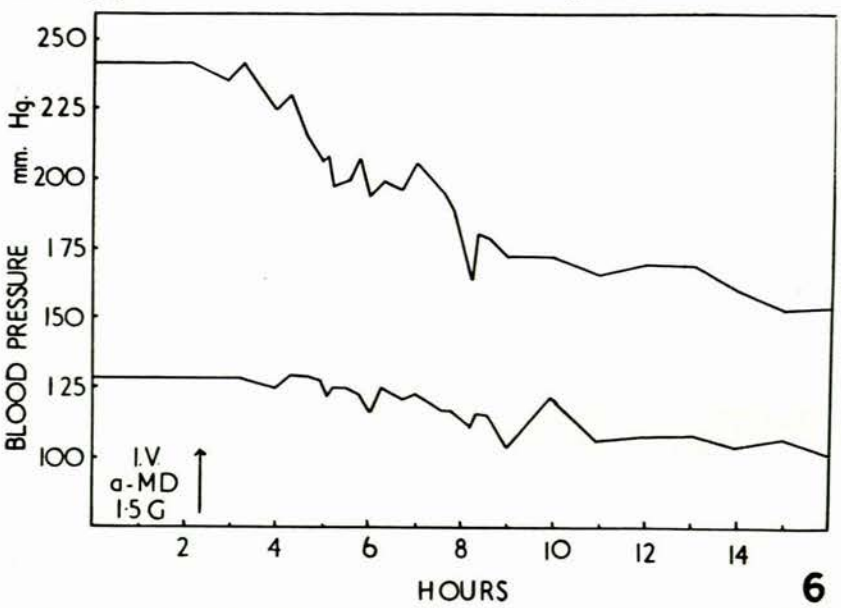

Fig. 6. Male aged 50. The response to a single intravenous injection of 1·5 G. α-methyldopa on the blood pressure with the patient supine. Hypotension occurred on standing, with faintness at the height of the response.

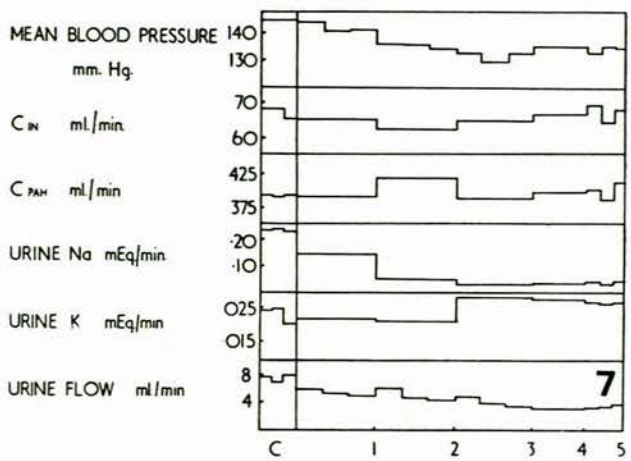

Fig. 7. The effect of intravenous alpha-methyldopa on the mean blood pressure, clearances of inulin (C IN) and para-aminohippurate (C PAH), rate of urine flow and sodium and potassium excretion in 5 patients. C=3 control periods each of about 15 minutes. 1—5 are periods after infusion of the drug and total approximately 6 hours. Mean blood pressure is sum of the diastolic + ⅓ pulse pressure.

Fig. 7 records the mean alterations observed in the 5 patients. In 2 patients there was a moderate reduction in blood pressure. In 1 of these and 1 other patient the clearances of inulin decreased temporarily to about 75% of the control levels. In 1 patient a similar decrease was noted in the clearance of PAH. In 4 of the 5 patients the rate of urinary excretion of sodium and chloride was reduced markedly to about 15% of the pre-injection levels and in 2 patients a moderate reduction in the flow of

urine was observed. The excretion of potassium remained unchanged or increased slightly as the sodium excretion diminished. There appeared to be no correlation between the alterations in blood pressure and clearances of inulin and PAH except that the one patient in whom the reduction in blood pressure was greatest also showed the greatest diminution in urine flow, sodium and chloride excretion, and reduction in a previously small clearance of inulin.

