the results of a previous survey in an industrial community, the Rhondda Fach. In comparable age-groups the mean values for haemoglobin, P.C.V., and M.C.H.C. were significantly lower in Wensleydale than in the Rhondda.

In Wensleydale the prevalence of anaemia in males aged 15–24 was 3.4%, falling to zero in those aged 25–34 and then rising in later decades to 25% in the one 75 years and over. In females of 15–24 years the prevalence of anaemia was 28%. This figure fell to 12% in age-group 55–64 years and subsequently rose to 21% in the later age-groups. Most of the anaemia was of the iron-deficiency type.

Many people contributed to the success of this survey, which was carried out during the tenure of a Cardiff Royal Infirmary Research Fellowship in Medicine. It is a pleasure to acknowledge my indebtedness in particular to Dr. J. S. Lawrence, Dr. Joan M. Bremner, and the members of the Empire Rheumatism Council Field Research Unit; to the Board of Governors of the United Cardiff Hospitals for

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CLINICAL TRIAL OF METHOSERPIDINE IN GENERAL PRACTICE

BY

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Methoserpidine ("decaserpyl"), a synthetic isomer of reserpine, is a hypotensive drug prepared by Velluz (Velluz *et al.*, 1958a; Velluz, Peterfalvi, and Jequier, 1958b; Velluz, 1959). Previous reports on the drug (Velluz *et al.*, 1958b; La Barre, 1960; Mir and Lewis, 1960) have shown that the hypotensive properties of the rauwolfia preparations have been retained while the undesirable side-effects have been practically eliminated.

Trials in 1959 and 1960 (Brun and Rondelet, 1959; Gros *et al.*, 1959; Mériel *et al.*, 1959; Merlen and Gérard, 1960; Tricot *et al.*, 1960) showed an effective reduction of diastolic pressure—that is, generally at least 20 mm. Hg in two-thirds of hypertensive patients. These reports mention marked subjective improvement—relief of headache, giddiness, and tinnitus, and a feeling of general well-being. Bradycardia in some cases was also noted. In these trials the dosage ranged from 15 to 60 mg. daily by mouth, 30 mg. daily being the most suitable dose in the majority of cases. Side-effects were uncommon. There were occasional instances of nausea and epigastric discomfort, and more rarely diarrhoea or nasal congestion. Previous reports refer to the absence of major depressant effects on the nervous system even with 100 mg. or more a day.

It has been our experience with hypotensive drugs in general practice that they do not on the whole achieve the results claimed for them on the basis of hospital trials. It would appear that the effect of a drug on a patient living a normal everyday life is very different from that on a patient undergoing hospital regimen. We found that small doses of many drugs in ambulant patients did not produce a significant or maintained hypotensive effect. Larger doses often produced unpleasant side-effects.

We decided to carry out a trial of methoserpidine on hypertensive patients drawn from three separate practices in Glasgow. The duration of the trial was one

year. Many of the patients were known to be hypertensives. Practically all had subjective complaints due to hypertension. No patient was included in the trial who was already progressing favourably on alternative treatment.

Of the 48 patients treated, 43 suffered from benign essential hypertension. The other five were cases of hypertension with aortic incompetence, hypertension with thyrotoxicosis, pre-eclamptic toxæmia, pre-malignant hypertension, and malignant hypertension.

Method

The patients were initially assessed objectively and subjectively. They were seen weekly or fortnightly at first, and in some cases the intervals were later extended to a month. The initial dosage of methoserpidine depended upon the overall clinical assessment. The dose was increased or decreased at subsequent attendances until a suitable maintenance dose was achieved. From experience we found that 30 mg. in three divided doses was the best initial dosage in most cases.

To assess the hypotensive effect of the drug, the means of all the systolic and diastolic readings taken during the trial have been calculated for each patient and compared with the *lowest* level of blood-pressure previously recorded in the absence of any hypotensive drug therapy. This method of assessment has been used because, in the absence of a double-blind technique, it provided us with the best safeguard against introducing a bias into the results.

Results

The principal data in each of the 43 cases of essential hypertension are summarized in Table I. The frequency of the different dosage levels initially and that at the termination of treatment or of the trial are shown for comparison in Table II.

