of our leading biologists have emphasized this new element in human development; they insist that social and psychological innovations now predominate over the much slower processes of biological change in the continuing evolution of mankind.

All this, however, belongs to the realm of speculation; and this speculation is darkened by the constant reminder that man has discovered, and perfected, the means of his own destruction—and may yet employ them.

Though biologists agree about the enormously increased rate of human psycho-social evolution, they tend still to think in terms of generations, if not of centuries or millenniums. When we lower our horizon to the limits of the present century we can more confidently predict the outcome of certain dominant trends in recent social and political history.

Explosive Expansion of Scientific Knowledge

Until quite recent times every major culture had its own traditions, its own cosmology, its own interpretation of the nature and significance of man (which was usually formulated in terms of man's relationship to God). But during the last hundred years, and with increasing momentum during the last few decades, something quite new has supervened. We have seen the growing acceptance, in *every* culture, of a similar *eidos*, or way of thinking, based upon the scientific method.

The explosive expansion of scientific knowledge, crossing all national frontiers, and its application to agricultural and industrial production and especially to communications, introduces something quite new into human experience. It is creating a mental climate favourable to new forms of political organizations, world-wide in their scope.

During the rest of this century the mountainous accumulation of scientific information is likely to continue. Pupils of the future cannot possibly digest all the facts. Fortunately, this is a task which we shall soon be able to delegate to computers and electronic storehouses of factual data. Machines will relieve us of the drudgery of calculation and free us to devote more time to other studies: to learning the principles on which scientific hypotheses are based; to cultivating an appreciation of literature and the arts; and to developing a clearer understanding of our own personalities and our deeper motivations.

It may seem incongruous to think of ourselves as a people becoming more psychologically perceptive. This seems at variance with our traditions, in which sensitivity has generally been subordinated to the predominance of rather philistine, practical men and women; and yet there has always been a strong element of poetry and imagination in our country.

A by-product of this process of self-understanding is that it tends to make one less censorious of other people's peculiarities, including those of our own teenagers. Eccentricity is a social asset in a world full of stereotypes. Perhaps there will be fewer misfits in our society if we learn to emulate the Indians in their remarkable tolerance for harmless eccentrics.

Belief in Individual Worth

In our own social history we may expect the continuation of our halting progress towards a more equalitarian society. If the methods of scientific experiment and validation become increasingly adopted by social scientists—as I believe they will—future experiments in social reform will tend to be designed on experimental lines, so that whether they succeed or not they will add to our knowledge. Neither science nor sociology, however, can provide the values which ultimately inspire such interventions. I suggest that the ultimate value behind attempts to remedy the diverse patterns of social failure is simply this: a belief in the individual worth and dignity of every human being. This is a value to which both humanists and Christians subscribe.

I am grateful to my wife, Mrs. Vera Carstairs, for preparing this summary of my lectures.

HYPOTENSIVE ACTION OF METHYLDOPA

BY

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It has been established that methyldopa is capable of reducing the blood-pressure when given orally (Brest *et al.*, 1961; Gillespie, 1960; Irvine *et al.*, 1962; Onesti *et al.*, 1962) or intravenously (Wilson *et al.*, 1961; Gillespie *et al.*, 1962). Sannerstedt *et al.* (1962) found after oral methyldopa that the rises of blood-pressure induced by exercise were smaller. Schaub *et al.* (1962) noted considerable reduction of blood-pressure in a patient with phaeochromocytoma. Although the requisite dosage is much greater than many of the highly potent agents introduced recently, the relationship between the occurrence of side-effects and hypotensive activity is at least sufficiently favourable to merit a consideration of its hypotensive activity from a practical standpoint. An outline of our experience with 53 patients who have received this drug is given.