DISCUSSION

These results confirm the findings of others that α-methyldopa is an effective agent for lowering the blood pressure in about two-thirds of patients with hypertension. The effect of treatment is sustained and no instances of tolerance to the drug have been observed except recently in a patient who after 11 months of adequate antihypertensive control now seems to be escaping from the effect of the drug. Control of blood pressure is smooth and is maintained throughout the day with no marked hypotensive symptoms. While mild or moderate cases appear to respond best, good effects with improvement in retinal lesions have been observed in patients with severe hypertension. The supine and standing blood pressure are both reduced but particularly that recorded with the patient standing. We have not observed hypotensive symptoms occurring with exertion but the antihypertensive effect persists during the exercise.[15] Side-effects are mild, usually transitory, and seldom of a degree sufficient to warrant cessation of treatment. No worsening of renal function attributable to the drug was observed. The acute studies reported here showed no consistent change in the clearances of inulin or PAH, and Sannerstedt *et al.*[15] found no significant alteration in renal haemodynamics after treatment of patients for 2 weeks.

Toxic effects were not seen in this series. Fever, hepatitis and depression have been reported by others in a small number of cases.[4,6,7,8] In all these cases they disappeared on stopping the drug. Decarboxylase inhibition by α-methyldopa is not confined to the decarboxylation of dopa to dopamine. Decarboxylation of other aromatic amino acids is known to be affected as well and it might be expected that interference with these metabolic pathways would result in abnormalities which manifest as toxic effects. The type, extent and incidence of these have still to be adequately determined.

Sodium and water retention has been reported to occur during this treatment and this may be associated with the development of cardiac failure.[5] The reason for it is not known. It has been shown in a series of patients who, however, gave no evidence of sodium retention, that the rate of production of aldosterone was not altered by treatment.[4] During the acute experiments reported here a decreased excretion by the kidney of sodium, chloride and water was noted after intravenous injection of the drug. This did not appear to be associated with alteration in blood pressure, renal plasma flow, or glomerular filtration rate as judged by the clearances of PAH and inulin, and was more than was likely to occur with the normal diurnal variation in sodium excretion. It may be that it was due to a direct effect of α-methyldopa or one of its metabolites on the kidney and in turn may be related to the changes reported during maintenance therapy.

The sodium and water retention that occurs in a proportion of treated patients is controlled by diuretics. These appear to enhance the antihypertensive effect of the drug and it would seem rational to combine α-methyldopa with a diuretic when treatment is instituted.

The decrease in blood pressure during treatment probably results from a reduction in total peripheral resistance. Wilson *et al.*[20] found that the fall in blood pressure following the intravenous administration of α-methyldopa was associated with a decrease in the cardiac index; and Onesti *et al.*[13] also observed a decline in the cardiac output after intravenous administration of the drug, and in the calculated total peripheral resistance as well. On the other hand, in another series[11] no characteristic alteration in the cardiac output was found and it was considered that the fall in blood pressure was due to a reduction in peripheral resistance. Similarly, during maintenance therapy of patients with hypertension it has been shown that the reduction in blood pressure could be accounted for by a decrease in the peripheral resistance without any consistent change in the cardiac output.[15]

The mode of action of α-methyldopa in reducing the blood pressure is not clear. That it is not likely to be produced by the inhibition of decarboxylase activity alone is suggested by the fact that other decarboxylase inhibitors do not necessarily produce an alteration in blood pressure.[7] Furthermore, inhibition of decarboxylase activity does not parallel in time the depletion of the brain and peripheral tissues of noradrenaline, which persists for several days and is still present when tissue levels of dopamine and serotonin have returned to normal.[9,14] It has been suggested that there is a decrease in the capacity of tissues to bind norepinephrine (noradrenaline)[9] and that this is responsible for the prolonged depletion following administration of α-methyldopa.

In spite of the fact that the noradrenaline content of the tissues is reduced by the drug, it is not established that the hypotensive response results from a blockade of adrenergic activity. Both reserpine[2] and guanethidine[3] deplete tissues of noradrenaline. These drugs relax the nictitating membrane, produce miosis, and block the pressor response to stimulation of the central end of the cut vagus nerve in dogs. They enhance the pressor effect of an infusion of noradrenaline.[19] But α-methyldopa does none of these things. All 3 substances, however, reduce the pressor responses elicited by the sympathomimetic amines, phenethylamine and amphetamine.[19] It has been suggested that these differences can be explained on the assumption that there are separate stores of catecholamines—one located in the neurone and depleted by reserpine and guanethidine, and the other more diffusely situated in the tissues and depleted by all 3 agents. The central vagal response is thought to be mediated on the efferent side by sympathetic nerve transmission whereas the response to sympathomimetic amines may be due to an effect on the store of catecholamines outside the neurones. Reserpine and guanethidine may lower the catecholamine content of both sites and so inhibit the central vagal response and diminish the effect produced by phenethylamine and amphetamine. On the other hand, α-methyldopa may act primarily on the tissue stores and thus influence only the response to the sympathomimetic amines.[19]