Hypotensive Effect.—The distribution of the degrees of mean reduction in the systolic and diastolic pressures is shown in Table III. There was a mean reduction in diastolic pressure of over 20 mm. Hg in 10 cases (the largest being 34 mm.) and of 10–20 mm. in 19 cases (including a patient who was also treated with

oedema associated with effort dyspnoea, present in five (Cases 4, 17, 19, 37, and 39), disappeared or was much reduced. Of the 11 patients with improvement in one or both of these symptoms, the mean reduction in diastolic pressure was 10 mm. Hg or more in eight.

One patient (Case 17) who was subject to attacks of nocturnal dyspnoea, and who had atrial fibrillation for which she received digoxin, seemed to be less prone to the attacks after the addition of methoserpidine to her treatment.

Symptoms Associated with Hypertension.—Symptoms of a subjective nature associated with hypertension were experienced by 35 of the 43 patients. All but two

TABLE I.—Cases of Essential Hypertension

Case No.	Sex and Age	Dosage (mg. Day)	Duration of Treatment (Months)	Minimal Untreated Blood-pressure (mm. Hg)	Mean Reduction in Blood-pressure (mm. Hg)	
					Systolic	Diastolic (% Reduction in Parentheses)
1	F 56	20-40	10	240/140	37	11 (8)
2	F 59	20-40	10	210/130	2	12 (9)
3	M 71	15-60	10	200/140	11	11 (8)
4	F 68	20-40	5	150/110	+4	7 (6)
5	F 67	20-40	10	210/130	12	10 (8)
6	F 60	20-40	9	190/130	9	18 (14)
7	M 59	10-30	8	180/110	41	26 (24)
8	F 54	20-40	10	180/115	14	11 (10)
9	F 63	30-60	7	280/160	52	18 (11)
10	M 62	20-40	8	170/110	12	10 (9)
11	M 56	20-40	5	180/110	31	13 (12)
12	M 55	30-40	4	170/110	11	2 (2)
13	M 57	20-40	5	160/110	10	8 (7)
14	F 48	15-40	4	160/110	+6	16 (15)
15	F 53	20-60	4	160/110	+1	5 (5)
16	F 63	15-40	10	180/110	+2	+3 (0)
17	F 62	15-30	9	150/120	+16	3 (2)
18	M 55	15-40	8	160/110	7	8 (7)
19	M 69	15	4	190/100	15	12 (10)
20	F 46	30-60	5	270/125	34	20 (16)
21	F 58	30-60	5	250/110	21	11 (10)
22	M 45	30	6	215/150	22	34 (23)
23	M 65	15	4	210/110	26	15 (14)
24	F 76	30	6	260/110	51	8 (7)
25	F 75	15-40	6	280/130	61	27 (21)
26	M 63	10-15	4	220/110	38	18 (16)
27	F 51	20-30	3	200/100	6	10 (10)
28	F 48	30-45	1	200/110	17	7 (6)
29	F 60	30-60	1	220/120	+11	2 (2)
30	F 60	15-30	10	260/120	68	20 (17)
31	F 65	15-20	4	260/130	53	30 (23)
32	F 53	10-20	4	225/120	54	26 (22)
33	F 71	10-20	6	250/120	65	20 (17)
34	F 69	10-15	3	230/100	33	8 (8)
35	F 59	20-30	1	205/115	40	32 (28)
36	F 71	15-30	2	230/120	51	20 (17)
37	F 67	10-30	10	205/118	21	21 (17)
38	F 66	15-30	11	220/115	43	28 (24)
39	F 44	15-30	6	240/130	37	22 (17)
40	F 61	30	5	180/110	15	5 (5)
41	F 69	15-30	5	240/130	21	8 (6)
42	F 40	30	3	230/120	22	9 (7)
43	F 45	20	1	175/110	37	25 (23)

TABLE II.—Distribution of Dosages at Beginning and End of Trial Periods in 43 Cases

		Dosage (mg. Daily)				
		10-15	20	30	40-45	60
At beginning		9	10	16	8	0
At termination		12	14	10	4	3

guanethidine and hydroflumethiazide). The mean reduction in systolic pressure exceeded 20 mm. Hg in 24 patients, and in 10 of these it was greater than 40 mm.

