Gastric biopsy showed that superficial gastritis was common during an attack of ulcerative colitis, although not seen in any specimens taken from five patients who were symptom-free.

The possible mechanisms and the practical significance of these changes in the small intestine and the stomach during an attack of ulcerative colitis are briefly discussed.

We wish to thank Dr. T. Parry for assistance with the photography.

REFERENCES

- Benson, J. A., Culver, P. J., Ragland, S., Jones, C. M., Drummey, G. D., and Bougas, E. (1957). *New Engl. J. Med.*, **256**, 335.
Bertalanffy, F. D., and Nagy, K. P. (1961). *Acta anat. (Basel)*, **45**, 362.
Callender, S. T., Turnbull, A., and Wakisaka, G. (1954). *Brit. med. J.*, **1**, 10.
— and Evans, J. R. (1955). *Clin. Sci.*, **14**, 387.
Cooke, W. T. (1958). *Brit. med. J.*, **2**, 261.
Creamer, B. (1962). *Gut*, **3**, 295.
Crosby, W. H., and Kugler, H. W. (1957). *Amer. J. dig. Dis.*, **2**, 236.
Floch, M. H., and Sheehy, T. W. (1962). *Gastroenterology*, **43**, 32.
Fourman, L. P. R. (1948). *Clin. Sci.*, **6**, 289.
Holmes, R., Hourihane, D. O'B., and Booth, C. C. (1961a). *Lancet*, **1**, 81.
— (1961b). *Postgrad. med. J.*, **37**, 717.
Joske, R. A., Finckh, E. S., and Wood, I. J. (1955). *Quart. J. Med.*, **24**, 269.
Leblond, C. P., and Messier, B. (1958). *Anat. Rec.*, **132**, 247.
— and Stevens, C. E. (1948). *Ibid.*, **100**, 357.
McMinn, R. M. H. (1954). *J. Anat. (Lond.)*, **88**, 527.
Quastler, H., and Sherman, F. G. (1959). *Exp. Cell. Res.*, **17**, 420.
Santini, R., jun., Sheehy, T. W., and Martinez-de-Jesus, J. (1961). *Gastroenterology*, **40**, 772.
Shiner, M. (1956). *Lancet*, **1**, 85.
Truelove, S. C., and Richards, W. C. D. (1956). *Brit. med. J.*, **1**, 1315.
— and Witts, L. J. (1955). *Ibid.*, **2**, 1041.
van der Kamer, J. H., Huinink, H. ten B., and Weyers, H. A. (1949). *J. biol. Chem.*, **177**, 347.

Clinical Trial of 2-Guanidinomethyl (1,4) Benzodioxan (Compound 1003)

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Brit. med. J., 1964, **1**, 398–402

This paper reports the results of a clinical trial of a new hypotensive drug, compound 1003, developed by Pfizer Limited (U.K.) and given the trade name of "envacar."

The structure and pharmacology are described in detail in a paper to be published elsewhere (Reinert). 1003 is the sulphate of 2-guanidinomethyl (1,4) benzodioxan. It has been shown in animals to block the release of adrenaline and noradrenaline from the post-ganglionic sympathetic nerves, and to deplete the tissues of these substances, including the adrenal medulla and the hypothalamus. The pressor effect of noradrenaline infusion into dogs treated with 1003 is markedly reduced owing to the blocking of the α -receptor sites. In similarly treated cats, stimulation of the hypothalamus by means of implanted electrodes produces diminished "defence reaction" and a reduction in skin vasoconstriction and muscle vasodilatation compared with the untreated animal.

The two outstanding ways in which this drug differs from guanethidine in animal studies are in its α -blocking effect and its depletion of the hypothalamus of noradrenaline. In addition, in rabbits, 1003 depletes the adrenal medulla of noradrenaline and adrenaline whereas guanethidine does not, but in dogs it is depleted by both.