The substance alpha-methyl-L-3,4-dihydroxyphenylalanine or methyldopa ("aldomet") inhibits the enzymatic decarboxylation of dopa *in vitro* (Sourkes, 1954) and *in vivo* (Dengler and Reichel, 1957; Reichel and Dengler, 1958; Oates *et al.*, 1960). Thus (Fig. 1) the substance should interfere with the formation of

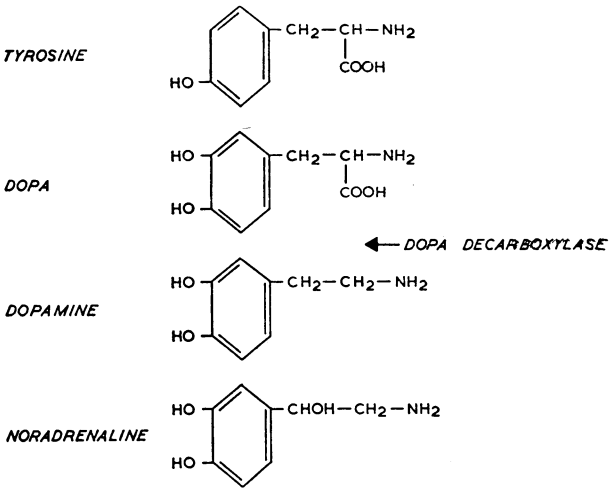

FIG. 1.—Steps in the synthesis of noradrenaline.

dopamine from dopa. Should there be a sufficient interference with the formation of dopamine it is conceivable that there would be a decrease in the synthesis of noradrenaline, the presumed neuro-transmitter of the orthosympathetic system. The fact that methyldopa reduces the blood-pressure lends support to the idea that it might interfere with the formation of the neuro-transmitter, but there are other known decarboxylase inhibitors which, however, do not cause falls of blood-pressure (Stone *et al.*, 1961). The enzyme also inhibits the decarboxylation of 5-hydroxytryptophan (5-HTP) (Westermann *et al.*, 1958; Smith, 1959; Oates *et al.*, 1960). When methyldopa is administered previously the pressor effect of dopa in rats is greatly diminished, presumably owing to decrease in the formation of dopamine, which itself has a pressor action (Smith, 1960). A generalization concerning the effect of methyldopa on the noradrenaline concentration in tissues does not appear as yet to be warranted, though some estimates have been made (Smith, 1960; Stone *et al.*, 1961). Stone *et al.* (1961) found a reduction of tissue catecholamines in the heart and spleen of the dog after administration of methyldopa.

The action of methyldopa in reducing the blood-pressure does not appear to be explained by a simple inhibition of the sympathetic nervous system, for, in dogs and cats at least, it does not give rise to any obvious relaxation of the nictitating membrane (Stone *et al.*, 1961). At first sight it seems reasonable to attribute blood-pressure reduction to decreased catecholamine level of the tissues. Against this explanation is the report that whereas the catecholamine level in mice is reduced to a greater extent by α-methyl-meta-tyrosine than by methyldopa, in rats α-methyl-meta-tyrosine does not possess the hypotensive action characteristic of methyldopa. Stone *et al.* (1961) came to the conclusion that it is unlikely that the antihypertensive action of methyldopa is related to interference with the sympathetic nervous system. Stone at the Second Hahnemann Conference pointed out the absence among clinical reports then available to him of such side-effects as stuffiness of the nose or interference with ejaculation or diarrhoea. Gillespie *et al.* (1962) also consider that it would be premature to attribute the hypotensive action of methyldopa to reduced sympathetic activity, but they do refer in their paper to impotence in a young male as a probable side-effect. Further detail, with an important discussion of the mode of action, has been published by Stone *et al.* (1962). In experiments on rats with genetic hypertension which apparently is neurogenically maintained, methyldopa has been shown by Phelan and Smirk (unpublished) to produce a much more considerable fall in blood-pressure than in normotensive rats.

There is already a widespread impression that methyldopa is an effective hypotensive agent in more than one type of high blood-pressure. Its comparatively mild side-effects in many patients make it an acceptable drug to many cases with high arterial pressure.

Methods

Effects on the blood-pressure have been evaluated in the individual patients by several all-day tests in which the blood-pressure is measured hourly or at more frequent intervals by technicians, as described previously (Smirk, 1957). Any side-effects are noted concurrently. For evaluation of blood-pressure falls reliance was placed mainly on the ability of the drug to reduce casual blood-pressures below the level of the patient's basal blood-pressure. Placebo tablets were also used. When blood-pressures have been brought to a satisfactory level the patients attend the routine hypertensive out-patient clinic, ordinarily at monthly intervals.