Cardiovascular Symptoms.—In five patients who were subject to attacks of angina pectoris the frequency of the attacks seemed to be reduced during methoserpidine therapy. The mean reduction in diastolic blood-pressure was 10 mm. Hg or more in three of these (Cases 5, 10, and 21) and less than 10 mm. in two (Cases 13 and 18).

Reduction in exertional dyspnoea appeared to result from the treatment in nine patients with this symptom (Cases 4, 5, 6, 17, 19, 21, 23, 24, and 25), and ankle

TABLE III.—Distribution of Reductions in Systolic and Diastolic Pressures in 43 Cases

Mean Reduction in Pressure	Systolic	Diastolic
Over 20 mm. Hg	24	10
10-20	9	19
Under 10	10	14

TABLE IV.—Symptoms Associated with Hypertension: Incidence and Relief with Treatment

Description of Symptom	No. of Cases with Symptom	Improvement			Unimproved
		Definite or Complete	Partial or Unsustained	Total	
Headache ..	30	22	6	28	2
Dizziness ..	24	16	5	21	3
Physical fatigue ..	10	5	4	9	1
Difficulty in mental concentration ..	7	3	2	5	2
Palpitations ..	5	3	2	5	0
Acroparaesthesiae	2	2	0	2	0

(Cases 12 and 43) of these reported some relief during methoserpidine therapy. The frequencies of occurrence of the different symptoms and of their relief with treatment are shown in Table IV. Complete or almost complete remission of symptoms usually occurred, but sometimes either the improvement was partial or the relief obtained initially was not maintained.

Side-effects.—We did not observe any toxic effects from methoserpidine during the trial. One patient (Case 3) complained of dizziness only while receiving methoserpidine, but with this exception none of the patients developed any unpleasant symptoms during treatment. So far, this is the only hypotensive drug used by us in general practice that has produced such a lack of side-effects.

Other Cases of Hypertension

The main features of the cases in which the hypertension was due partly or wholly to conditions other than essential benign hypertension are shown in Table V.

In Case 44 methoserpidine produced a mild reduction in mean blood-pressure and relief from headaches. Attacks of paroxysmal nocturnal dyspnoea were not prevented. Case 45 showed a moderate reduction in mean blood-pressure, especially in the systolic level.

A useful reduction in blood-pressure was obtained in Case 46, and the pregnancy proceeded satisfactorily to

TABLE V.—Data on Other Cases of Hypertension

Case No.	Sex and Age	Diagnosis	Dosage (mg. Daily)	Duration of Treatment (Months)	Minimal Untreated Blood-pressure (mm. Hg)	Mean Reduction in Blood-pressure (mm. Hg)	
						Systolic	Diastolic
44	F 76	Hypertension with aortic incompetence	20-45	1	220/100	8	12
45	F 43	 thyrotoxicosis	20-30	2	230/130	37	17
46	F 31	Pre-eclamptic toxæmia	20-40	3	180/120	36	24
47	F 57	Premalignant hypertension	40	4	260/160	22	12
48	F 54	Malignant hypertension	20-40	2	260/140	0	0

term. Methoserpidine has been used by us in several cases of pre-eclampsia since the trial and has proved most satisfactory. In Case 47 methoserpidine alone produced a mild reduction in mean blood-pressure and relief from headaches, dizziness, and palpitations. Subsequently an adrenergic-blocking drug was added to the treatment to produce a greater reduction in blood-pressure. No beneficial effects were obtained with methoserpidine in Case 48. Side-effects from the drug did not occur in any of these patients.

Discussion

In a number of trials of methoserpidine, as of some other hypotensive agents, a reduction in the diastolic level of 20 mm. Hg has been regarded as the minimum required to signify a definite hypotensive effect. However, this degree of reduction of diastolic pressure has often been based on a comparison of a reading taken at the end of a course of treatment with a casual reading taken immediately before the course was begun. It seems to us that this allows chance fluctuations in blood-pressure to influence unduly the levels recorded both before and after treatment.