Investigation

Sixty-two patients have been included in the trial, mostly severe hypertensives; 50% had initial diastolic blood-pressure of over 140 mm.; 48% between 120 and 140 mm.; and 2% (1 patient) below 120 mm. The age range was from 22 to 72 years, and there were 29 and 33 women.

Thirty-nine patients out of the 62 had had previous treatment with guanethidine, methyl dopa, or both; the results with 1003 in this group are discussed further separately in relation to the results of previous treatment.

Nine patients were in the malignant phase at the time of starting treatment and three had been so before treatment with other drugs. Ten patients had hypertension associated with renal disease and 52 had hypertension for which no cause could be found.

Blood-pressure Readings

The rate of response to the drug and its duration of action were assessed on patients who started on it while in hospital. The blood-pressure was measured with a sphygmomanometer in the lying and the standing positions and in some cases after exertion. Those followed as out-patients were assessed by casual blood-pressure readings with no deliberate preliminary period of rest.

Mode of Drug Administration

In-patients were started with a daily dose of 20 mg., usually given in one dose in the morning. The dose was doubled every fourth day until an effect was obtained; when partial reduction in blood-pressure occurred the dose was increased more slowly. On several occasions when a more rapid reduction in pressure was required a loading dose of 40 mg. was given followed by 20 mg. daily for the next two days, then increasing as before.

Out-patients were started on 10 mg. daily in a single dose or divided in two. The dose was doubled weekly until an effect was obtained, and again partial reduction in blood-pressure resulted in a more gradual increase in dosage.

If the blood-pressure had not been reduced satisfactorily at 160 mg. daily, the dose was halved and polythiazide 1 mg. ("nephрил," which is polythiazide 1 mg. plus 600 mg. of potassium chloride incorporated into each tablet) was added once a day. In some cases the dose was increased much beyond this before adding the diuretic, but with little further effect on the blood-pressure.

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Polythiazide was also added if fluid retention occurred, or if it was needed to enable the dose of 1003 to be reduced to minimize side-effects. In these cases also the dose was halved when adding the diuretic.

Patients well controlled as out-patients without polythiazide had an average dose of 60 mg. (range 20–140 mg.), and, with polythiazide, of 80 mg. (range 20–140 mg.). The maximum dose that has been given is 400 mg. daily. Those who were given polythiazide for relative resistance tended to have a higher dosage of 1003.

Tests for Toxicity

Haemoglobin, white blood count, platelet count, blood urea, electrolytes, serum bilirubin, alkaline phosphatase, thymol turbidity, serum glutamyl oxalate transaminase, and serum glutamyl pyruvate transaminase were measured at first weekly and later monthly.

Degree of Control

Control was considered good if the lying diastolic blood-pressure was less than 111 mm. and the standing less than 101 mm.; it was considered poor if the standing diastolic blood-

pressure was above 120 mm. Moderate control was all readings outside these categories provided that the standing diastolic pressure was lowered by 20 mm. or more; if reduced by less the readings entered the poor category.

Results

The collected series is shown in Table I.

Overall Results.—All 69 patients have been treated with 1003. Seven were not treated long enough for assessment; two defaulted; two died of coronary thrombosis, one two weeks and the other three weeks after starting treatment; one was taken off the drug because of the onset of an unrelated illness shortly after therapy started; one stopped the drug because he was about to be operated upon for renal artery stenosis; and the other has been on the drug for an insufficient length of time. Nine patients have had the drug for longer than eight months, 12 for between six and eight months, 8 for between four and six months, and 16 for between two and four months. Nine patients were treated only while in hospital; of these, six had a good response—two requiring polythiazide in addition—and three responded moderately, two having polythiazide. Fifty-three patients were treated as out-patients: 30 had good control, 19 with polythiazide; 18 had a moderate control, 11