In most of the tests concerned, especially with postural changes in blood-pressure, six successive pressures at approximately minute intervals were made in the standing posture, succeeded by six pressures in the lying posture. The relation between blood-pressure measurements made in the standing and lying postures is sometimes much influenced by the time interval between the changes of position.

The manner in which inquiries are made about side-effects has an important influence on the number reported. The procedure adopted in most instances was first to record only those symptoms complained of spontaneously or in response to a general inquiry as to comfort. Later, after several weeks on the drug, patients were asked in detail about specific symptoms. This latter procedure increased the apparent incidence of side-actions.

The methyldopa we have used clinically is the laevo-isomer. Apparently the dextro-isomer is inactive (Gillespie *et al.*, 1962).

Hypotensive Action of Methyldopa

In each of 19 patients (12 female, 7 male) who were not receiving any adjuvant drugs, methyldopa was administered in doses that were adjusted with the aim of producing a fall in blood-pressure to a near-normal level at the trough of the blood-pressure fall in the standing posture. The least daily dose given was 150 mg., the highest 2,000 mg., and the mean 1,043 mg. A summary of the results obtained is set out in the Table.

Effect of Methyldopa on Casual Blood-pressure (19 *Patients*, 12 *Female*)

	Before Drug	After Drug
Systolic, standing posture ..	198·0±28·2	137·5±19·6
„ lying „	208·6±24·7	160·4±19·0
Diastolic, standing posture ..	123·0±14·0	91·1±10·5
„ lying „ ..	120·8±14·9	101·9±11·6

Casual blood-pressures in the standing posture during drug administration fell well below basal blood-pressures taken before the drug was given in 16 out of 19 patients. In 11 patients the casual systolic pressure and in 10 patients the casual diastolic pressure in the lying posture fell below the basal blood-pressure but it was sometimes well above this level. The average casual blood-pressure after methyldopa fell by 60.5 mm. Hg systolic, 31.9 mm. Hg diastolic (standing), and 48.2 mm. Hg. systolic, 18.9 mm. Hg diastolic (lying) below the casual blood-pressure before drug administration. The average fall below the basal blood-pressure was 43.6 mm. Hg systolic, 14.2 mm. Hg diastolic (standing), and 10.6 mm. Hg systolic, 3.4 mm. Hg diastolic (lying). These results are a strong indication of effective drug action, and falls below the basal blood-pressure are probably a more severe test than comparison with a placebo. The effect on pulse rates varies, but the tendency is to a reduction in the pulse rate.

In eight patients placebos were given and the falls of blood-pressure (standing) on methyldopa exceeded the falls on administration of a placebo by 40, 38, 40, 30,

16, 46, 42, and 32 mm. Hg systolic and by 18, 30, 40, 10, 14, 38, 6, and 10 mm. Hg diastolic.

Drug Toleration

Dosage increase was required to maintain the blood-pressure falls obtained initially in 6 patients out of 14 where comparable observations were made. In two instances the dose required to maintain the requisite blood-pressure reduction increased from 750 to 2,000 mg. a day in periods of one and (approximately) four months respectively. Periods of three to eight and a half months of drug administration have occurred, however, without the need to increase the dose. Certainly drug toleration does not constitute a serious problem. It is by no means easy to be confident that dosage increase has to be equated with drug toleration. For example, the transfer from hospital to out-patient treatment may be associated with a need for dosage increase.

Side-effects of Methyldopa

The investigation of methyldopa illustrates the difference between the comparatively few spontaneous complaints and the more frequent reports of symptoms when direct inquiries are made. Most patients tolerate effective hypotensive doses of methyldopa well. A few patients have shown unmistakable psychiatric disturbances of a temporary nature. In some instances these pass off while drug administration continues.

Of 53 patients receiving methyldopa 44 were questioned in detail about side-effects. Of the remaining nine, three stated they were well and comfortable but were not questioned in detail; two were too ill to render a comment on side-effects useful; in three patients psychiatric symptoms, referred to later, determined stoppage of treatment and information on side-effects was incomplete; and one patient died before evaluation was complete.

