35 patients with hypertension and severe symptoms and signs is described. These compounds were used orally with variable results upon the blood pressure, but in 23 of the 35 patients there was a good symptomatic improvement with regression of the signs.

Hexamethonium also produced a symptomatic improvement in five patients with severe chronic nephritis and two with malignant hypertension.

We are grateful to Dr. E. Robertson for his work during the early part of this trial and to other members of the hospital staff for their assistance. Mr. E. J. Baines, of the New Products Division of May & Baker Ltd., kindly made available the supplies of the compounds used.

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M. & B. 1863, A HOMOLOGUE OF HEXAMETHONIUM, IN TREATMENT OF HYPERTENSION

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Following work by Paton and Zaimis (1949), Organe, Paton, and Zaimis (1949), and Arnold and Rosenheim (1949), pentamethonium and hexamethonium compounds have been used for the investigation and treatment of hypertension and peptic ulceration (Kay and Smith, 1950, 1951). It has been the experience of some (Freeman, 1950; Locket, Swann, and Grieve, 1951; Banton, 1951) that the oral administration of these in hypertension may fail to produce and maintain a lower blood pressure. Smirk (1950, 1951) and Frankel (1951) have suggested that, therapeutically, hexamethonium bromide should be given subcutaneously, much as insulin is given, the patient being instructed to inject an appropriate dose once or twice daily, or even more frequently.

Bromidism (Rosenheim, 1951; Holt and Litchfield, 1951; Locket *et al.*, 1951; Campbell and Robertson, 1951; Sommerville and Allan, 1951), cerebral thrombosis (Locket *et al.*, 1951; C. F. J. Cropper, 1951, personal communication), coronary thrombosis and death (Hirson

and Kelsall, 1951; Locket *et al.*, 1951) have been recorded with these drugs, and in our opinion injection by the patient himself in doses adequate to produce any fall in blood pressure can be an extremely dangerous procedure.

In a previous paper (Locket *et al.*, 1951) we expressed the view that much of the subjective improvement recorded in these patients was due to sedation, reassurance and its consequent relief of anxiety, and possibly other measures instituted, such as a salt-free diet. We did not feel, in view of the natural history of essential hypertension, that any of the symptomatic improvement could reasonably be attributed to the oral administration of the methonium compounds when used by us. Ayman (1930) pointed out that all methods of treatment of hypertension have in common the "enthusiastic treatment of a worried patient," and to this he attributed most of their success.

Through the good offices of Dr. R. Forgan, Messrs. May and Baker Ltd. have kindly provided us with a supply of hexamethonium bitartrate, and also an analogue of hexamethonium known at the moment as "M. & B. 1863." The chemistry of this new compound and related derivatives is described by Barber and Gaimster (1951) and the pharmacology by Wien and Mason (1951). It was originally issued as the bromide salt, but now as the bitartrate. Experimentally it is two to four times as active as hexamethonium bromide (C6) as a ganglion-blocking agent, and therefore might be expected to work in smaller dosage by mouth, with possibly a more sustained action. The formulae given below show the relation between M. & B. 1863 and C6.

M. & B. 1863

Hexamethonium Bromide

For our trials M. & B. 1863 was issued in tablets of 125 mg. of the bromide or 175 mg. of the bitartrate, for oral use only; it was also available in solution for injection.

Most patients have received the drug by mouth only, but a few have had increasing subcutaneous or intramuscular injections of hexamethonium bromide or M. & B. 1863. After 48 hours these have been given oral M. & B. 1863. The dose of this compound was increased until a fall in blood pressure occurred or side-effects prevented any further increase. Most of our cases received no M. & B. 1863 from midnight to 6 a.m.

This communication is mainly based on a detailed analysis of our results in the treatment of 14 patients, both as in-patients and as out-patients. Since completing this review, however, we have also given M. & B. 1863 to many others, both as in-patients and as out-patients. We do not feel that these later results have differed in any way from those obtained in the 14 recorded cases. In all we have used the drug in more than 40 cases.