TABLE I.—Cases and Results of Treatment with Compound 1003

Case No.	Age	Sex	Type	Blood-pressure	Daily dose	Polythiazide	Time	Final Blood-pressure		Comments
								Lying	Standing	
1	26	F	R	220/140	120 mg.	No	2½ wks	160/110	120/80	In-patient only
2	33	F	U	205/140	160 mg.	Yes	10 mths	180/110	170/115	
3	54	F	U	185/125	80 mg.	Yes	3 mths	200/125	130/90	Stopped for multiple side-effects
4	45	M	U	175/120	120 mg.	No	2 wks	160/110	145/100	In-patient only
5	45	F	U	210/130	320 mg.	No	3 mths	150/105	160/115	Control still being attempted
6	58	F	U	235/135	20 mg.	No	1½ wks	190/105	160/100	In-patient only
7	58	F	U	235/130	80 mg.	Yes	9 mths	220/115	200/100	
9	50	M	U	180/130	80 mg.	Yes	3 mths	240/130	170/100	Hypertensive dementia. Stopped
10	47	F	U	210/120	20 mg.	No	7 mths	165/95	130/85	
11	70	F	U	210/135	20 mg.	No	9 mths	190/120	160/110	Cerebral ischaemia limits dosage
12	23	M	U	160/120	80 mg.	No	2 wks	155/105	130/90	I-P only. Stopped for multiple side-effects
13	51	F	U-M	260/150	80 mg.	Yes	8 mths	160/90	155/80	
14	58	F	U	240/140	40 mg.	No	8 mths	200/110	190/110	
15	56	F	U	230/130	300 mg.	Yes	8 mths	260/140	260/140	Stopped. Never really controlled
16	42	F	U	240/140	80 mg.	Yes	3 wks	230/130	135/100	In-patient only
17	46	M	U-M	210/140	60 mg.	Yes	7 mths	160/100	130/85	
18	65	M	R	250/125	80 mg.	Yes	8 mths	260/95	240/80	
19	52	F	U	270/150	40 mg.	Yes	8 mths	160/100	120/80	
20	53	M	U	240/135	160 mg.	Yes	9 mths	150/80	140/80	
21	34	F	U	210/150	400 mg.	Yes	6 mths	230/135	200/125	Never really controlled. Stopped
22	41	F	U	225/125	20 mg.	Yes	7 mths	160/90	130/85	
23	72	M	U	240/125	100 mg.	Yes	7 mths	210/115	170/105	
24	51	M	U-M	215/145	80 mg.	Yes	3 wks.	185/125	105/65	I-P only. Stopped for postural hypotension
25	54	M	U	220/120	30 mg.	Yes	6 mths	145/100	120/85	
26	46	M	U	210/135	10 mg.	Yes	6 mths	140/90	110/80	
27	37	F	U	225/145	60 mg.	Yes	6 mths	140/100	125/85	
28	54	F	U	250/145	60 mg.	Yes	6 mths	180/100	150/90	
29	63	M	U	270/150	20 mg.	Yes	6 mths	250/135	240/140	Cerebral symptoms limit dose
31	54	F	U	200/130	80 mg.	Yes	6 mths	200/115	160/105	
32	33	M	M-U	225/150	30 mg.	Yes	4 mths	150/100	130/90	
33	34	F	U	190/135	40 mg.	No	5 mths	200/115	170/115	
34	43	F	R	170/120	20 mg.	T	3 mths	130/90	150/90	
35	43	F	R	240/130	20 mg.	No	10 days	175/120	135/95	I-P only, then drug stopped for reaction
36	41	M	U	220/140	160 mg.	Yes	6 mths	220/120	130/85	
37	64	F	U	220/140	40 mg.	No	5 mths	170/100	150/80	
38	48	M	R-M	240/140	120 mg.	Yes	4 mths	160/100	135/85	
39	56	M	M-U	250/150	80 mg.	No	4 mths	180/95	140/90	
40	58	F	U	260/145	20 mg.	Yes	4 mths	230/95	225/100	
41	56	M	U	230/140	80 mg.	Yes	2½ mths	160/90	145/80	
42	54	M	R	270/165	160 mg.	Yes	1 mth	265/140		Polio of legs; therefore B.P. sitting. 1003 stopped (persistent vomiting)
44	35	F	U	200/130	80 mg.	No	4 mths	160/100	130/90	
45	38	M	U	190/130	120 mg.	No	3½ mths	160/100	135/95	
46	49	M	M-U	260/150	80 mg.	Yes	2 wks	150/100	120/80	I-P only. Drug stopped for reaction
48	55	M	U	190/135	80 mg.	No	1 mth	165/105	180/115	Control still being attempted
49	55	F	U	250/145	240 mg.	Yes	4 mths	180/118	180/116	
50	43	M	R-M	280/150	80 mg.	Yes	3 wks	150/100	120/80	I-P only. Drug stopped for reaction
51	63	F	U	240/120	40 mg.	Yes	3½ mths	150/180	145/85	
54	55	F	U	235/120	40 mg.	No	3½ mths	230/120	180/110	Control still attempted
55	59	M	U-M	210/140	400 mg.	Yes	3 mths	185/115	120/95	
56	57	F	R	250/145	20 mg.	Yes	4 mths	260/105	220/110	Cerebral symptoms limit dose
57	54	F	U	190/95	20 mg.	Yes	2½ mths	150/85	135/75	
58	52	M	U-M	260/130	200 mg.	No	3 mths	200/90	180/90	
59	42	M	U	240/140	50 mg.	Yes	3½ mths	180/95	140/80	
60	34	F	U	180/120	30 mg.	No	2½ mths	180/105	160/90	
61	51	M	U	200/130	80 mg.	No	2½ mths	170/90	150/90	
63	55	F	U	210/140	40 mg.	Yes	2½ mths	210/135	110/90	
64	49	M	R-M	210/140	40 mg.	No	2½ mths	190/110	180/105	Control still attempted
65	39	F	U-M	260/140	60 mg.	No	2 mths	210/115	200/105	Control still attempted
66	42	F	R	230/130	20 mg.	Yes	1½ mths	160/90	155/80	
67	59	M	U	240/135	40 mg.	No	2 wks	210/110	170/100	
68	62	M	U	260/140	40 mg.	No	1 mth	160/110	140/100	
69	63	M	U	220/140	30 mg.	No	2 mths	200/100	180/90	

