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RESULTS OF METHONIUM TREATMENT OF HYPERTENSIVE PATIENTS*

BASED ON 250 CASES TREATED FOR PERIODS UP TO 3½ YEARS,
INCLUDING 28 WITH MALIGNANT HYPERTENSION

BY

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Except in malignant hypertension, the outlook of the individual hypertensive patient treated only by rest, sedation, and the amelioration of complications is difficult to assess unless the prognosis has evidently deteriorated because of substantial cardiac failure or renal impairment.

Individual prognosis is hazardous, especially in milder cases, but the expectation of survival among large groups of hypertensive patients has been well worked out in terms of their presenting clinical features. Among such groups of patients the expectation of survival is related to the extent of hypertensive changes in the retina, the presence or absence of heart failure, cardiac asthma, breathlessness, substantial electrocardiographic changes and, in a general way, with the height of the blood pressure, especially the diastolic pressure. The age at which the patient begins to show such abnormal manifestations, and the sex, have a strong bearing on outlook. While different views are expressed, a scrutiny of the manner in which authors have gathered their clinical material, and of the age and sex of the patients, reveals that the divergencies are less than would appear at first sight. Differences in case selection, not always of an obvious kind, influence comparisons of the results of medical and surgical treatment.

In many publications on groups of patients submitted to sympathectomy, those who have impaired renal function, who have had heart failure or a previous stroke, or who are 60 years or more may be rejected. The selection may be such that the patients who are operated on have in any case a better outlook than the generality of cases, or a worse one if patients with malignant hypertension constitute a large proportion of the sympathectomy cases. It is important, therefore, to divide up hypertensive cases into a sufficient number of age groups and clinical categories, as these differ greatly in their outlook. Perhaps the clearest demonstration of the importance of subdividing the classes of hypertensives comes from Keith, Wagener, and Barker (1939), who showed the re-

lationship between retinal changes and outlook in a series of hypertensive patients collected at the Mayo Clinic. Their series comprised 146 cases of malignant hypertension (grade IV), 37 of grade III, 26 of grade II, and only 10 of grade I. Possibly the preponderance of severe cases is related to the fact that patients are sent from a distance to the Mayo Clinic. My experience has been that cases referred from a distance are on average more severe.

The object of the present paper is to give an account of our experience with methonium treatment of hypertensive cases, mostly of substantial severity, over a period of three years and seven months. Over 250 patients have been treated. The effects of treatment upon the clinical manifestations secondary to hypertension have been of the same kind irrespective of the cause of high blood pressure. Later results confirm and to some degree improve on those published earlier (Restall and Smirk, 1950; Smirk and Alstad, 1951). This paper mainly concerns problems which could not be dealt with adequately at an earlier stage. Results in malignant hypertension (excluding nephritis) and in patients with hypertensive heart failure or cardiac asthma are given in detail. In the mortality studies on malignant hypertension we have reported on 28 patients, including all who died and all living patients on treatment for five months or more. In mortality studies on patients in grades III, II, and I, almost all the 142 patients have been on treatment for periods between one and three and a half years. For comparison there is a series of 71 untreated patients investigated by the same methods. These control cases were mainly patients who presented themselves for investigation and possible treatment on or after November, 1949, and were judged suitable for methonium treatment. They were not treated, either because of shortage of supplies or because they decided against treatment. On the whole these cases were somewhat milder than those treated.

It has become clear that there is a significant improvement in the life expectation of malignant hypertension cases. Other groups also show an improvement, but further observation will be needed before definite conclusions can be drawn.

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Reports of clinical improvement with effective methonium treatment have been published by Rosenheim (1952), McMichael (1952), and Morrison (1953). There is general agreement concerning the character of clinical improvement when it occurs.

Method

The technique of treatment and the methods of determining the adequacy of control over blood-pressure levels have remained the same in principle but have improved in detail in the course of the past three and a half years. The methods used have been described elsewhere (Smirk, 1950, 1952b, 1952c; Smirk and Alstad, 1951; Kilpatrick and Smirk, 1952). The method at present advocated has been described recently (Smirk, 1953a, 1953b). Greater detail is available in the latter paper.