Of the 44 patients questioned in detail, 32 made no spontaneous complaint in the first two weeks and 12 made complaint of some symptom, usually drowsiness. On direct inquiry, or by reference to notes made while the patients were on all-day tests, it was clear that 34 had had some drowsiness (stated to be trivial by four and considerable by six). Seven patients stated they had not been drowsy. Our interrogation was inadequate in two patients. In the great majority of cases drowsiness disappeared within a few days but others remained drowsy for at least several weeks.

Dry mouth was infrequent as a spontaneous complaint, but of 34 patients who were asked directly a complaint of dryness of the mouth at some stage was made by 23 patients and 11 said that they had no mouth-dryness. The majority of patients stated that their bowel habit was unaltered by methyldopa. Severe diarrhoea of some weeks' duration was attributed by one patient, with emphasis, to methyldopa, but when diarrhoea ceased he accepted advice to resume the drug and had no recurrence. It seems likely that the diarrhoea was unrelated. A female patient, however, experienced seven or eight bowel motions a day for which we found no alternative explanation. One additional patient had mild diarrhoea.

Two or three patients complained of nausea or vomiting but not of severe degree. It is not certain if these symptoms were specifically related to methyldopa administration. In one instance the nausea ceased on stopping potassium chloride administration given in connexion with diuretic therapy.

Five patients made complaint, usually spontaneously, about an unpleasant taste in the mouth. Such complaints have occurred occasionally with most of the potent hypotensive drugs. Five patients complained of mild headache.

Disturbances of sexual function have not so far been complained of in our patients on methyldopa. A patient previously on ganglion-blockers expressed gratification at the return of sexual potency on transfer to methyldopa.

More than trivial rashes were reported by two patients. The first, widespread with much irritation, rather like the start of an exfoliative dermatitis, seems to be the result of paraphenylenediamine hair dye. In the second case the rash was petechial, and was associated with a positive Hess test and a reduction of the platelets to 95,000/c.mm. The rash disappeared in two weeks after withdrawal of methyldopa and the platelets returned after eight weeks to 200,000/c.mm. Resumption of methyldopa at the request of the patient did not lead to return of the rash, but platelets diminished without return of the positive Hess test. The condition may have been due to the drug, but the evidence is by no means certain.

Psychiatric Manifestations and Disturbance of Sleep Rhythm Encountered After Methyldopa

The most interesting of the side-effects of methyldopa has been the occurrence in a few patients of psychiatric manifestations. Such symptoms have sometimes disappeared spontaneously while the drug was continued, and appear to be more frequent in, but not confined to, patients who had shown psychiatric disabilities beforehand. As it happened, there was an unusually high proportion of persons with some psychiatric background in this series. Disturbances of sleep rhythm are mentioned also among the case histories set out below.

Case H.1484.—A nervous woman aged 41 with severe hypertension who had exhibited previously a brief episode of hemiplegia with recovery. She was regarded as a queer type; there was a family history of psychiatric illness, added to by the suicide of her sister. After methyldopa she was exceedingly sleepy while at the all-day clinic, but on her return home she began talking unceasingly and uncontrollably. She recognized this as abnormal and was frightened. The drug was withdrawn and the symptoms did not recur.

Case H.1668.—A woman aged 76 became depressed and there was much weeping for several days. The drug was withdrawn, with prompt recovery.

Case H.1604.—A slight, nervous man aged 54 who had experienced no psychiatric illness was very satisfied with methyldopa and said he had no side-effects. On questioning him directly, however, he confided that on two occasions he had inexplicably and without reason broken down and wept. He continued on treatment and the symptom did not recur.

Case H.1603.—A frankly neurotic woman aged 44 was unwilling to continue treatment as she was mentally upset and weepy. While she remained neurotic on treatment with other drugs the symptoms attributed by her to methyldopa ceased with its withdrawal.

