cortisone was donated by the Medical Research Council. Since this article was written we have learnt that Messrs. Squibb have made 9α-fluorohydrocortisone available to hospitals in tablets of 1-mg. and 0.1-mg. strength.

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USE OF MECAMYLAMINE IN THE MANAGEMENT OF HYPERTENSION

BY

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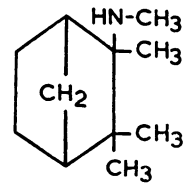
The discovery by Stone *et al.* (1956) that mecamylamine ("inversine"), a secondary amine, has pharmacological properties in many ways similar to those of the quaternary ammonium compounds, which are tertiary amines, is of interest not only in relationship to the properties of the substance itself but also because other secondary amines as yet untested may prove to be more satisfactory as ganglion-blocking drugs than any of those now available.

On the basis of both animal (Ford *et al.*, 1955; Stone *et al.*, 1956) and clinical studies (Ford *et al.*, 1955; Freis, 1955; Freis and Wilson, 1955, 1956; Moyer *et al.*, 1955) it is evident that mecamylamine causes blockade of both sympathetic and parasympathetic ganglia. It differs from the methonium compounds, however, in being readily and completely, or almost completely, absorbed from the alimentary canal. It has also been reported (Freis and Wilson, 1955, 1956) that, contrary to the invariable course of events with the methonium compounds, the continued administration of mecamylamine leads to little or no drug toleration, a point of great practical and theoretical interest. The structural formula of mecamylamine (3-methylamine*iso*camphane hydrochloride) is here shown.



The present study describes our experiences with the use of mecamylamine in the management of 40 cases of hypertension treated for from four to eight months.

Method

Mecamylamine was administered by subcutaneous or intravenous injection and by mouth. The blood pressure was measured by the method recommended by the Committee for the Standardization of Blood Pressure Readings (1939) in order to maintain uniformity with observations published previously on hexamethonium, pentolinium ("ansolysen"), and chlorisondamine ("ecolid") (Restall and Smirk, 1950; Smirk and Alstad, 1951; Smirk, 1953; Smirk and Hamilton, 1956).

Over a period of from four to eight months (average 4.6) 40 patients (20 males, 20 females) have received a trial of mecamylamine. Fundal gradings were or had been grade IV (Keith, Wagener, and Barker, 1939) in five cases, grade III in nine, and grades II or I in the remainder, most of whom had other severe manifestations such as congestive cardiac failure. Twenty-five patients had had treatment with other ganglion-blocking agents previously. In the remainder treatment was instituted with mecamylamine.

Drug Toleration

Before comparing the potencies of mecamylamine and other ganglion-blocking drugs it is necessary to consider whether mecamylamine causes drug toleration. At an early stage it became evident that toleration either did not occur or was present to a comparatively minor degree following the repeated administration of mecamylamine. Indeed, if drug toleration does develop it must do so early in the course of administration of gradually increasing doses; for once a fully effective dose has been discovered there is no consistent change in the dose needed to reproduce the same fall of blood pressure. In some instances the requisite dose has increased somewhat after several weeks or months of treatment; in other instances, somewhat less frequently, the requisite dose has decreased. In Fig. 1 is shown the