1. Mortality Experience in Treated and Untreated Patients

Survival Times of Patients with Malignant Hypertension

All cases classified here as malignant hypertension have shown a clear-cut papilloedema, with some other retinal manifestations, such as circumpapillary oedema, hard and soft exudates, retinal haemorrhages, etc. In case of doubt the binocular ophthalmoscope was employed. No case diagnosed as malignant hypertension has been excluded from the series, but cases of nephritis are not included even though the fundal changes are of the grade IV type. Our malignant hypertension patients comprise 28 who have been on continuous treatment with methonium salts; four others who were on treatment for a time and then stopped; and 11 patients who were untreated, these having been seen mostly in the years before methonium treatment started. The results are set out in Tables I and II.

TABLE I.—Mortality Experience in Malignant Hypertension

Group A				Group B				Group C			
Died		Survived		Died		Survived		Died		Survived	
Case No.	M. S.	Case No.	M. S.	Case No.	M. S.	Case No.	M. S.	Case No.	M. S.	Case No.	M. S.
<i>Treated with Methonium</i>											
206	6	53	43	None		40	37	49	31	51	39
		54	39			204	24	52	15		
		41	37			207	23	76	10		
		123	33			220	24	227	2		
		124	32			306	14	337	4		
		161	28			357	9	E.8	1		
		216	23			361	11				
		336	12			364	9				
		371	7								
		382	8								
		400	5								
		E.7	21								
<i>Controls Untreated</i>											
L.C.	6	135	24	A.S.	1½	None		S.C.	½		None
		150	32*	P.R.	½			R.G.	2		
				E.A.	4						
				F.M.	2						
				160	1						
				A.H.	3						

M.S. = Months of survival. * Sympathectomy.

Of the treated patients seven died after periods of treatment lasting 10, 15, 31, 6, 2, 4, and 1 months. The clinical state and reaction to treatment of the patients who died are set out below:

Case E8 was admitted in a moribund condition. Case 227 was close to uraemia with repeated vomiting and high total N.P.N. He improved for a time, but died in three months from uraemia. Cases 76, 52, and 49 were admitted in advanced congestive failure with severe cardiac asthma. They improved for a time: Cases 76 and 52, up to the time of their deaths by cerebral haemorrhage, were active, able to climb stairs, and looked after their own homes. Case 49 recovered from heart failure and was able to climb stairs, but developed bilateral pneumonia, from which she died. She had poor renal concentrating capacity, and the underlying condition was partly responsible for a fatal outcome. Case 206 had extreme dryness of the mouth and loss of appetite under effective methonium treatment which had cleared his papilloedema. During attempts to modify and improve the regime he got out of control and developed acute pulmonary oedema, from which he died. Case 337 had advanced renal changes and died from intercurrent infection. Of the patients who were not treated, 9 out of the 11 were dead in six months; two are alive, one at 24 months and one at 32 months, the latter having had a sympathectomy. The four additional patients who had a period of treatment and then stopped treatment had 3, 3, 17, and 7 months under methonium treatment and showed the usual degrees of clinical improvement while on treatment; they survived periods of 3, 15, ½, and 2 months without treatment before death occurred.

Of the 21 surviving patients, 15 are leading productive lives: 11 men are at work, and 4 women are doing housework. Two male patients are expected to return to work within a few weeks (Tables III and IV).

One female patient who managed her house and garden for 28 months became completely incapacitated by a hemiplegia during the last nine months.

Mortality Figures in Patients Who Could Have Been Considered for Surgical Treatment

A high proportion of our patients with malignant hypertension presented in a condition in which sympathectomy could not have been contemplated (group A on the classification of Keith, Woolf, and Gilchrist, 1949). There were others with disabilities which would not have altogether prevented sympathectomy—such as a previous major cerebral accident (two cases), an older age group than is ordinarily accepted (two cases), or a degree of cardiac failure or cardiac asthma (four cases) which, though it does not prevent sympathectomy in less serious cases, is associated with a worse prognosis in malignant hypertension (group B on the classification of Keith *et al.*, 1949). Seven patients presented with advanced cardiac or renal changes (group C).