SUMMARY AND CONCLUSIONS

Although the mode of action of α-methyldopa is not known it has been found to be an effective agent for the lowering of blood pressure in patients with hypertension. It has proved suitable for long-term treatment of a group of hypertensive patients, in whom it reduced the blood pressure in both the supine and standing positions. Side-effects when they occurred were mild and usually not of a degree sufficient to interfere with treatment or incapacitate the patient. Although toxic effects were not observed in this series of patients, reports indicate that there may be a low incidence of these. So far none have proved serious and all have remitted on discontinuation of treatment. It is necessary, however, to study the incidence of toxic effects in a larger series, and to find whether any permanent sequelae may occur. Sodium and water retention have been reported to occur during maintenance therapy. Acute experiments done suggest that this may be due to a direct effect of α-methyldopa or a metabolite on the kidney.

ADDENDUM

The additional patients treated with α-methyldopa as mentioned on page 755 now number 22. Three of them developed a skin rash on treatment, in 1 associated with fever. On stopping the drug the rash disappeared. In 1 patient the drug was started again with a recurrence of the rash, which again disappeared when it was stopped. No other toxic effects have been observed and the efficiency of the preparation in these cases has been the same as in the trial series reported.

REFERENCES

1. Brest, A. N., Seller, Z., Onesti, G., Sekine, G. and Moyer, J. H. *in* Brest, A. N. and Moyer, J. H. eds. (1961): *Hypertension, Recent Advances*, p. 424. Philadelphia: Lea & Febiger.
2. Burn, J. H. and Rand, M. J. (1958): J. Physiol., **144**, 314.
3. Cass, R., Kuntzman, R. and Brodie, B. B. (1960): Proc. Soc. Exp. Biol. (N.Y.), **103**, 871.
4. Cannon, P. J., Whitlock, R. T. and Laragh, J. H. (1962): Paper presented at Seventh International Congress of Internal Medicine, Munich.
5. Dollery, C. T. and Harington, M. (1962): Lancet, **1**, 759.
6. Gillespie, L. (1960): Ann. N. Y. Acad. Sci., **88**, 1011.
7. Gillespie, L., Oates, J. A., Crout, J. R. and Sjoersdma, A. (1962): Circulation, **25**, 281.
8. Hamilton, M. and Kopelman, H. (1962): Paper presented at Seventh International Congress of Internal Medicine, Munich.
9. Hess, S. M., Connamacher, R. H., Ozaki, M. and Udenfriend, S. (1961): J. Pharmacol. Exp. Ther., **134**, 129.
10. Irvine, R. O. H., O'Brien, K. P. and North, J. D. K. (1962): Lancet, **1**, 300.
11. Kuschke, H. J., Wolper, H. J., Igata, A. and Becker, G. (1962): Paper presented at Seventh International Congress of Internal Medicine, Munich.
12. Oates, J. A., Gillespie, L., Udenfriend, S. and Sjoersdma, A. (1960): Science, **131**, 1890.
13. Onesti, G., Brest, A. N., Novack, P. and Moyer, J. H. (1962): Amer. J. Cardiol., **9**, 863.
14. Porter, C. C., Totaro, J. A. and Leiby, C. M. (1961): J. Pharmacol. Exp. Ther., **134**, 139.
15. Sannerstedt, R., Varnauskas, E. and Werkö, E. L. (1962): Acta med. scand., **171**, 75.
16. Smith, S. E. (1960): Brit. J. Pharmacol., **15**, 319.
17. Sourkes, T. L. (1954): Arch. Biochem., **51**, 444.
18. Stone, C. A., Porter, C. C., Watson, L. S. and Ross, C. A. *in* Brest, A. N. Moyer, J. H. eds. (1961): *Op. cit.*,[1] p. 417.
19. Stone, C. A., Ross, C. A., Wenger, H. C., Ludden, C. T., Blessing, J. A., Totaro, J. A. and Porter, C. C. (1962): J. Pharmacol. Exp. Ther., **136**, 80.
20. Wilson, W. R., Fisher, F. D. and Kirkendall, W. M. (1961): J. Clin. Invest., **40**, 1089.