These results and conclusions relate to the long-term treatment of hypertension. We have found that a small intravenous dose (5 mg. of M. & B. 1863) will produce a most dramatic amelioration of dyspnoea in pulmonary oedema and "cardiac asthma" due to left ventricular failure in hypertension (not associated with coronary thrombosis). The results in some cases were infinitely better than when

using morphine and oxygen, and also were more sustained. So-called hypertensive encephalopathy, however, did not respond to this treatment (see for example Case 3 in this paper). This emergency use of the drug is not discussed further here.

The group of 14 patients is made up of two cases of severe rapidly progressive hypertension (albuminuria, papilloedema, slight diminution in renal function), one case of severe hypertension and papilloedema of at least five years' duration, three cases of chronic nephritis with high or very high diastolic pressure, a case of essential hypertension with superimposed toxæmia of pregnancy, and seven cases of essential hypertension with severe subjective symptoms, one associated with diabetes mellitus and hypertensive encephalopathy and the others with recurrent attacks of left ventricular failure and/or hypertensive encephalopathy. All these 14 patients had diastolic pressures of over 120 mm. Hg when treatment was begun, and all but three had diastolic pressures over 150 mm. Hg; in several cases the diastolic pressure frequently exceeded 180 mm. Hg.

Details are given of four of these cases, as they seem to be of particular interest.

Case 2

A married woman aged 39 had had essential hypertension for many years, with three stillbirths due to superimposed toxæmia of pregnancy. When she became pregnant for the fourth time she was given injections of pentamethonium bromide (C5) at six weeks, and later put on to oral C5. During the middle trimester of pregnancy her blood pressure fell to normal levels, but at the seventh month hypertension reappeared. The oral C5 was increased with no effect on her hypertension. She was then—when her blood pressure had risen to 190/130—given oral M. & B. 1863, and the dose was rapidly increased until she was receiving 250 mg. every one and a half hours. She felt very well, but her blood pressure steadily rose. The foetus was apparently very small for the state of pregnancy.

In spite of increasing doses of M. & B. 1863, and after a further week of treatment, the foetus died. The patient's high blood pressure was maintained for 48 hours until delivery of the macerated foetus and placenta occurred, and it then fell to the previous hypertensive level. At no time did the serum bromide exceed 50 mg. per 100 ml. There was no papilloedema at any stage, and the patient at all times felt very fit and well. During the last six weeks of her illness she remained in bed.

Comment.—In this case it is interesting to note the physiological fall in blood pressure in the middle trimester of pregnancy, and the failure of injected and oral C5 and oral M. & B. 1863 to keep the blood pressure within normal limits. (See accompanying Graph.)

Blood-pressure record of Case 2. (1) On admission to hospital, complete rest in bed. (2) Pentamethonium bromide started. (3) Patient discharged to antenatal clinic on pentamethonium bromide. (4) Readmitted to hospital, complete rest in bed. (5) M. & B. 1863 started. (6) Foetal death in utero.

The marked tendency of the blood pressure to fall in the middle trimester of pregnancy in the normal and hypertensive patients (Hare and Karn, 1929; Reid and Teel, 1939; Chesley, Annitto, and Jarvis, 1947; Browne, 1947) and in pregnant hypertensive animals (Page and Ogden, 1939) is quite well known, but we feel it should be emphasized in view of the use of the methonium compounds.

Case 3

A married woman aged 40, one of three cases developing definite papilloedema and albuminuria while receiving hexamethonium bromide or M. & B. 1863 orally, developed recurrent attacks of paroxysmal nocturnal dyspnoea and hypertensive encephalopathy while taking 4 g. of hexamethonium bromide daily. At this time her blood pressure, when she attended the out-patient department, was found to be 260+/180 mm. Hg, and she was immediately readmitted to hospital. After 48 hours of subcutaneous hexamethonium at two-hourly intervals she was given oral M. & B. 1863, and eventually received 250 mg. three-hourly. She was then allowed up. Her blood-pressure level persisted at 180–200/120 mm. Hg, and except for slight episodes of giddiness she felt relatively well.