When, however, we consider the results of adequate methonium treatment in patients who do not have any of the above-mentioned objections to sympathectomy, we find that up to the present only one patient out of a total of 13 has died. This patient lived for six months. The surviving patients in group A have lived for an average of 24 months. In a group of patients selected in a similar way by Keith *et al.* (1949) and treated by rest and sedation, five died at

TABLE II.—Average Periods of Survival

	Group A				Group B				Group C			
	Died		Survived		Died		Survived		Died		Survived	
	No.	M.S.	No.	M.S.	No.	M.S.	No.	M.S.	No.	M.S.	No.	M.S.
Treated with methonium	1	6	12	24	0		8	18.9	6	10.3	1	39
Controls (local)	1	6	2	28	6	1.87	0		2	1.25	0	
Controls (Keith <i>et al.</i> 1949)	5	13.3	4	26	8	1.8	2	9	4	1.3	0	

M.S. = Months of survival.

13.3 months and four survived for an average of 26 months. We had eight patients who came to us before methonium treatment was available and also three patients with malignant hypertension who refused treatment or came when supplies were insufficient. Of these 11 patients, nine died at an average of 1.8 months, and two, including a sympathectomy case, have survived for an average of 28 months after the first diagnosis of malignant hypertension was made.

TABLE III.—Occupational State of Malignant Hypertension Patients Under Treatment

Case No.	Sex	Additional Clinical Features Before Treatment	Age Starting Treatment	Occupation During Treatment	Months Survived on Treatment
<i>Leading a Productive Life</i>					
41	M	—	48	Accountant	37
53	M	—	46	In general medical practice	43
123	M	—	56	Business executive	33
204	M	Left ventricular failure	45	Railway employee	24
207	M	" "	57	Engineer—active	23
216	M	" "	42	Sheep shearing, wool classing	23
336	M	Minor cerebral accident	47	Farmer	12
371	M	Encephalopathic attacks	46	Stokes furnace	7
382	M	" "	43	Garage work	8
400	M	Left ventricular failure	41	Priest—educational work	5
E7	M	—	45	Farmer	21
124	F	Subarachnoid haemorrhage	46	Housewife	32
161	F	2 minor cerebral accidents	32	"	28
220	F	Encephalopathic attacks	63	"	24
357	F	Left ventricular failure	52	"	9
<i>Partially or Potentially Productive</i>					
51	M	Congestive failure. Low I.Q. Osteoarthritis	59	Worked 2 years on farm. Now in old men's home; sweeps and cleans up	39
306	M	Left ventricular failure. One leg amputated	55	Return to work expected soon	14
361	M	Cerebral accident before treatment. Recovering from aphasia	47	Physically fit. Return to work expected soon	11
<i>Leading a Productive Life up to Time of Death by Stroke</i>					
52	F	Severe heart failure	47	Housewife	14
76	F	" "	43	"	10

TABLE IV.—Occupational State of Malignant Hypertension Patients Under Treatment

Case No.	Sex	Additional Clinical Features Before Treatment	Age Starting Treatment	Reason for Not Working	Months Survived on Treatment
<i>Incapacitated by Conditions Arising Before Treatment Started—Substantially Free from Original Hypertensive Symptoms</i>					
364	M	Cerebral vascular accident	44	Stroke	9
<i>Incapacitated by Hypertensive Condition Developed During Treatment</i>					
40	M	Heart failure	58	Well for 34 mths. Mental confusion 2 weeks	37
54	F	Severe encephalopathy	46	Ran her own house for 33 months, then incapacitated by severe stroke	39
<i>Much-improved Activity, But Remaining Semi-invalid up to Time of Death</i>					
49	F	Severe heart failure and renal insufficiency	52	Lassitude	31
<i>Died in Hospital Without Making Substantial Improvement</i>					
206	M	—	48	In hospital	6
227	M	Uraemia	44	" "	2
337	F	Diabetes. Kimmelstiel-Wilson disease	41	" "	4

Comparison of the Groups with the Series of Keith *et al.* (1939)

Our control series of untreated malignant hypertension cases is only 11 in number, but our experience has corresponded with that of Keith *et al.* (1939) in a much greater series. In the present series of untreated patients 18% were alive at 18 months; in the methonium-treated group 75% were alive at 18 months.