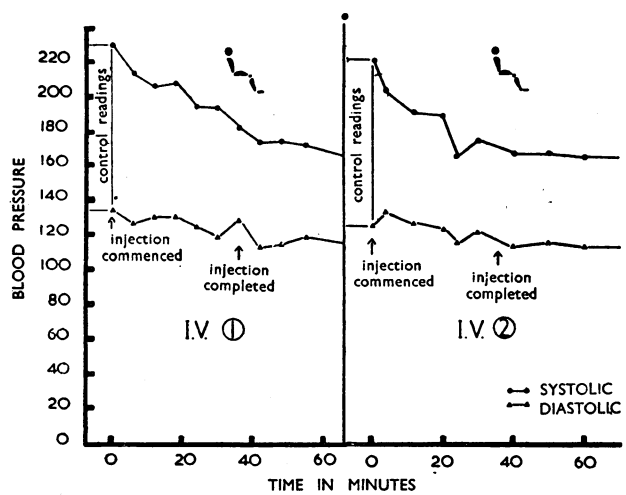


FIG. 1.—Effect on blood pressure of identical doses of mecamylamine given intravenously. I.V. (1) shows effect of an initial dose of 14 mg. of mecamylamine given slowly over the period shown, in the posture indicated. I.V. (2) shows effect of the same dose given in the same manner after two weeks of oral therapy, during which time the patient received 14 mg. of mecamylamine twice daily.

result of a test in which the initial effective dose was determined by intravenous titration. This was repeated after two weeks of oral therapy, with the production of an identical response.

Comparison of the Effective Doses of Mecamylamine, Pentolinium, Chlorisondamine, and Hexamethonium

The effective dose of mecamylamine may be compared either with the initial doses of quaternary ammonium compounds or with the doses of such compounds which may be required after repeated administration. In a series of 40 patients treated with mecamylamine the least dose to produce any significant effect was 3 mg., and 5 mg. is a suitable initial oral dose. The effective single oral dose reducing the blood pressure in the standing posture to about 120 or 130 mm. systolic, with corresponding reduction in the diastolic pressure, was 10 mg. or more in 80% of cases.

The duration of action of mecamylamine is in excess of 12 hours. Consequently, when two or more daily doses are given the effect obtained from one dose is influenced by the residue of the effect from the preceding dose. Hence increase of the night dose will have some effect on the level of the blood pressure next morning, and will influence the size of the dose which should be administered then. A fairly good control over blood-pressure levels can be obtained usually by two doses a day, the night dose being, for preference, approximately 30% higher than the morning dose. We have found it an advantage to give a small supplementary dose about 2 p.m., as otherwise there is often a rise of pressure in the late afternoon or early evening. Doses are adjusted in terms of the hypotensive action. The average daily dose in those of our patients who continued on mecamylamine was 33 mg. This average is probably higher than the average daily dose in unselected cases, as about half of our patients on mecamylamine had been selected because of the large dose of pentolinium or chlorisondamine which had been needed to reduce the blood pressure adequately. Among all cases maintained on treatment the highest dose was 70 mg.

By comparison, the effective oral dose of pentolinium per 24 hours at the time of initiation of treatment may vary from 40 to 160 mg., whereas when full drug toleration has been acquired, 60 to 1,800 mg. a day may be necessary, although most patients are controlled with doses of between 160 and 360 mg. a day. Correspondingly effective doses of chlorisondamine are of the order of 25 to 75 mg. at initiation of therapy and 50 to 750 mg. in the fully tolerant patient, and of hexamethonium salts 100 to 300 mg. initially and 300 to well in excess of 3,000 mg. when full tolerance has been acquired.

Direct comparison of mecamylamine with pentolinium was possible in 21 patients. In all of these pentolinium had been administered long enough for full tolerance to develop. Most of these cases had required unusually high doses of pentolinium. In 10 of these pentolinium had been given parenterally, in 11 orally. The results are shown in Table I.

The group originally receiving parenteral pentolinium was made up of patients having in general a particularly high requirement of quaternary ammonium compound. This is reflected in the larger requirement of mecamylamine in this group than of the group previously on oral pentolinium, and of the whole series (33 mg.).

It is of interest to note that oral mecamylamine and parenteral pentolinium, when full tolerance had developed to the latter, were equally potent.