In the out-patient department two weeks later her blood pressure was 260+/160 mm. Hg, but she felt very well. However, during the 48 hours before attending she had had a recurrence of occipital headache. Intractable constipation alternating with bouts of diarrhoea had been very troublesome. She still had albuminuria and papilloedema and a presystolic gallop. After some weeks her condition began to deteriorate, with no change in her blood pressure, though the dose was increased to 375 mg. seven times daily. She was readmitted in coma with a diastolic pressure averaging 180 mm. Hg, and, though a fall in her blood pressure was produced by intravenous M. & B. 1863, she died 36 hours after admission. In spite of papilloedema, albuminuria, and some diminished renal function, necropsy revealed arteriosclerosis but no evidence of malignant hypertension.

Case 4

A man aged 60 developed papilloedema, albuminuria, and a higher diastolic pressure (160 to 190 mm. Hg) while receiving 8–10 g. of hexamethonium bromide daily. There was no improvement in his condition at all to increasing doses of M. & B. 1863, and his average blood pressure was actually higher on that drug than it was without it.

Case 6

A married woman aged 35 had active chronic nephritis and severe menorrhagia. Her blood urea was 137 mg. per 100 ml.; standard urea clearance, 20–28% of average normal; urine albumin, 2–4 parts per litre; haemoglobin, 47%; blood pressure, 240–260/130–140 mm. Hg. M. & B. 1863, 125 mg. four-hourly, produced anorexia, nausea, and vomiting, but the diastolic blood-pressure level appeared to have been reduced by 20 mm. Hg. The dose was reduced with relief of her symptoms. The blood pressure did not rise. The urea clearance showed a steady fall, the albuminuria remained constant, and the blood urea rose to more than 270 mg. per 100 ml.

The patient's condition continued to deteriorate slowly, though with cessation of her menorrhagia the haemoglobin increased to 70%. The drug was then discontinued, and during the next six weeks her urea clearance rose by about 10% and her blood urea fell by more than 100 mg. per 100 ml. After a further month, during which she apparently remained fit, her blood urea began to rise again, and two months later she died in uraemic coma. Necropsy revealed chronic nephritis.

Discussion and Review of Results

In this series we did not meet with any case of bromide intoxication or bromide rash. The serum bromide level did not exceed 60 mg. in any case receiving the bromide salt.

Severe constipation was a more pronounced feature than in our past experience with pentamethonium and hexamethonium bromide and hexamethonium bitartrate. However, three patients attending the out-patients department complained of diarrhoea, which would follow several days' intractable constipation. Nausea and vomiting were complained of in six cases and were severe enough to necessitate a reduction in dosage in four cases.

In three patients the mean blood pressure was actually higher whilst the drug was being taken, and in many cases higher peaks of diastolic pressure occurred than during the control period. Increase in lability of the blood pressure was very marked. It was, however, difficult to decide whether this was due to the drug or was a normal feature of the disease.

One patient whose diastolic pressure rose to 170 mm. Hg on 2.0 mg. of M. & B. 1863 three-hourly showed a marked fall when given 250 mg. two-hourly. This fall was associated with gross deterioration in his physical condition and sense of well-being. A spontaneous thrombosis of his axillary artery developed. At this period he had a prothrombin time of 22 seconds (control, 13.5 seconds). Discontinuation of the drug relieved his general malaise, and his blood pressure rapidly rose to its previous level, but in a few days he had obvious congestive heart failure. Routine treatment of his heart failure eventually resulted in great improvement and a "maintained fall in blood pressure." Repeated electrocardiograms, including full unipolar chest leads, showed no evidence of coronary thrombosis, his blood culture was negative, and neither clinically nor radiologically was there any evidence of chronic rheumatic heart disease.