Comparing similar groups of patients with malignant hypertension, methonium treatment has been associated with extension of the survival period.

Survival Times of Patients with Essential Hypertension (Grades III, II, and I)

The grades of hypertension referred to above are those of Keith *et al.* (1939). Grade I cases show minimal or no retinal changes; grade II show distinct hypertensive changes in the retinal arteries, such as nipping of the arteriovenous crossings or waist-like narrowings of arteries, but no other changes; grade III show haemorrhages, hard or soft retinal exudates, retinal oedema, or some combination of these but without papilloedema. In certain cases retinal oedema encroaches on the disk edge and blurs its outline, but does not lead to actual elevation of the disk: such cases have been classified as grade III, the doubtful cases being examined for papilloedema by the binocular ophthalmoscope. Thirty-three patients and 15 controls were classified grade III: 89 treated patients and 38 controls were grade II; 20 treated patients and 7 controls were grade I. A total of 142 were treated (the great majority for 12 to 42 months). The 60 controls were collected over the same period of time.

The deaths are set out in Tables V and VI. With both treated and control patients it is evident that the mortality experience with grade III is less favourable than with grade II, and grade II less than grade I, in which latter there were no deaths in either the treated or the control series. The results of treatment in grade II may be approaching statistical significance, but the results in grade III as set out in Table V do not seem so promising. The number of patients in this group and the duration of experience are insufficient to justify any conclusion. It should be mentioned, however, that seven of the grade III cases were of much greater severity than any of the control series, and four of the deaths occurred in this group. Were these seven patients not counted, so making the treated and control

TABLE V.—Mortality Experience With Hypertension of Grades III, II, and I

Age	Grade III		Grade II		Grade I	
	Died	Survived	Died	Survived	Died	Survived
<i>Controls</i>						
70+	0	0	1	0	0	0
60-69	1	2	4	5	0	0
50-59	2	3	1	11	0	2
40-49	2	5	4	11	0	3
30-39	0	0	0	1	0	1
20-29	0	0	0	0	0	1
Total	5 (33%)	10	10 (26.3%)	28	0	7
<i>Treated</i>						
70+	2	0	0	4	0	0
60-69	1	2	1	14	0	1
50-59	2	10	7	28	0	4
40-49	3	7	3	25	0	8
30-39	0	4	0	6	0	6
20-29	1	1	0	1	0	1
Total	9 (27.3%)	24	11 (12.3%)	78	0	20

TABLE VI.—Mortality Experience Grades III and II Combined

	Died	Survived	Total
Controls	15 (28.2%)	38 (71.8%)	53 (100%)
Treated	20 (16.4%)	102 (83.6%)	122 (100%)

series more comparable, the difference in mortality would still not be great—33% deaths among controls and 22% among treated patients.

When grades II and III are considered together the mortality difference shows that more experience is needed before a definite pronouncement can be made. The obvious betterment in health and the statistical significance of the results in malignant hypertension give grounds for hope that the figures may be improved by the use of more effective methods of obtaining control over blood-pressure levels—as, for example, by the use of M. & B. 2050A orally or in a solution of polyvinylpyrrolidone for subcutaneous injection (Smirk, 1952a, 1953a, 1953b).

2. Changes in the Physical State of Patients with Malignant and other Forms of Hypertension

Effect of Control of Blood-pressure Level on Retina in Malignant Hypertension

Papilloedema cleared in 21 out of 23 patients who were on effective treatment for five months or more; the two who have not cleared at five and six months are much improved and look like doing so. Eight other patients showed improvement, but papilloedema was still perceptible at the last observation made. These include patients who did not maintain treatment (two cases) or went off treatment (two cases) or died within six months (three cases with renal insufficiency). The remaining patient has been on treatment about three months. In most instances disappearance of papilloedema takes three to four months, sometimes six months, of intensive treatment; and a reduction of blood pressure to normal or near normal levels at the trough of the fall is necessary. With the better control obtained latterly, it has been our experience that papilloedema can be dispersed in almost all instances and that failure to do so after four months' treatment is usually an indication that the blood-pressure reduction is insufficient in degree and duration. A clear reduction in the amount of papilloedema should be evident in three to four weeks, with reappearance of a physiological cup or of a part of the disk edge. The last residues of oedema take longest to disperse. It often happens that one disk is entirely clear of papilloedema and the other has lagged behind in improvement.