In our assessment of the effect of methoserpidine on the blood-pressure we have calculated the means of the systolic and diastolic readings taken each time a patient was seen while receiving the treatment. The average number of readings was eight, with a range of 2 to 16. This method minimizes the chances of distortion of the results caused by spontaneous fluctuations in blood-pressure. We feel, moreover, that this is a more appropriate method of assessment in general practice, where the doctor is concerned with the continuous care of the patient, and that to have relied on a final reading after completion of a course of treatment would have been particularly unsuitable in our trial. We have compared the means of the blood-pressure readings during treatment, not with the means of pre-treatment systolic and diastolic levels, but with the *lowest* pre-treatment levels previously recorded. It is unlikely that mean reductions below the latter levels could reflect to any extent spontaneous fluctuations in blood-pressure. Hence we regard a reduction in *mean* diastolic level of 10 mm. Hg or more as significant of a real hypotensive action of the drug.

On this basis we have found a hypotensive effect with methoserpidine in 29 (67%) out of 43 cases of essential hypertension. It is interesting to note that, despite the use of a variety of methods of assessment, the published reports on this drug contain a close similarity in the proportion of patients in whom a hypotensive effect is produced. As in our trial, the proportion has been found to be about two-thirds of cases by Merlen and Gérard (1960), Tricot *et al.* (1960), and Mignault (personal communication, 1960), and about three-quarters of the cases by Brun and Rondelet (1959) and Read (1961).

Of our 29 patients with essential hypertension in whom a hypotensive action of the drug was demonstrable, we would regard the reduction as definitely beneficial clinically in just over a half—that is, in at least one-third of all the patients with essential hypertension. We have judged this, firstly, by a reduction in the mean diastolic pressure to 100 mm. Hg which was obtained in 16 out of 40 patients (three patients were excluded as their minimal pretreatment diastolic level was itself 100 mm. Hg). A similar result is obtained by

using the criterion suggested by Fife *et al.* (1960) that a reduction in blood-pressure levels of 16% or more could be regarded as “a clinically useful” hypotensive response. Such a response of 16% or more in the diastolic level was obtained in 15 of our patients. This is a better result than that obtained by Fife *et al.* with reserpine in a dosage of 1.5 mg. daily, in a trial also carried out in Glasgow, a reduction of 16% or more in diastolic pressure being obtained in only one-quarter of their cases (5 out of 20).

A remarkable property of methoserpidine that we have confirmed has been the subjective relief it affords to hypertensive patients. Nearly all our patients benefited from the treatment in this way. Exertional dyspnoea, sometimes associated with ankle oedema, headaches, dizziness, and palpitations, were the principal symptoms from which the patients obtained partial or complete relief. In addition, in five patients with angina pectoris the frequency of attacks seemed to decrease during the treatment. Our observations show that the relief from symptoms takes place quite independently of a reduction in blood-pressure. Similar observations have been made in all the previous clinical reports on methoserpidine, including an instance of relief from attacks of angina pectoris reported by Read (1961).

It is known that methoserpidine, like the natural rauwolfia alkaloids, has various effects on the circulation in addition to its hypotensive action. In particular, it slows the heart rate. It has also been beneficial in cases of Raynaud's syndrome (Peacock, 1960), and it is possible that, as with reserpine, symptomatic relief might be obtained in migraine and in some cases of thyrotoxicosis—conditions in which vascular changes also occur. We therefore suggest that the beneficial effect of methoserpidine on hypertensive symptoms may be attributable to its reversing circulatory changes with which these symptoms might conceivably be associated. This could certainly be the case, at least, when palpitations, and perhaps headaches and dizziness, associated with a tachycardia are relieved by the treatment.

An outstanding advantage of methoserpidine is its freedom from side-effects. All our patients felt generally well while receiving the drug, and the only side-effect observed was one instance of dizziness. Fife *et al.*, in their trial, recorded that the patients receiving reserpine complained more frequently of tiredness and of lethargy and drowsiness than the controls. The tendency for reserpine to cause lethargy and mental depression, as well as nasal congestion, loose stools, and other side-effects, is well known. With methoserpidine we did not observe any tranquillizing, depressant, or gastrointestinal side-effects.

There was no evidence of patients acquiring tolerance to the drug. In fact, a reduction in the dosage required occurred more often than an increase. The most frequent dosage used at the beginning of treatment was 30 mg. daily, while the most frequent at the end of treatment was 20 mg. daily (Table II). However, there were individual variations in the optimal dosage level, 12 patients being satisfactorily controlled on as little as 10–15 mg. daily, whereas three required as much as 60 mg. daily.