One female patient, in spite of more than five months' continuous treatment with intramuscular and oral hexamethonium bromide, and later with M. & B. 1863, developed what appeared clinically to be the phase of malignant hypertension.

Two out of three chronic nephritic patients whose very high diastolic pressure possibly contributed to their poor renal condition showed some reduction of blood pressure: in one (Case 6) this was associated with deterioration in the renal condition; the other patient was a chronic nephritic with acute exacerbation who was admitted with pulmonary oedema, and whose condition followed the usual course in these cases.

Seven of 14 patients receiving M. & B. 1863 had the same feeling of well-being as those receiving hexamethonium bromide, and this was not related in any way to the fall in blood pressure: in fact, a fall of any significant degree was often associated with a feeling of ill-health.

Five patients showed an unequivocal fall in blood pressure compared with the immediate pre-drug level. One of these died later from severe hypertension while receiving massive doses of the drug; another improved subjectively and objectively on discontinuing the drug, but later died in uraemic coma. In the third case the fall in pressure was associated with marked deterioration of the patient's condition and did not prevent the onset of heart failure a few days later. In the fourth case it was merely the usual result of subsidence of an acute exacerbation of nephritis in a chronic nephritic. The fifth case might represent a genuine therapeutically induced fall in blood pressure, but when followed up in the out-patient department she showed a quick return to her pretreatment level in spite of the continuance of oral therapy.

In several out-patient cases subcutaneous M. & B. 1863, given twice daily, had to be abandoned because of persistent complaints of ill-health and syncope.

We would like again to point out the curious fact that many authorities claim a high incidence of relief of symptoms in hypertension—usually essential or malignant hypertension—with the treatment they propose, without relating this improvement to any fall in blood pressure—for example, the "rice treatment" (Empner, 1949; Gounelle, Teulon,

and Chéroux, 1950)—and Sodi-Pallares and Espino-Vela (1951) quote P. B. Camponovo and J. Masello as demonstrating 31% successful results using vitamin K as a hypotensive agent, with 69% of cases claiming subjective improvement without any fall in blood pressure. Chris (1951), in a follow-up of 35 selected patients submitted to sympathectomy, found that, whereas 25% have maintained a fall in blood pressure, some 66% had been relieved of incapacitating symptoms without any relation to the fall in blood pressure.

Using preparations of *Veratrum viride*, Hite (1946) found that 60% of his patients showed a fall in blood pressure; Freis and Stanton (1948) found a fall in blood pressure in 87%, and subjective relief in 79%, and Wilkins, Stanton, and Freis (1949) had similar results. Coe, Best, and Kinsman (1950), however, found the drug unsatisfactory: most of their patients failed to show a fall in blood pressure; and 64% noted subjective improvement on the drug and 60% on a placebo. McNair, Griffith, and Elek (1950), using a higher dose than Freis and Stanton, did not find any significant fall in blood pressure; and Barrow and Sikes (1951), using a purified extract, found that in only 20% was there a fall in blood pressure which might have been significant. Saville (1950), in her communication on pentamethonium bromide, rather dismisses the blood-pressure effects of the drug, but emphasizes its ability to relieve symptoms; and Turner (1950) wondered whether it might not be better to assess the effect of the drug by the patient's symptomatic relief.

It would seem as though any treatment produces a fall in blood pressure in some 20% to 30% of patients and a symptomatic improvement not related to a fall in blood pressure in 50% to 75% of cases.

It has been suggested in correspondence with one of us (S. L.) that the dosage we have used is too large. Paton (1951, personal communication) would put the odds against this causing therapeutic failure as 1,000 to 1, though there is evidence in animals that tetraethyl-ammonium, by promoting the secretion of adrenaline, may swamp its own ganglion-blocking effect. Experimentally, an increase of the dose of hexamethonium increases its ganglion-blocking effect or its duration, or both. Also, the excretion of these drugs in the urine shows that only a small amount is absorbed from the alimentary canal.