Within the first month of effective treatment soft exudates should have disappeared, there should be no fresh haemorrhages, and as a rule old haemorrhages have been dispersed. Hard exudate at this stage usually stands out shiny and with sharp edges. With effective treatment the hard exudate begins to soften at the edges and loses some of its shiny clear-cut delineation, looking more like soft exudate in some instances. Substantial dispersal of hard exudate is unlikely under six months and some may remain after 12 months, but it will be absorbed in most patients who have been under effective treatment for 12 to 18 months. In a few instances the edge of the disk will remain a little fuzzy as the result of post-papilloedema changes.

Examinations of such patients with the binocular ophthalmoscope have been made in most cases by Dr. Rowland Wilson in order to be sure that this was not residual papilloedema. New blood vessels round the edge and sometimes on the disk are a common residual finding after the papilloedema. In some instances the disk is pale, suggesting a minor grade of optic atrophy even though vision is good. The generalized vasospasm of so many patients with malignant hypertension tends to disappear and the general calibre of the arteries returns almost to a normal level. Such arterial changes as nipping of the arteriovenous crossings and waist-like narrowings in the course of arteries remain behind, but I am unable at this stage to comment on the question of whether any recession in such changes occurs or not.

At an early stage of our work a few patients with malignant hypertension were treated by continuous subcutaneous administration of hexamethonium bromide over a period of approximately 12 days, using an electrically operated power-driven syringe (Smirk, 1951). By this means the blood

pressure was kept only a little above the normal level day and night. Papilloedema then seemed to clear much more rapidly than with intermittent blood-pressure falls from thrice-daily injections of aqueous hexamethonium bromide. Preparations have been devised which are absorbed more slowly owing to admixture with polyvinylpyrrolidone or dextran. The most satisfactory of these is the longer-acting methonium compound M. & B. 2050A dissolved in 20% aqueous polyvinylpyrrolidone, ephedrine hydrochloride being added to 1 in 200 concentration in order to prolong absorption by local vasoconstriction. With two, or at times three, injections daily of this preparation it has been possible to obtain a much better control than with three injections daily of aqueous hexamethonium bromide. In most instances oral administration of M. & B. 2050A is equally satisfactory. Under these conditions, apparently related to the better control over blood-pressure levels, dispersal of papilloedema and of other retinal manifestations seems to be accelerated.

Effect of Control of Blood-pressure Level on Retina in Patients with Grade III Changes

The appearance in these patients is similar to that in malignant hypertension except that there is no elevation of the optic disk. The disappearance of retinal haemorrhages, soft exudate, retinal oedema, and finally of hard exudate takes place in much the same way as in malignant hypertension.

Effect of Control of Blood-pressure Level in Heart Failure, Cardiac Asthma, and Simple Breathlessness

Hypertensive congestive heart failure or cardiac asthma was relieved by methonium therapy without the use of digitalis, mersalyl, or salt-free diet in 20 of the 36 cases. In most instances patients returned to the degree of activity appropriate to their time of life. Of the remaining 16 cases, seven required digitalis or mersalyl initially; but later, when methonium therapy was well-established, digitalis and mersalyl were withdrawn without recurrence of failure. In one patient who went into heart failure while on digitalis the failure was controlled by blood-pressure reduction; digitalis was omitted, but it was not possible to manage without a salt-free diet. In five other patients who went into failure while on digitalis (ages 51, 71, 70, 60, and 80) the breathlessness was considerably lessened, but remained an important disability and the digitalis could not be withdrawn. In three patients there was deterioration. In one we had been unable to establish an effective regime because of side-effects; in another case necropsy revealed that an extensive left ventricular infarction had maintained heart failure; in another uraemia and left heart failure were associated.

Of 27 patients under 60 years, six did not work, 11 men returned to gainful employment (one died later from a stroke), and 10 women were engaged in housework (two died later from a stroke).

With a few exceptions it has been possible to remove cardiac asthma and congestive heart failure and to render breathlessness unimportant without recourse to digitalis, mersalyl, or salt-free diet, except that a regime of "no added salt except in cooking" is sometimes advised. In a few instances where digitalis was in use before the patient came into hospital the dose was maintained at the level on which the manifestations of congestive failure had developed.