Missing numbers correspond to those cases not assessed for reasons discussed in text. U = Hypertension of unknown origin. R = Hypertension associated with renal disease. M = Malignant hypertension. I-P = In-patient. Case 34 had triamterine (T) instead of polythiazide.

with polythiazide; and 5 had poor control, 4 of whom were taking polythiazide. Two of the moderately controlled cases (Nos. 11 and 56) and one of the poorly controlled (No. 29) could not tolerate higher doses because of symptoms of cerebral ischaemia. It is possible that those only moderately or poorly controlled, who at the time of assessment were not having polythiazide, may have a better degree of control when the diuretic is added.

Results Related to Initial Blood-pressure.—Thirty-one patients had diastolic pressures of 140 mm. or above before treatment: 17 became well controlled, 11 were moderately controlled, and 3 remained poorly controlled. Thirty patients had diastolic pressures between 120 and 140 mm. before treatment: 18 became well controlled, 10 were moderately controlled, and 2 remained poorly controlled. One patient had a pretreatment diastolic pressure of less than 120 mm. and became well controlled.

Malignant Hypertension.—Nine patients had malignant hypertension at the onset of treatment, as judged by papilloedema, bilateral haemorrhages and exudates, or both. Six became well controlled and three moderately controlled. A further three patients had had malignant hypertension at some time, but at the start of treatment with 1003 were not in the malignant phase. Two became well controlled and one moderately controlled.

Hypertension Associated with Renal Disease.—Ten patients had hypertension associated with renal disease; six became well controlled, three were moderately controlled, and one remained poorly controlled.