We have not emphasized the symptomatic improvement that can occur in many of these cases. We feel that in the present state of our knowledge of hypertension it would be catastrophic to stress the value of a potentially dangerous drug for the treatment of a disease in which symptomatic improvement often occurs with a placebo. We do not feel that we can accept any result as satisfactory without objective evidence of improvement.

It has been suggested that the small quantity of drug absorbed orally may produce a partial ganglion block which relieves the patient without a fall in blood pressure. Sympathetic vasoconstrictor impulses are not the cause of essential hypertension. Inhibition of these impulses is used as a purely non-specific hypotensive mechanism. In a disease in which, so far as we know, the mechanical effect of the hypertension leads to vascular, cerebral, renal, and myocardial changes that are the cause of the symptoms, it is hard to imagine how relief of the symptoms can be produced without any fall in blood pressure or objective evidence of improvement in the patient, unless these symptoms which are relieved are not due primarily to the raised blood pressure. The supposition of partial ganglion block leads to the rather absurd postulation of the disease state of essential hypertension with hypertensive symptoms without rise of blood pressure. In our opinion it is useless to make these assumptions without producing objective evidence of the suggested underlying changes. We feel that, in hypertension, the value of a drug of this kind—namely, one which blocks the ganglia—can be assessed only by its effect on the blood pressure, and, when hypotension is present, by its relief of symptoms.

TABLE I.—Case "Pop"

Date:	M. & B. 1863														
	30/4	3/5	4/5	5/5	7/5	8/5	9/5	10/5	11/5	12/5	13/5	14/5	15/5	16/5	17/5
Dose in mg.	120	100	0	50	0	500	500	500	1,000	1,000	1,000	1,000	1,750	2,500	3,500
Route of administration	i.m.	s.c.		s.c.		p.o.	p.o.	p.o.	p.o.	p.o.	p.o.	p.o.	p.o.	p.o.	p.o.
Amount excreted in 24 hours (mg.)	112	51	5.5	15	0	9	11	21	11	42	43	47	40	149	91
% excreted in 24 hours	93	51		30		1.8	2.2	4.1	1.1	4.2	4.3	4.7	2.3	5.9	2.6

TABLE II.—Case "New"

Date:	M. & B. 1863					C6				C5			
	16/5	18/5	19/5	20/5	21/5	22/5	23/5	24/5	25/5	26/5	27/5	28/5	29/5
Dose in mg.	60	105	0	100	0	140	0	295	0	250	0	300	0
Route of administration	s.c.	s.c.		s.c.		s.c.		s.c.		s.c.		s.c.	
Amount excreted in 24 hours (mg.)	19	233	15	93	44	40	28	214	81.3	140	55	193	123
% excreted in 24 hours	32			93		28		73		56		64	

Date:	M. & B. 1863															
	30/5	31/5	1/6	2/6	3/6	4/6	5/6	6/6	7/6	8/6	9/6	10/6	11/6	12/6	13/6	14/6
Dose in mg.	105	0	0	150			1,000	0	0	0	0	0	0	2,000	0	0
Route of administration	s.c.			s.c.			p.o.							p.o.		
Amount excreted in 24 hours (mg.)	120			49; 94.6*	45; 0*	14; 10*	17.3; 7.4; 5; 0†	6.0	trace	6.2	0	0	0	219; 168.5; 130.7; 372.3†	110	27
% excreted in 24 hours. .			14.8				1.4							44.5		

* Excretion during 12-hour periods. † Excretion during 6-hour periods. i.m.=intramuscularly. s.c.=subcutaneously. p.o.=by mouth. C6=hexamethonium. C5=pentamethonium.