Attacks of cardiac asthma can be cut short by the administration of an appropriate dose of hexamethonium bromide or one of the other effective methonium salts, the patient being propped up in the sitting posture. If by fractional administration the blood pressure is reduced to as near normal as the patient will tolerate, a great degree of relief from breathlessness is commonly encountered as the blood pressure falls, even in cases of severe cardiac asthma. Fractional administration is advised because, were the dose given an excessive one, the normal counter-measure of

lowering the patient to the horizontal position in order to re-elevate the blood pressure could scarcely be applied if there was considerable orthopnoea.

It is a considerable advantage to heart-failure patients if the use of digitalis, mersalyl, or salt-free diets can be avoided because in most cases heart failure due to hypertension can be relieved without these measures. Recurrence of breathlessness provides a very useful warning that the degree of control over blood-pressure levels is insufficient. Sometimes, however, it is not possible to dispense with additional measures at the outset. It is better then to supple-

ment methonium treatment by occasional injections of mersalyl, since when these are omitted it will soon be discovered whether the regime has allowed a sufficient recovery of the cardiac muscle. In about one in four cases, and especially in the elderly, a digitalis regime may be required as well as blood-pressure control.

Effect of Control of Blood-pressure Level on the Electrocardiogram

Reference was made in an earlier publication (Smirk and Alstad, 1951) to improvement in the electrocardiogram

Before

After

FIG. 1.—Case 204, male aged 45. The x-ray film prior to treatment was taken August 28, 1951, and corresponded with mild congestive heart failure and attacks of cardiac asthma. These cleared on methonium treatment without other measures. The patient returned to work. Second film was taken May 4, 1953.

Before

After

FIG. 2.—Case 14, male aged 46. Before treatment there was mild breathlessness but no congestive failure or cardiac asthma. The first x-ray film was taken on January 27, 1950. Breathlessness cleared on methonium treatment. The second film was taken on June 12, 1953.

following effective blood-pressure reduction. These changes did not take place at once in response to the lower blood pressure, but were progressive over a period of up to a year or more. The results in our series of cases have been analysed since by Doyle (1953), and his report on hypertensive patients in general applies equally to malignant hypertension cases. With effective blood-pressure reduction of sufficient duration, the voltage of the R and S waves is decreased; the depressed ST segments in leads reflecting left ventricular potentials ordinarily return to the isoelectric level; inverted T waves in the left ventricular leads either become less inverted or become positive; raised ST segments and over-average T waves in leads reflecting right ventricular potentials and the cavity side of the left ventricular potentials show a return of the ST segment towards the isoelectric level and a decrease in the height of the T waves. A useful working rule is that if electrocardiographic defects show no improvement within a few months there is need for a more substantial control over blood-pressure levels. At a later stage any relapse of electrocardiographic signs has the same significance. Necropsy evidence has shown that, at least in some instances, gross muscular hypertrophy remains even though the electrocardiogram has returned almost to normal.

Effect of Control of Blood-pressure Level on Heart Size

It has been reported already that an unequivocal decrease in heart size is encountered not only in patients who have had congestive heart failure but in a small proportion of

FIG. 3.—The figure surveys the changes in transverse heart diameter following methonium treatment. The number of patients with increase of diameter is shown by hatched columns; the number of patients showing decrease is denoted by black columns.

patients who have not had heart failure. Taking patients who have not had heart failure, there appears to be a general trend towards decrease in heart size as judged by measurement of the cardiac silhouette, though most of the individual changes in heart size lie within the possible range of variation for repeated x-ray pictures on the same individual. Fig. 1 shows an example of the effect on heart size of hexamethonium bromide in a patient with congestive heart failure; Fig. 2 an example of decrease in heart size in a patient who had no heart failure. Fig. 3 shows the changes of heart size in 76 patients after periods of several months to three years on treatment. It will be seen that when the change is outside the usual limits of variation it is more usually in the direction of decrease.