Case H.1602.—A woman aged 57, a patient at a private mental hospital, had been sent to us for treatment of her hypertension. She was treated with methyldopa for two weeks and became depressed. As her mental state was

deteriorating the drug was withdrawn. She stated that the depression disappeared in a few days.

Case H.1123.—An intelligent, loquacious, busy spinster, aged 72, when interviewed stated enthusiastically that methyldopa was "the best ever." Asked, however, about any changes in temperament or attitude, she related that at the outset of treatment she had peculiar feelings of unreality, a detached "watching herself." On one occasion when she had to speak in public she felt as though she was not "altogether there," but apparently did not do badly. She had a minor recurrence with increase of dose.

Case H.1590.—A man aged 56 was depressed at the onset of administration but lost the symptom entirely while continuing on the drug. He had bronchial asthma as well as hypertension, and this was troublesome about the time of the depression, which, in any case, was not of great severity.

Case H.1585.—A man aged 59 after initial drowsiness had a period of very troublesome insomnia. This was treated by a sedative, which was later withdrawn. He then slept well without sedation.

Case H.399.—A woman aged 58 found herself lively and unable to sleep when methyldopa was taken at bedtime, but was able to sleep satisfactorily if the last dose was taken at 6 p.m. instead of at bedtime.

Case H.1281.—A man aged 62 had a tendency to dream, but on taking methyldopa he had nightmares.

Postural Hypotension from Methyldopa and Other Drugs

An impression was gained early on that the postural falls of blood-pressure after methyldopa were somewhat less in most patients than those encountered with at least some ganglion-blocking drugs. The differences between methyldopa and the drugs available at present were observed chiefly when doses had been given which proved sufficient to reduce the blood-pressure in the standing posture to a near normal level.

In seven patients a total of 22 comparisons were made of the extent of the postural falls of blood-pressure after methyldopa with the falls after certain ganglion-blocking agents—namely, hexamethonium, pentolinium, and pempidine.

At the trough of the blood-pressure fall the averages of the pressures in the standing posture were similar: 128/91 mm. Hg after ganglion-blocking drugs; 133/93 mm. Hg after methyldopa. In the lying posture, however, the averages of the corresponding blood-pressures were 176/106 after ganglion-blocking drugs and 157/102 after methyldopa. The average change in blood-pressure on assumption of the erect posture was therefore 48/15 after ganglion-blocking drugs and 24/9 after methyldopa.

Similar results were obtained in a total of 22 tests on seven patients in which the postural changes in blood-pressure, after bretylium tosylate, were compared with the changes after methyldopa. The average blood-pressure in the standing posture after bretylium tosylate was 134/87, and after methyldopa 135/87. The averages of the corresponding pressures in the lying posture were 180/103 after bretylium tosylate and 156/93 after methyldopa. The average postural falls were therefore 46/16 for the bretylium tosylate and 21/6 for methyldopa. The reason for the close correspondence of the blood-pressure in the standing posture is that the aim in each test was, by dose adjustment, to bring the blood-pressure in this posture down to a near or fully normal level at the trough of the blood-pressure fall.

While one can state that, in general, certain drugs such as methyldopa exhibit somewhat less postural hypotension than certain other drugs, the generalization does not apply to all patients. There are large individual variations in the extent to which different patients exhibit postural hypotension. Occasionally, moreover, the amount of postural hypotension with the same drug and the same patient will change considerably during the course of treatment.

Only a few comparisons were made in which the postural falls of blood-pressure from guanethidine and methyldopa were compared by administering both drugs to the same patients. A survey was made, however, comparing the postural falls of a number of patients treated with guanethidine with the response of other patients treated with methyldopa. The impression was