Diuretics.—The numbers of patients in the above categories receiving a diuretic in addition to 1003 is shown in Table II. In all, 37 patients have had polythiazide in addition to 1003—18 for relative resistance, six to lower the dose of the drug to minimize side-effects, and five for a combination of these two reasons. A further seven patients had it to counteract fluid retention, and one took triamterine for the same reason. One patient was already on polythiazide when treatment with 1003 was started. Of the 23 cases on polythiazide for relative resistance, including the five also troubled by side-effects, 11 became well controlled, 9 were moderately controlled, and 3 remained poorly controlled.

Tolerance.—There has been no evidence as yet of tolerance developing towards the drug. Once a good control of blood-pressure is established it has been uncommon to have to increase

the dose; only one patient (Case 36) has required a marked increase. In three cases (Nos. 17, 27, and 32) the dose had to be reduced after several weeks' good control because the blood-pressure fell too low without any evidence of marked decrease in renal function as judged by levels of blood urea.

Withdrawal of Drug.—Seven patients were taken off the drug because of side-effects—two because of resistance and five for social reasons, such as leaving hospital for another part of the country.

Clinical Effects

Compound 1003 produces a lowering of both systolic and diastolic pressures in the lying and standing positions; there is almost always a significantly greater fall in the standing pressures, accompanied by an increase in heart rate. In many cases there is also a further drop in pressure on exertion such as climbing stairs. The control is good over the period 6 a.m. to 10 p.m. as measured in patients up and about in hospital (Table III).

Speed and Duration of Action.—After an initial effective dose the blood-pressure begins to drop by 24 hours, and by 48 hours the maximum effect has usually been obtained. The addition of polythiazide produced a further fall, usually within 24 hours in those cases that responded; as is usual with a diuretic, the initial response shows a marked postural effect almost certainly due to the reduction in circulating blood volume. However, after a week the hypotensive effect is still present and persists thereafter. On stopping 1003 the blood-pressure remains down for up to 48 hours and then starts to rise again.

Side-effects

Lack of Energy.—This was the most common complaint, 29 patients having it at some time and 24 had it on their final dose. Seven patients were troubled by it, but none had to stop the drug for this reason. In some patients the complaint lasted all day; in others it occurred for an hour or two related to taking the drug; some had it on occasional days only. It could often be minimized by taking the whole dose at night.

Diarrhoea.—Thirty patients had diarrhoea at some stage during treatment, but only five had it on their final dose. It has never been troublesome enough to stop the drug. When the diarrhoea first appeared it was mostly well controlled by codeine if necessary, and usually the codeine could be stopped later without return of the side-effect. However, nine patients took codeine more or less regularly to control it. In some cases it was an urgency of defaecation with formed stools. The diarrhoea tended to occur for 30–60 minutes after the morning dose and lasted about an hour; less commonly it also occurred after the evening dose. Thus it was often predictable, which was a help to the patient.

Nausea.—Nineteen patients complained of this at some time, eleven on their controlling dose. Six patients were troubled by it, and in one case (No. 42) the drug was stopped because of persistent vomiting. It tended to occur 30 minutes after the dose and lasted for 30–90 minutes; it was often helped by taking the tablet with meals. Nausea rarely occurred at a dose below 80 mg. daily.

Postural Dizziness.—This occurred at some time in 21 patients, and 15 had it on their controlling dose. One patient

TABLE II.—Results of Treatment with Compound 1003 With and Without Polythiazide

	Cases	Good Control		Moderate Control		Poor Control	
		Alone	Poly-thiazide*	Alone	Poly-thiazide*	Alone	Poly-thiazide*
In hospital ..	9	4	2	1	2	—	—
In out-patients ..	53	11	19	7	11	1	4
Diastolic B.P. :							
>140 mm. ..	31	5	12	3	8	—	3
120–140 mm. ..	30	10	8†	5	5	1	1
<120 mm. ..	1	—	1	—	—	—	—
Type :							
With renal disease	10	1	5†	2	1	—	1
Unknown aetiology	52	14	16	6	12	1	3
Malignant hypertension ..	12	2	6	2	2	—	—

* The dose of polythiazide used was 1 mg. daily.