TABLE I

No. of Patients	Average Effective Daily Dose Pentolinium (mg.)	Average Effective Daily Dose Mecamylamine (mg.)
11	460 (oral)	32 (oral)
10	39 (parenteral)	39 ,,

When hypertensive patients receive two or three doses daily there is usually less variation of the blood pressure throughout the day after mecamylamine than after chlorisondamine or pentolinium. Indeed, in some patients the degree of control which can be obtained by mecamylamine alone is approximately equal to that which can be obtained by chlorisondamine or pentolinium in combination with reserpine. Unfortunately, in some patients the development of side-effects makes it impracticable to administer a sufficient dose of mecamylamine. Our impression of the relationship between control over the blood-pressure level by mecamylamine as contrasted with pentolinium and chlorisondamine is that the best control over blood-pressure levels can be obtained with mecamylamine in those patients who are fortunate enough to be able to tolerate it. Unfortunately, mecamylamine in fully adequate doses is more often associated with prohibitive parasympathetic side-effects than either pentolinium or chlorisondamine. The responses to these drugs are highly individual, some patients for an equivalent degree of control over the blood pressure being more comfortable on mecamylamine, and some on pentolinium, and some on chlorisondamine.

Other Findings

Relationship Between the Effective Subcutaneous and Oral Doses of Mecamylamine.—It has been reported by Freis (1955), Freis and Wilson (1955, 1956), Moyer *et al.* (1955), and Ford *et al.* (1955), that mecamylamine has approximately the same hypotensive action whether administered subcutaneously or orally. Certainly the difference between the subcutaneous and oral doses is very much less than with the various quaternary ammonium compounds. We have found that on the average the oral dose must be a little greater than the parenteral dose in order to produce an equal fall of blood pressure, although in a number of patients the same dose was equally hypotensive when given orally as when given parenterally (Table II, Fig. 2).

Postural Hypotension After Administration of Mecamylamine.—The occurrence of postural hypotension following the administration of ganglion-blocking drugs has been referred to on many occasions. The action of mecamylamine appears to be indistinguishable in this respect from that of quaternary ammonium compounds. The relationship between the extent of the fall in blood pressure in the horizontal posture and the additional fall in the blood pressure which occurs on standing varies from patient to patient.

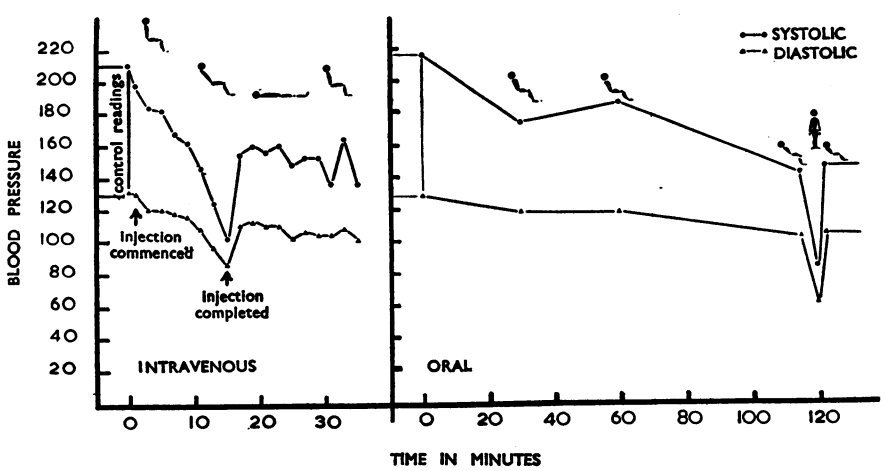


FIG. 2.—Effect of 8 mg. of mecamylamine intravenously over period shown compared with that of a single oral dose of 8 mg. given to same patient on a subsequent occasion. Effect of posture as shown.

TABLE II

Case No.	Parenteral Dose (mg.)	Route	B.P. Before	Lowest B.P. After	Oral Dose (mg.)	B.P. Before	B.P. After
7	9	H.I.	216/122	120/62	12	198/116	118/64
8	12	H.I.	242/126	176/90	20	214/104	162/78
26	10	H.I.	198/120	124/68	16	190/112	166/100
29	20	I.V.	230/136	154/94	20	200/122	166/100
30	6	H.I.	176/100*	118/76	6	186/100	128/80
35	10	H.I.	150/100*	140/96	12	170/100	142/96
38	15·5	I.V.	216/108	138/84	15	182/100	138/78
R.M.†	14	I.V.	212/108	124/92	14	208/104	166/104
E.D.†	8	I.V.	204/132	102/86	8	216/128	114/82
H.F.†	7	H.I.	238/124	180/108	7	258/130	156/94

* These cases had received doses of mecamylamine on the previous day and some residua drug action is present
† Additional to series.