Effect of Control of Blood-pressure Level on Headache and Giddiness

The effect on headache and giddiness was referred to in earlier papers (Restall and Smirk, 1950; Smirk and Alstad, 1951), where it was indicated that failure to relieve headache and giddiness with an adequate regime was most exceptional. In preliminary discussions with patients the prospect of such relief may be mentioned as highly probable if they are prepared to take an amount of trouble comparable to that of a diabetic patient on insulin. In order to obtain such results the regime must be adjusted in terms of the reaction of the individual patient to the hypotensive agent. Thus, three adequate injections daily of hexamethonium bromide subcutaneously with adoption of

the sitting posture throughout the night (body inclined at 45 degrees from the horizontal) commonly relieves headache. Some patients, however, still have morning headaches on this regime. The administration of an extra dose of hexamethonium bromide before retiring or the administration of an appropriate number—say 1 to 4—tablets of hexamethonium bitartrate with a little food to prolong the absorption will often, when combined with the sitting posture, prevent the development of headache the next morning. The administration of hexamethonium bromide in 20% polyvinylpyrrolidone proved more effective than the simple aqueous solution.

Latterly a further advantage has been obtained by the use of M. & B. 2050A in polyvinylpyrrolidone with 1 in 200 ephedrine hydrochloride incorporated in the mixture in order to delay further the absorption from subcutaneous tissues. A suitable injection at night commonly prevents morning headache. Alternatively or additionally an appropriate dose of M. & B. 2050A by mouth, usually taken with a little food so as to delay the absorption further, will relieve morning headache. From what has been said it should be clear that, in order to obtain relief from headache in almost all cases, a number of clinical trials have to be made and individual regimes devised to suit particular patients.

Discussion

Our results represent, at the most, the experience of three and a half years, and with the majority of patients a shorter time; but, even so, if our data be accepted there has been a fundamental change in the immediate outlook as regards survival of malignant hypertension patients as well as amelioration of symptoms and signs as reported previously (Restall and Smirk, 1950; Smirk and Alstad, 1951). This is achieved by methods which unfortunately need scrupulous long-term control and great expenditure of time, and which in general are not, but sometimes are, hard on the patient because of side effects.

The object of treatment is to reduce the blood pressure to near normal levels for as much as possible of the 24-hour day. A few patients have been treated by hexamethonium bitartrate by mouth, others by three daily injections of appropriate doses of aqueous hexamethonium bromide. Later the hexamethonium bromide was dissolved in 20% or 25% polyvinylpyrrolidone in order to prolong the period of absorption, and in some instances a further prolongation was effected by the addition of 1 in 200 ephedrine hydrochloride to the injection mixture. In the last fifteen months several patients have been treated by a new methonium compound, M. & B. 2050A (Smirk, 1952a, 1953a, 1953b; Wien and Mason, 1953; Maxwell and Campbell, 1953). This substance, dissolved in 20% polyvinylpyrrolidone, particularly when 1 in 200 ephedrine hydrochloride is added to prolong absorption by local vasoconstriction, acts more effectively than some 12 other methonium compounds which we have tested. The substance has the advantage that it may be administered also by mouth in most cases, with effective reduction of blood pressure. The detail of the method of controlling the dose of a methonium compound has been simplified (Smirk, 1953a, 1953b), but the method of control here advocated does not differ in principle from the more cumbersome methods used at an earlier stage in the treatment of this series of patients. Without control over the blood-pressure level of sufficient degree and duration the results of methonium therapy are most disappointing.

Common errors include: neglect of day and night control of posture; control of dosage in terms of occasional casual blood pressures; neglect of drug toleration; use of oral hexamethonium in cases in which this is ineffective; in injection treatment the use of syringes graduated in 0.2 ml. instead of 0.01 ml.; and the absence of effective instruction to patients with a written account of their regime.

In our patients, blood pressures are measured by technicians throughout six or seven hours of the day at approximately half-hourly intervals for five or six days of the week

and for three weeks. During this period each dose is adjusted in terms of response to previous doses—a kind of biological assay. The patient thereby gains a considerable insight into the principles underlying treatment. After the initial three weeks the patient attends the hypertensive clinic—weekly at first and later at longer intervals. Occasional all-day tests are made, but most of the control at this stage is in terms of hypotensive symptoms. Casual blood pressures are taken, but they are of very little use in the control of dosage. Quite high blood pressures may be encountered in out-patients whose blood pressure, with methonium, is satisfactory under home conditions.