† These groups include one case when triamterine 100 mg. b.d. was used.

TABLE III.—Average B.P. of Patients in Hospital with B.P. Controlled by a Daily Dose of 1003 over 4 Days

Case No.	Initial		6 a.m.		10 a.m.		2 p.m.		6 p.m.		10 p.m.	
	L	S	L	S	L	S	L	S	L	S	L	S
32	225/140	215/135	160/103	123/83	167/108	138/87	163/110	140/95	168/100	133/80	155/103	113/73
64	210/140	205/135	142/82	111/68	145/95	128/82	165/100	150/100	175/115	155/107	148/86	117/65
45	190/130	170/120	136/99	119/85	133/96	117/81	127/94	102/79	127/92	98/73	142/91	110/81
46	210/150		168/111	150/100	169/105	129/92	168/108	118/82	173/112	138/93	162/106	135/87
5	170/115	170/130	157/100	136/95	155/98	139/92	152/97	139/89	162/101	146/104	166/105	135/96

(Case 24) stopped the drug because of it. In the others it was not troublesome; it occurred mainly on rising and could be controlled by more careful change of posture.

Exertional Dizziness.—Eight patients complained of this, five on their controlling dose. In none was it troublesome. A typical case (No. 26) had a lying pressure of 140/90, standing of 110/80, and on climbing 40 stairs of 80/60.

Sexual Complaints.—Two men complained of impotence and three of failure of ejaculation out of 10 men questioned.

Nasal Congestion.—Five patients complained of this; in none was it troublesome. Two patients, one of whom had stopped guanethidine (Case 31) and the other reserpine (Case 26) because of this, tolerated 1003 better.

Weight Gain.—Seven patients gained weight, which was lost on the addition of polythiazide; one patient (Case 9) gained 3.5 kg. and another (Case 51) nearly 3 kg. All were on a dose of 20 mg. daily or less of 1003. Five patients had not responded at this dose but did so when the diuretic was added. The other two of the seven were in mild congestive cardiac failure at the time of starting the drug but were not on a diuretic, and these rapidly gained weight and developed signs and symptoms of fluid retention soon after starting 1003. This fluid retention occurs with other hypotensive drugs and the reasons are not clear (Dollery *et al.*, 1960; Bayliss and Harvey-Smith, 1962).

Toxicity.—Two patients (Cases 46 and 50) developed fever and severe diarrhoea which went on stopping the drug and returned on reintroducing it; both had an associated eosinophilia. One further patient (Case 35) had these symptoms as an out-patient, which disappeared on stopping the drug and returned on starting it once more. This patient was also on nitrofurantoin at the time, and had been on it for a week when the symptoms arose. These three patients had been on 1003 for between two and three weeks before the onset of these symptoms; on stopping the drug they rapidly recovered. Apart from eosinophilia in Cases 46 and 50, there were no changes in the blood or platelet counts or liver-function tests. Any change in blood urea or electrolytes followed administration of polythiazide. As well as those mentioned above, two patients stopped 1003 for multiple side-effects.

Comparison with Other Agents

In this trial no direct attempt has been made to compare the results of therapy with 1003 with those of any other drug. Comparison of the effects of any one drug with another would have to be done under strictly controlled conditions as a separate trial, and this has not been attempted. However, 39 out of the 62 patients had also been treated with guanethidine, methyldopa, or both, and the results of treatment with 1003 related to this previous therapy is discussed.

Guanethidine

Ten patients had been resistant to guanethidine as out-patients at a dose of 50 mg. daily or above with a thiazide diuretic. Treatment with 1003 produced good control in four cases, three requiring polythiazide; moderate control in two cases, both with polythiazide; and poor control of four cases, three with polythiazide.