Some patients have a substantial fall of blood pressure in all postures with comparatively little postural hypotension. Others have a very little fall of pressure when lying flat but a considerable decrease in the blood pressure on assumption of the erect posture (Table III).

TABLE III.—*Relationship Between Lying and Standing Blood Pressures and Pulse Rate Before and at the Trough of Blood-pressure Fall After Mecamylamine*

Case No.	Before Mecamylamine*			After Mecamylamine		
	B.P. Lying	B.P. Standing	Pulse	B.P. Lying	B.P. Standing	Pulse
2	238/122	210/118	82	194/108	186/88	80
3	204/106	162/118	76	146/96	142/90	76
4	208/120	194/110	84	154/102	126/90	80
6	254/142	240/160	100	182/134	144/96	98
8	246/112	208/100	84	142/68	140/72	84
9	196/116	214/136	60†	154/116	118/90	64†
10	240/112	208/114	96	170/98	118/70	92
11	222/112	210/114		172/98	140/88	
14	238/116	222/120	102	178/92	168/96	92
20	174/120	178/100	80	142/90	116/80	84
21	216/130	150/108		168/114	124/102	
23	238/140	194/108	56	116/70	92/40	60
24	272/110	232/118	100	210/118	118/72	88
25	190/100	196/104	76	170/98	140/82	72
26	202/124	198/120	72	132/72	124/68	72
27	176/120	168/116	90	162/104	132/98	90
28	220/120	200/118	62	170/110	148/104	76
31	232/108	208/106	70	166/92	156/80	72
32	180/112	168/114	80	174/110	142/96	80
33	188/126	174/120	72	134/80	130/80	72
34	204/100	186/102	62	150/70	130/70	68
35	188/134	198/142	80	180/94	162/74	88
36	208/122	174/100	72	162/82	120/48	68

* All cases had received doses of mecamylamine on the previous day and in some cases residual drug action is present.
† Patients with auricular fibrillation having digitalis.

Effect of Mecamylamine on Pulse Rate.—There is no consistent change in the pulse rate following the administration of mecamylamine, except where congestive heart failure or impaired circulatory activity has been improved by its administration. The pulse rate may rise or fall slightly.

Effect of Meals on Hypotensive Action of Mecamylamine.—Just as with hexamethonium, pentamethonium, "M. & B 1863," "Ciba 9295," pentolinium, and chlorisondamine, so also mecamylamine administration is associated with an additional fall in the blood pressure after a meal. Probably this is due to inability of vascular reflexes to compensate for splanchnic dilatation.

Side-effects After Administration of Mecamylamine.—Most of the side-effects which may follow the administration of mecamylamine are of the same kind as those already encountered following the administration of chlorisondamine, pentolinium, and hexamethonium. In addition to the side-effects exhibited by hexamethonium and pentolinium, the administration of chlorisondamine and mecamylamine may lead to vague and indefinable feelings of malaise which make the patients unwilling to continue with the drug, often without their being able to explain exactly the nature of their symptomatology. Such complaints have been rather more prominent with mecamylamine than with chlorisondamine. In an individual patient parasympathetic side-effects such as blurring of the vision, dry mouth, and constipation may be either greater or less with mecamylamine than with chlorisondamine or pentolinium. We have found that urinary retention has occurred more often after mecamylamine and that nausea and vomiting have been more frequent after mecamylamine and chlorisondamine than after pentolinium. On the other hand, patients who have had attacks of ileus or abdominal distension or other intolerable alimentary side-effects on large doses of pentolinium, necessitating in some cases their transfer to subcutaneous injections, have usually been more comfortable on mecamylamine. In this series of 40 patients, half of whom had been selected for trial because of difficulty with side-effects or with control of blood pressure, the side-effects encountered were of such severity as to cause substantial discomfort in 25 (Table IV).