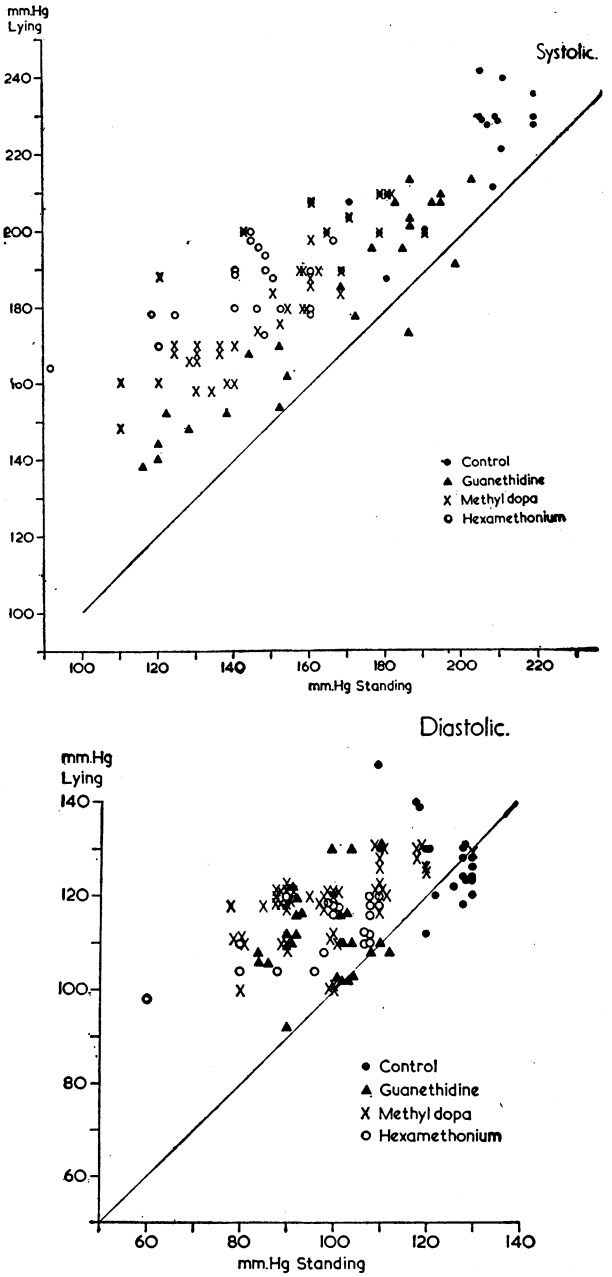

FIG. 2.—Case H.1608. Systolic and diastolic blood-pressures in the lying and standing postures at various stages in the course of action of guanethidine, methyldopa, and hexamethonium. The points marked "control" represent changes brought about by habituation to the procedure without drug administration. All readings are on the same patient.

gained that there was no conspicuous difference between the drugs in this respect. From a few detailed studies it appears that some individuals show larger postural falls with methyldopa (Case H.1608, a woman aged 54, Fig. 2) and others have larger postural falls with guanethidine (Case H.1582, a woman aged 53, Fig. 3). The figures represent the results of a series of blood-pressure determinations in the lying and standing postures in two hypertensive patients following administration of guanethidine and methyldopa respectively; and in Case H.1608 of hexamethonium also. The points marked "control" represent the changes in pressure in the absence of drug action as the patient became accustomed to the procedure. The further the points lie to the left of the 45-degree line the greater the amount of postural hypotension. The considerable extent of the postural hypotension from hexamethonium will be noted in Fig. 2.

In some instances the relationship between blood-pressures measured in the standing and lying postures are surprisingly consistent. In other cases the relationship may alter even in the course of several weeks.