One case badly controlled as an out-patient on guanethidine 50 mg. daily without a thiazide was moderately well controlled on 1003 with polythiazide.

One patient moderately controlled as an out-patient on guanethidine 50 mg. daily with a thiazide became well controlled on 1003 with polythiazide.

A further four out-patients had unsatisfactory control on an unknown dose of guanethidine at other hospitals, and it is also

not known whether any diuretic combinations were used. Of these, three were well controlled on 1003 plus polythiazide, one having been treated only as an in-patient, and the other was moderately controlled on 1003 + polythiazide also only as an in-patient.

Six patients stopped guanethidine for side-effects, but in addition none was well controlled. Five of these tolerated 1003 better; all were taking polythiazide in addition. In two of these the control was good and in the other three moderate. The other case was moderately controlled on 1003 but still had the same side-effect—postural dizziness.

Methyldopa

Four out-patients were resistant to methyldopa 1.5 g. daily or above, together with a diuretic. Three of these remained poorly controlled on 1003, but one did not have polythiazide to help control. The other case was well controlled on 1003 without a diuretic, but was treated only as an in-patient.

A further four patients were resistant to methyldopa 1.5 g. a day without a diuretic—two were out-patients and were moderately controlled on 1003 without polythiazide as out-patients, and two were in-patients and were well controlled on 1003 without a diuretic also as in-patients.

Two out-patients had “unsatisfactory control” on an unknown dose of methyldopa at other hospitals, and it is not known whether diuretics were used. Both these cases were well controlled on 1003 and polythiazide.

Three patients stopped methyldopa for side-effects and all tolerated 1003 better. All three had had moderate control on methyldopa and on 1003—one was well controlled without polythiazide and two were moderately controlled, one with polythiazide and one without.

Patients whom it is known had had less than guanethidine 50 mg. daily or methyldopa 1.5 g. daily have not been discussed.

Compound 1003

In this series there were five patients badly controlled on 1003. Three were also resistant to both guanethidine and methyldopa, alone, in combination with a diuretic, and in combination with each other. One patient had cerebral arteriosclerosis and could not tolerate having his blood-pressure lowered to generally acceptable levels, and on a small dose of 1003 his pressure varied widely at different attendances. The other patient had not received full doses of 1003 and the effect of a diuretic had not been tried.

Five of the patients who have stopped 1003 have been followed up on other regimes.

Case 3.—This patient, who stopped 1003 for multiple side-effects when moderately controlled with polythiazide, is moderately controlled on methyldopa 250 mg. q.d.s. and a thiazide diuretic, but still has many of the complaints she had while on 1003.

Case 35.—This patient, who probably had a drug reaction, is moderately controlled on methyldopa and polythiazide; she was moderately controlled as an in-patient on 1003 without polythiazide.

Case 42.—This patient, who stopped 1003 for persistent vomiting while also badly controlled on 1003 160 mg. daily plus polythiazide, will respond only to subcutaneous pentolinium.

Case 46.—This patient, who was well controlled with 1003 with polythiazide in hospital before he developed a drug reaction, has proved resistant as an out-patient to methyldopa and to guanethidine, both with polythiazide.

Case 50.—This patient, who also was well controlled by 1003 with polythiazide in hospital, is resistant to methyldopa and a thiazide, and gets excessive diarrhoea on guanethidine; he is now well controlled on pempidine.

Discussion

The trial has shown that compound 1003 will lower the blood-pressure in severe and moderately severe hypertensives to a good level of control in 58% and to a moderate level of control in 34%; 8% remain poorly controlled. Not enough mild hypertensives have been treated to comment on these. The response in the renal and malignant hypertensives is good.

No significant rise in the blood urea occurred during treatment with 1003 alone, although, as with other hypotensive drugs, there was often a rise on adding polythiazide, which in some cases returned to previous levels, but in others remained elevated.