TABLE IV.—*Side-effects of Mecamylamine*

Alimentary	Dryness of mouth	11
	Nausea and vomiting	9
	Constipation and abdominal distension	14 (partial ileus in one)
	Diarrhoea	2
Urinary	Dysuria	5 (retention of urine in one)
Visual	Blurring of vision	5

Clinical Appraisal

It must be borne in mind that our experience with mecamylamine has been derived from a group of patients more than half of whom had previously proved difficult to manage with other ganglion-blocking agents and who probably constitute a particularly severe test for any therapeutic regime.

Of the total of 40 patients in whom the trial was undertaken, mecamylamine continues to be used as the ganglion-blocking agent of choice, with or without a rauwolfia alkaloid, in 22. Of the remainder, two died, and in three further cases supply difficulties curtailed the trial. It is of some interest to consider the 13 in whom mecamylamine was abandoned. In one case control of hypertensive cardiac failure was less satisfactory than with the original regime using parenteral pentolinium. In the remaining 12, severity of parasympathetic side-effects was the determining factor. Eight patients reverted to other ganglion-blocking agents (three parenteral pentolinium, three oral pentolinium, one oral chlorisondamine, one oral "139.C.55"*), one was satisfactorily managed on reserpine alone, and three defected from treatment, an unusual event for this clinic.

Since tolerance occurs to a limited extent only, if at all, and since the parenteral and oral doses so nearly correspond, the method of intravenous titration can be used very profitably to initiate treatment. Our experience has been that intravenous administration at the rate of 0.5 mg. a minute with continuous blood-pressure recording is safe and not too time-consuming.

Use of Mecamylamine in Conjunction with Rauwolfia Alkaloids

We have used mecamylamine in conjunction with reserpine (0.5 mg. or less in 24 hours), rescinnamine (0.75 mg. or less in 24 hours), or canescine (1 mg. or less in 24 hours). We have encountered no difficulties in using these combinations of drugs. Smaller doses of mecamylamine suffice when rauwolfia alkaloids are administered concurrently. The extent of the potentiation of ganglion-blocking activity requires further study, but the initial impression is that it is of the same order as that observed after pentolinium.

Summary

Mecamylamine, a secondary amine, exhibits in man the pharmacological properties characteristic of a ganglion-blocking drug. In contrast with quaternary ammonium compounds, mecamylamine is well absorbed

*N′-(5-cyano-5:5-diphenylpentyl)-*N′*:*N′*:N²-trimethylethylene-l-ammonium-2-morpholinium sulphate (Burroughs Wellcome and Co.).

from the alimentary canal, so that the oral dose is little more than the parenteral dose. The degree of drug toleration is slight, and is not sufficient to cause difficulty in determining the requisite dose of the drug. The action is more prolonged than that of pentolinium or of chlorisondamine, so that the degree of control over the blood-pressure level is better, provided that a sufficient dose can be administered. Adequate control over the blood-pressure level is hindered in some instances by the occurrence of parasympathetic side-effects, which appear to be rather more prominent in most cases than those we have encountered with pentolinium. There are, however, individual differences in patients such that, with equal falls of blood pressure, side-effects may be less in some patients when they are treated with mecamylamine and less in others when they are treated with pentolinium.

Mecamylamine may be used satisfactorily in combination with rauwolfia alkaloids. Delayed toxicity has not been encountered with mecamylamine during our experience of eight months.

This work was supported in part by the Life Insurance Medical Research Fund of Australia and New Zealand. We wish to acknowledge the generosity of Messrs. Merck, Sharp, and Dohme in the supply of mecamylamine, and to thank Miss Noeleen Richardson for her assistance with the secretarial work.