Our experience with the drug in cases other than of essential benign hypertension is too limited to allow us to form any definite opinion. However, investigation of its possible value in pre-eclamptic toxæmia would seem to be worth while, and it may well have a place

as an adjuvant to ganglion and adrenergic blocking drugs in the treatment of premalignant and malignant hypertension.

Summary and Conclusions

A co-operative clinical trial in general practice carried out by three practitioners in Glasgow is reported.

The drug concerned was a new hypotensive agent, methoserpidine ("decaserpyl"), a synthetic isomer of reserpine.

The effect of the drug was investigated mainly in 43 patients with essential (benign) hypertension. A definite hypotensive action was demonstrated in approximately two-thirds of the patients and was judged sufficient to be certainly beneficial clinically in one-third.

Almost all the patients obtained symptomatic improvement. The drug was found to be virtually free from side-effects and tranquillizing action.

Dosage of the drug should usually be 30 mg. daily initially, it being subsequently increased or decreased, if required, within the range of 10–60 mg. daily.

The findings broadly confirm the results reported in other investigations of this drug. Our experience indicates that methoserpidine is a useful drug for the management of mild and moderate cases of essential hypertension in general practice.

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CLINICAL EVALUATION OF PROPATYLNITRATE IN ANGINA PECTORIS

BY

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Although many preparations have been investigated for use as long-acting coronary vasodilators in angina pectoris few have survived a controlled unbiased study. Many claims of success have been based on a subjective assessment by the patient of improvement in his anginal attacks. Apart from the frequent spontaneous fluctuations in this symptom in the natural course of ischaemic heart disease, there is ample evidence that improvement will occur in any patient with angina with any new preparation irrespective of its active or inert properties (Greiner *et al.*, 1950). The necessity for a controlled double-blind trial is therefore apparent. In addition, however, an objective assessment of the anti-anginal activity must be made which relies as little as possible on the patient's own interpretation of his progress, and this is best accomplished by some form of exercise-tolerance test.

With these considerations in mind it was decided to carry out a clinical evaluation of a new coronary vasodilator, propatyl nitrate ("gina"), which is chemically related to both glyceryl trinitrate and erythrol tetranitrate. Preliminary experimental observations have indicated its effectiveness in producing coronary vasodilatation in animals, and clinically it has been found to give both rapid relief of pain in an acute attack of angina pectoris and a prophylactic sustained action (Nordqvist and Varnauskas, 1960). For the present study an exercise-tolerance test has been devised which is more physiological than the Master two-step test (Master and Oppenheimer, 1929).

Patients and Methods

Thirteen out-patients aged 43 to 70 with well-authenticated and typical features of angina pectoris were studied (Table I). The angina had been static for the previous 12 months. There were nine men

and four women, and in all of them the presumptive cause was coronary artery disease; one woman aged 43 (Case 12) had familial hypercholesterolaemia. Four patients had electrocardiographic evidence of previous myocardial infarction. All the patients were taking glyceryl trinitrate freely for their anginal attacks.

TABLE I.—Age-and-Sex Distribution of Patients Studied

Case No.	Age in Years	Sex	Duration of Angina
1	50	M	7 years
2	58	M	13 "
3	60	F	8 "
4	61	M	3 "
5	51	M	3 "
6	70	M	2 "
7	58	M	5 "
8	60	F	5 "
9	52	F	3 "
10	65	M	9 "
11	58	M	2 "
12	43	F	7 "
13	54	M	2 "

A double-blind technique was employed. Both the immediate and prolonged action of propatyl nitrate were studied. In investigating the immediate action in relieving anginal attacks a comparison was made with glyceryl trinitrate tablets in treating attacks occurring both during normal activity and after exercise-tolerance tests. The sustained effect of the drug in reducing the frequency of anginal attacks was compared with that of pentaerythritol tetranitrate (PETN; "mycardol").

An initial control period of one month was allowed when no additional coronary vasodilators were taken apart from glyceryl trinitrate. In the next three months of the study, individual monthly supplies of tablets of identical appearance containing propatyl nitrate, an inert placebo, and PETN were provided in random order, neither the patient nor the observer being aware of which drug was given. The dosage of propatyl nitrate was 10 mg. sublingually four times daily. The patients

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