Summary

On three and a half year's experience it appears already that the prognosis of malignant hypertension is much improved by effective control over the blood-pressure level by the administration of methonium salts.

The result of treating all of 28 malignant hypertensive patients, including seven with substantial renal insufficiency or advanced heart failure, is that 21 are living and seven dead. The average survival time of those who died is 9.7 months and of those who are still alive 22.8 months. A considerable majority of the survivors are leading productive lives, the men working at their previous occupations and the women doing housework.

In hypertensive patients with retinal grades II and III, taken together, the mortality figures are better in 122 treated cases (16.4%) than in 53 controls (28.2%), but no claim of statistical significance is made.

Objective improvements include: (a) the disappearance in most cases of such changes as papilloedema, retinal oedema, soft exudates, haemorrhages, and, after long treatment, of star-shaped macular figures; (b) the return to work of most patients under 60 presenting with malignant hypertension, cardiac asthma, or congestive heart failure, including in most instances the elimination of the use of digitalis, mersalyl, or substantial salt restriction; and (c) the electrocardiographic improvement and tendency to decrease of heart size. The consistency with which these results have been reproduced during three and a half years leads me to state that less satisfactory degrees of improvement are usually due to inadequacy of the regime used.

In a minority of patients the doses of methonium salts which relieve hypertensive manifestations lead to much discomfort from side-effects. Methods of alleviation which have helped some cases are suggested.

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ORAL CORTISONE TREATMENT OF HYPOPITUITARISM

BY

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In early trials of the therapeutic value of cortisone in hypopituitarism, the hormone was given in large dosage (75 to 100 mg. daily) for periods of about one to three weeks. The results were encouraging, but in some ways not satisfactory (Summers and Sheehan, 1951). Other workers using this dosage observed no beneficial effects (Robertson and Kirkpatrick, 1951; Brown and Greenblatt, 1952). Since then, a much lower dosage of cortisone has been tried for the continued treatment of these patients. Originally the cortisone was given either by injection or by implantation of pellets, but more recently oral therapy has been found just as efficient and far more convenient. Reports of single cases treated for long periods with doses of 12.5 to 25 mg. daily have been published by Thorn *et al.* (1950, 1951), Clark *et al.* (1951), Levy (1952), Perkins and Rynearson (1952), Roberts *et al.* (1952), McCullagh and Schaffenburg (1953), Tardy (1953), Dontigny (1953), Mathisen (1953), and Fourman and Horler (1954). More recently, a series of three cases treated in this way have been recorded by Hart (1953), and two cases by McCullagh *et al.* (1954). All these workers have reported good results from prolonged therapy at low dosage.

A few investigations have been made of the therapeutic value of cortisone in the treatment or prophylaxis of hypopituitary coma (Allott and Simmons, 1951; Sheehan and Summers, 1952; Paniagua *et al.*, 1952; Caughey *et al.*, 1952; Hijmans, 1952; Heyde, 1953). In addition there have been several reported studies of the effects of cortisone administered for very short periods for diagnostic tests or physiological studies, but these are not of direct relevance to the subject under consideration here.

Treatment of Present Cases

The following account concerns four patients with severe hypopituitarism who have been given small doses of cortisone orally over periods of about two years. Three of these were typical examples of severe hypopituitarism due to post-partum necrosis; the fourth was a man with hypopituitarism of unknown aetiology, probably due to some form of atrophy and scarring of the pituitary.

The patients were studied for a preliminary observation period of two to three weeks without treatment, and for a further control period of five weeks, during which 3 gr. (0.2 g.) of thyroid sicum was given daily. No significant effect was noted from the administration of thyroid. (This point merits a short interpolation. The warnings given in almost all textbooks about the dangers of thyroid therapy in patients with hypopituitarism appear to be overstated. Most of these patients tolerate ordinary dosage of thyroid without any recognizable ill effect. From a study of the occasional cases reported in the literature where the administration of thyroid was followed rapidly by coma, it seems probable that the patients were already on the point of developing coma in any event. Nevertheless, when