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Q FEVER DOWN THE DRAIN

BY

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There is nothing very original about Q fever contracted in the laboratory. Since the early days of research on this disease in Australia and the United States infections have regularly occurred in institutes where live organisms (*Rickettsia burneti*) have been handled, although the incidence has probably diminished since vaccination was introduced in 1948 (Smadel *et al.*, 1948). In most published accounts the mode of infection is apparently airborne, sometimes after transport on clothing (Oliphant *et al.*, 1949 ; Beeman, 1950), and often after very short exposure.

The main purpose of this paper is to describe two infections in the Department of Pathology, Cambridge, by a route which this highly versatile organism has not previously succeeded in exploiting. Since the investigation of Q fever has now ceased in the department, the opportunity is also taken to review briefly other infections which occurred among members of the staff while the work was in progress.

General Arrangements and Vaccination Procedure

Research on Q fever was carried out in a set of three rooms on the top (third) floor of the department, in an animal-room and post-mortem room on the same floor, and in five small huts on the roof.

Serological investigation of Q fever began in 1947, but living strains of *R. burneti* were not handled until October, 1949. From this date until March, 1955, the rickettsia was grown in large numbers for production of antigen and other purposes. All those who worked in the Q fever laboratory itself were given a course of two or three injections with vaccine kindly supplied by Dr. H. R. Cox, of the Lederle Laboratories. From December, 1953, vaccination was extended more widely to those who were known to visit the laboratory, and, in all, 31 of a total of 83 members of the staff of the department were vaccinated.

Vaccination was not more extensive, because of limitation of supply and also because a chronic sterile abscess sometimes formed at the site of inoculation. In two individuals this progressed to form a discharging sinus which took many months to heal. This complication is thought to occur more frequently after booster injections (Meiklejohn and Lennette, 1950), so these were not generally given.

No cases of Q fever were identified between 1949 and 1953. Between October, 1953, and July, 1954, however, five members of the staff developed typical attacks of Q fever, which were confirmed serologically. Investigation failed to reveal outside sources, and it was assumed that infection took place within the department.

Several outbreaks of Q fever in other laboratories have followed the first growth of *R. burneti* in the yolk sacs of chick embryos, which yield very highly infective material. The number of eggs harvested and the method of processing in Cambridge had not varied much since 1949, however, and the onset of laboratory infections in late 1953 seemed to coincide more with an increase in the number of workers who were handling the organisms, even though, with one exception, they did not themselves succumb.

Of the five individuals who developed Q fever, four (patients B, C, D, and E) worked elsewhere in the building and were unvaccinated. They had all been in their occupations for a number of years. The remaining patient (A) had recently arrived to work on Q fever and was consequently vaccinated. Two patients (D and E) were infected together from a blocked drain. The remainder were unconnected sporadic infections.

Sporadic Laboratory Infections (Not Associated with the Blocked Drain)

Patient A received 1-ml. injections of vaccine on January 4 and 11, 1954. On January 21 he harvested yolk sacs heavily infected with *R. burneti*. On February 11, 21 days after this exposure, he developed Q fever. Complement-fixing antibody was absent on the third day, but appeared on the fourth day—very much earlier in the course of the disease than is usual—and was presumably due to the previous vaccination. The attack was nevertheless moderately severe, until after chlortetracycline was given on February 15.

It is clear that insufficient time had elapsed between completion of the course of vaccination and exposure to large numbers of rickettsiae.

Patient B worked in the histology department on the first floor. Eighteen days before the onset of his illness, on February 21, 1954, he briefly entered the Q fever laboratory to deliver a message. He had no other contact that could be discovered, and it seems highly probable that he was infected during the few seconds that he was in the laboratory.

Patient C, who became ill on October 4, 1953, also worked in the histology department on the first floor. Although he lived in the country no obvious source of *R. burneti* to which he was exposed could be discovered outside the department. He paid occasional visits to the Q fever laboratory, but could remember none during the probable period of exposure. He had contact, however, with one of the assistants in the Q fever laboratory who often took tissues (not infected with *R. burneti*) for sectioning, and it is possible that the rickettsia may have been carried in the clothes or hair (see Beeman, 1950).