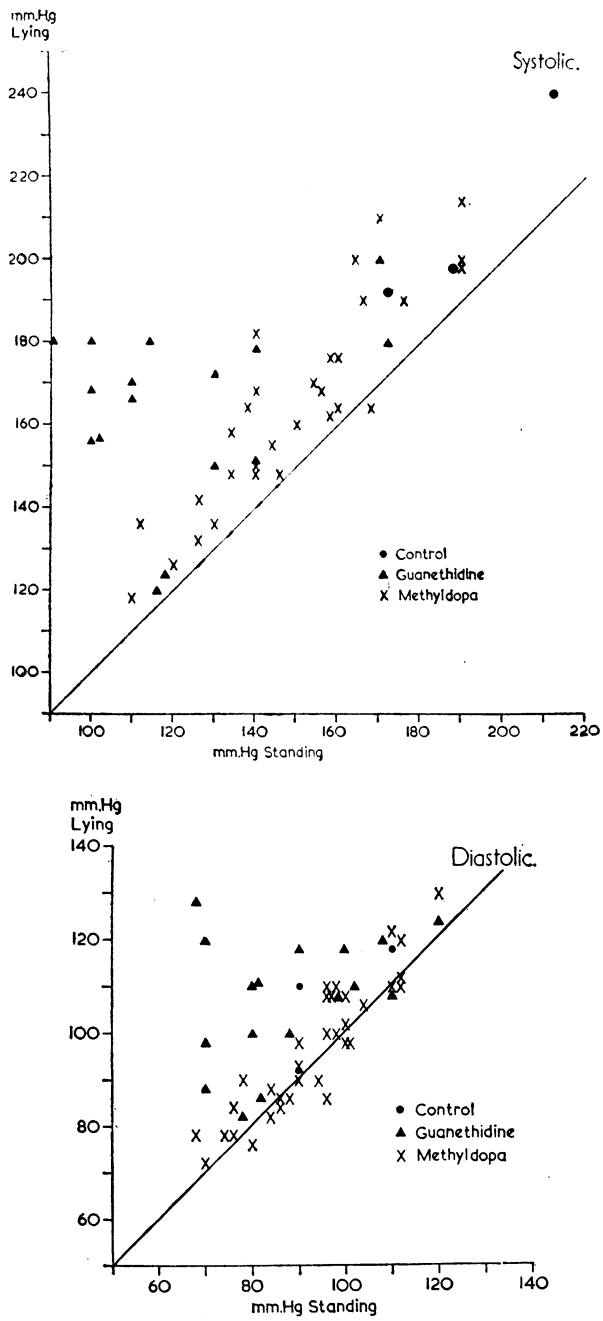

FIG. 3.—Case H.1582. Systolic and diastolic blood pressures in the lying and standing postures at various stages in the course of action of guanethidine and methyldopa. The points marked "control" represent changes brought about by habituation to the procedure without drug administration. All readings are on the same patient.

Discussion

Methyldopa, a potent inhibitor of the enzyme decarboxylase, which is concerned with a step in the synthesis of noradrenaline, is also a hypotensive agent capable of controlling the blood-pressure level even in some patients with malignant hypertension. But while it is tempting to assume that the hypertensive action is due to decreased synthesis of noradrenaline, generally regarded as the neurotransmitter at endings of the sympathetic nervous system, it has not been shown as yet that the action is upon the sympathetic nervous system. Indeed, as there are other inhibitors of the same enzyme system which are not hypotensive, it is possible that the blood-pressure fall is unconnected with the inhibition of decarboxylase.

The drug, however, must take its place among the considerable number of chemical substances of widely differing chemical constitution and modes of action which can now be used in practice to reduce the blood-pressure level. None of them appear to be suitable for or tolerated by all hypertensive patients, but by choice either of a single drug, or more usually in severe cases of a combination of drugs, it is surprising in how many patients a comfortable regimen can be found.

There are a number of patients with severe hypertension who have found in such drugs as methyldopa and guanethidine the best means so far of obtaining adequate blood-pressure falls with a few or even no side-effects. Background therapy with hypotensive diuretics, sometimes with small doses of rauwolfia alkaloids, remain valuable adjuvants, and in a number of severe cases difficulties in obtaining adequate blood-pressure falls have been overcome by introducing additionally small doses of ganglion-blocking drugs. When most of the control over the blood-pressure level is obtained by other drugs, parasympathetic side-effects from ganglionic blockade do not constitute an important problem. So far it seems that methyldopa can be used without difficulty in a variety of drug combinations.

The psychiatric manifestations in this series may be more frequent than will be encountered ordinarily. Like Gillespie *et al.* (1962), we have encountered an easily reversible depression. Other manifestations such as peculiar feelings of detachment and emotional disturbance and alteration of sleep rhythm with insomnia as well as drowsiness have been noted. Many of the manifestations are temporary and likely to be tolerated if patients are warned beforehand that slightly queer sensations may be encountered at the outset. We have encountered patients who had drowsiness persisting for a month and desired to discontinue the drug for this reason.