TABLE III.—Case "Ho"

Date:	M. & B. 1863											C6						C5
	4/5	8/5	9/5	10/5	11/5	12/5	13/5	14/5	15/5	16/5	17/5	18/5	19/5	20/5	21/5	22/5	23/5	
Dose in mg.	1,875 (15 tabs)	95 (1.9 ml.)	0	220 (4.4 ml.)	330 (6.6 ml.)	0	120 (2.4 ml.)	0	180 (3.6 ml.)	0	100	0	180	0	180	0	270	
Route of administration	p.o.	s.c.		i.v.*	i.v.*		s.c.		s.c.		s.c.		s.c.		s.c.		s.c.	
Amount excreted in 24 hours (mg.)	143	194	50	430	308	122	99	32	230	32	119	22	360	8	103	14	177	
% excreted in 24 hours	7.6				94		82								57		66	

* Intravenous drip.

TABLE IV.—Five Cases Treated with M. & B. 1863

Date:	Case "Free"			Case "Hins"			Case "Web"						Case "Con"		Case "Han"
	18/5	19/5	22/5	18/5	19/5	22/5	18/5	19/5	20/5	21/5	22/5	23/5	30/4	16/5	8/5
Dose in mg.	1,000	0	50	1,000	0	30	1,000	1,000	1,000	1,000	0	0	1,400	3,500	1,760
Route of administration	p.o.		s.c.	p.o.		s.c.	p.o.	p.o.	p.o.	p.o.			p.o.	p.o.	p.o.
Amount excreted in 24 hours (mg.)	1.9	10	4	338	11	7	47	39	46	67	40	12	336	176	13.0
% excreted in 24 hours	0.2		8	33.8		22	4.7	3.9	4.6	6.7			24	5	0.74

The difference between our results and those of authors who used the drug only by injection (Smirk, 1950) may be due to the fact that in our previous communication (Locket *et al.*, 1951) and in the present one we have depended mainly upon oral administration of the hexamethonium derivatives. However, our experience with continuous intravenous drip and subcutaneous and intramuscular administration of the methonium compounds does not make us feel any more optimistic about our ability to produce a sustained lower blood pressure unless the injections are given at very frequent intervals and the patients are kept *immobile and erect*. The answer to the different immediate results may lie in the inadequate absorption of the methonium compounds when given by mouth (Milne and Oleesky, 1951).

The different rates of absorption of the drug and the different percentages absorbed when given by different routes form one of the factors accounting for the variability of results. Some of these results are briefly discussed by Wien and Mason (1951). One thing is certain after consideration of these figures—namely, that it is entirely impossible to predict the percentage absorbed or the rate of absorption when the drug is given orally. Even were it possible to predict the response to any given dose "absorbed" by any route and thus to grade the response, it would be impossible

to do this with the oral method. The figures in Tables I-V illustrate this better than words, and make it impossible for one to understand how any clinicians can obtain consistent results when giving the drug by mouth, and how they can claim even to adjust the response by alteration in the oral dose.

Thus Table IV shows that Case "Free" with clinical uraemia excreted only 0.2% of the oral and 8% of the subcutaneous dose, yet Case "Hins," with just as advanced renal disease, excreted 33.8% of the oral and 22% of the subcutaneous dose. Case "Con," with simple hypertension, excreted 24% of 1,400 mg. and only 5% of 3,500 mg. given orally. Case "New" (Table II) excreted 1.4% in 24 hours of a single oral dose of 1,000 mg. and 2.1% of the dose in

TABLE V.—Three Cases Treated with C6 Bitartrate

Date:	Case "Dub"	Case "Simp"	Case "Saw"
	18/5	20/5	3/5
Dose in mg.	5,950	2,000	3,500
Route of administration	p.o.	p.o.	p.o.
Amount excreted in 24 hours (mg.)	734	119	396
% excreted in 24 hours	12.3	5.9	11.3

four days, whereas she excreted 44.5% in 24 hours of a single dose of 2,000 mg. given orally and 56.4% in three days. This latter dose was associated with syncope, ileus, and urinary retention. Case "Pop" (Table I) showed a daily excretion of 1.1% to 4.7% of 1,000 mg., but 5.9% of 2,500 mg. and 2.6% of 3,500 mg. given in single doses orally. Subcutaneous administration usually showed excretion figures of 80% in 24 hours, but even these varied from 30% or less to over 80% in the same patient.

When the daily excretion figures exceeded the dose administered, it was because of delay in excreting a dose of drug often given many days earlier. The figures quoted in this paper can be repeated many times from other records.

This failure and delay in absorption might account for the disparity of our results with groups receiving the drug by injection only (Smirk, 1950; Restall and Smirk, 1950), as we have found that the drug is removed from the blood almost as fast as it is injected. It was impossible, with the methods available to us at the time, to estimate blood levels of the methonium compounds, even when blood samples were taken whilst the drug was given by intravenous drip. This failure in intestinal absorption would not account for the difference between our results and those of the series receiving the drug only or mainly by mouth (Campbell and Robertson, 1950; Frankel, 1951).

We have produced an unequivocal maintained fall in blood pressure in one patient treated with oral hexamethonium bromide (and quoted in our earlier communication) and one patient treated with M. & B. 1863, and there were also four doubtful cases with M. & B. 1863—this out of a total of more than 90 patients treated with the drugs, mainly orally, and in spite of the fact that many of our hexamethonium bromide series of patients have now had this drug or M. & B. 1863 for more than a year.

In view of the dangers associated with injection of the drug and the poor and very variable absorption when given by mouth, we consider that further trial of the methonium compounds at present available should be restricted to hospital patients receiving it by injection. Further, that oral use of the drugs is of little value, and, with variable absorption associated with the possible storage of large amounts of the drug in the inert bowel, it might be extremely dangerous in patients not treated in hospital. We have a fair amount of evidence to suggest that oral administration of the drug always causes some degree of intestinal stasis before any reasonable amount of absorption can occur (see Case "New" in Table II). This ileus may be associated with a persistent hypotension because of delayed passage of the drug along the gut and therefore continuance of absorption. There does not appear to be any record of ileus occurring unless the methonium compound is given by mouth, and all recorded fatal cases of this condition were associated with oral administration of the drug.

In conclusion, we ourselves have abandoned the oral use of these compounds in the treatment of any variety of hypertension. We feel that at the moment a regime of rest in bed, sedation, and a salt-free diet is still the safest and most universally applicable method of treatment. However, the continued investigation of the methonium compounds under strict clinical control in hospital centres where there is a full appreciation of the natural variation of hypertension in those diseases in which it occurs is, in our opinion, more than ever necessary in order to obtain a complete picture of the possible restricted field where their administration may be of value.

Summary

M. & B. 1863, an analogue of hexamethonium, was tried orally in several severe cases of hypertension due to essential or malignant hypertension, toxæmia of pregnancy, or chronic nephritis. In none of these cases had there been previously an appreciable fall in blood pressure on rest in bed and ancillary treatment without the hexamethonium derivative.

These detailed results, discussed in the light of more extensive experience, were no more satisfactory than with oral pentamethonium bromide or hexamethonium bromide or bitartrate.

Spontaneous thrombosis of the axillary artery occurred in one patient receiving M. & B. 1863, and another patient apparently developed malignant hypertension while taking it by mouth.

Rest and M. & B. 1863 in combination appeared to produce a fall in blood pressure in five patients; two with chronic nephritis, one of whom is now dead; one in whom the fall in blood pressure was associated with marked general malaise and giddiness followed by congestive heart failure; and two in whom there was, later, a recurrence of symptoms and increase in blood pressure, with death in one case.

In a case of toxæmia of pregnancy associated with essential hypertension, in spite of the proved lability of the blood pressure, intramuscular pentamethonium bromide, oral pentamethonium bromide, and oral M. & B. 1863 failed to produce any improvement or prevent death of the foetus for the fourth time.

Absorption, blood levels, and excretion of the methonium compounds are briefly discussed.

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