Several experienced patients regard the drug as a distinct advance in that they had fewer side-effects, including less postural hypotension.

Summary

Methyldopa is a useful hypotensive agent.

While doses up to 2 g. or more daily may be required, the effective dose can usually be administered without lasting side-effects.

Psychiatric symptoms and disturbances of sleep rhythm, often of a temporary nature, seem not to be infrequent when asked for specifically.

Dosage with methyldopa is less critical than it is with ganglion-blocking drugs.

The degree of postural fall in the blood-pressure is usually less than with hexamethonium or bretylium tosylate and of the same order as that encountered with guanethidine; but the extent to which postural hypotension is exhibited varies with the individual patient and with the drug used. There are patients who with methyldopa have unmistakable degrees of postural hypotension and others who exhibit practically none.

I am much indebted to the Medical Research Council of New Zealand for financial support. Supplies of methyldopa were generously supplied by Merck Sharp & Dohme through the courtesy of Dr. Mezey. The services of Mrs. E. G. Hobbs and other technicians in the hypertensive clinic are much appreciated.

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A bronze plaque to commemorate the visit to Hungary in 1815 of Richard Bright, the British physician, was recently unveiled on the wall of the chateau at Keszthely, at the southern end of Lake Balaton. The plaque bears the following inscription in English and Hungarian: "Richard Bright (1789–1858), Physician, Scientist, and Traveller, a pioneer in the accurate description of Lake Balaton. He sojourned in this building in 1815." Richard Bright described his three months' tour of Hungary in *Travels from Vienna through Lower Hungary*.

TREATMENT OF SEVERE HYPERTENSION WITH METHYLDOPA

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Methyldopa has been shown to inhibit the decarboxylation of dopa (Sourkes, 1954), an essential precursor to the biosynthesis of noradrenaline, in addition to a similar inhibitory effect upon the biosynthesis of other aromatic amines (Westermann *et al.*, 1958; Oates *et al.*, 1960; Sjoerdsma *et al.*, 1960). By virtue of this former action it has been used to control not only experimental hypertension in animals (Gillespie, 1960; Oates *et al.*, 1960; Sjoerdsma *et al.*, 1960) but also the less severe forms of human hypertension (Dollery and Harrington, 1962; Bayliss and Harvey-Smith, 1962; Irvine *et al.*, 1962; Daley and Evans, 1962). Though shown to be an effective hypotensive agent, doubt is now cast on its mode of action, Gillespie *et al.* (1962) suggesting that it may exert some central effect rather than acting peripherally by inhibition of amine synthesis.

We here report our experience in the treatment of 69 patients suffering from severe hypertension for periods ranging from 1 to 14 months.

Method of Study

Before starting the treatment, all patients underwent the customary investigations, including renal arteriography if considered necessary, to exclude any remedial cause of the hypertension. Only those in whom no such cause was demonstrated were included in the study. After completion of these investigations, seven patients were treated as out-patients: the remaining 62 were admitted to hospital in order to initiate treatment, which was subsequently controlled with the patient attending the out-patient follow-up clinic. All 69 patients suffered from severe hypertension needing treatment by blood-pressure reduction; all showed a persistent hypertension under observation before treatment; in no case was treatment given for a manometric hypertension only, in the absence of other indications for blood-pressure reduction.

Methyldopa ("aldomet") was administered orally in all cases, at first as capsules and later as tablets, each containing 250 mg. The initial dose was 250 mg. four times daily, increasing to a maximum dose of 4 g. daily if necessary. While in hospital the blood-pressure was measured hourly throughout the day, with the patient lying and standing, both pressures being recorded. After discharge all were followed regularly as out-patients, the dose of methyldopa being regulated by blood-pressure readings recorded either as casual measurements obtained in the follow-up clinic or, more usually, as day test measurements as advocated by Smirk (1957), with the patient attending the ward from 9 a.m. to 5 p.m. and two-hourly blood-pressure measurements being made during that period. All in-patients were weighed once weekly and out-patients at each attendance.

Control of blood-pressure was regarded as good if the diastolic pressure was maintained consistently below