Clinically, the actions and side-effects of 1003 are similar to those of guanethidine, but in some cases it has proved effective where guanethidine has failed, and in others has produced fewer side-effects.

In 64% of the out-patients polythiazide was given in addition to 1003 to help control; this figure is similar in our experience to that in treatment with guanethidine and methyl dopa.

Lack of energy was the most troublesome side-effect; diarrhoea was also common initially, but was easily controlled with codeine phosphate and usually wore off with continued treatment. Postural and exertional dizziness and sexual symptoms occurred about as often as in guanethidine therapy. Nausea was troublesome in some patients but in only one case did the treatment have to be stopped because of it.

There were two certain cases of drug reaction and a probable third out of 62 cases assessed. However, symptoms quickly settled on withdrawing the drug.

The action of compound 1003 in depleting the hypothalamus and the adrenal medulla of pressor amines led us to look for

any obvious differences from guanethidine in its mode of action in the clinical control of patients with hypertension; we found no very apparent difference, but attempts to correlate action in a particular area in the animal with the effect of lowering the blood-pressure in man are extremely difficult. At present this applies to most drugs used in the treatment of hypertension, since it is by no means clear which of their many pharmacological actions is responsible for lowering the blood-pressure.

Compound 1003 has been shown to be a suitable drug for the treatment of patients with hypertension of moderate or severe degrees, whether associated with renal disease or not.

Summary

A trial is reported of a new hypotensive compound 1003 ("envacar"). In 62 cases it has been shown to provide good control in 58%, moderate control in 34%, and poor control in 8%.

Most of the patients had severe hypertension, 50% had diastolic pressures of more than 140 mm., and 48% between 120 and 140 mm. The drug is effective in malignant hypertension and in hypertension associated with renal disease. In some cases it has been effective where other drugs have failed. Side-effects include lethargy, nausea, and diarrhoea.

Our thanks are due to Pfizer Limited, Sandwich, Kent, for supplies of compound 1003.

REFERENCES

- Dollery, C. T., Emslie-Smith, D., and Milne, M. D. (1960). *Ibid.*, 2, 381.
Bayliss, R. I. S., and Harvey-Smith, E. A. (1962). *Lancet*, 1, 763.

Clinical Trial and Pharmacological Study of Compound 1029 ("Vatensol")

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Brit. med. J., 1964, 1, 402-406

Although the role of noradrenaline in the causation and maintenance of hypertension has not yet been clearly established a number of anti-hypertensive drugs directly affect adrenergic mechanisms, the pharmacological actions being direct antagonism and effects on the storage, release, or synthesis of the transmitter.

This paper describes a clinical and pharmacological study of a new anti-hypertensive agent developed by Pfizer Ltd. (U.K.). This compound, designated 1029, is [(2-(2, 6-dichlorophenoxy) ethyl) amino] guanidine sulphate ("vatensol"), which has been shown to have the following pharmacological actions: (1) inhibition of dopamine beta-oxidase, (2) adrenergic neurone blockade, (3) depletion of noradrenaline in the C.N.S., and (4) depletion of peripheral tissue noradrenaline. In the adrenal medulla there was depletion of noradrenaline and, to a larger extent, adrenaline.

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Animal Pharmacology

The anti-hypertensive effect and modes of action of compound 1029 were demonstrated in animals and *in vitro* by the following experiments:

(a) Repeated oral administration of 1029 (20 mg./kg., per os, for three days) to beagle dogs with experimentally induced nephrogenic or neurogenic hypertension produced a sustained anti-hypertensive effect, reduced the tyramine pressor response, and increased the dimethyl-phenyl piperazine and noradrenaline pressor responses in the non-anaesthetized dog.

(b) *Adrenergic Neurone Blockade*.—(1) Abolition of the response of the nictitating membrane to pre- and post-ganglionic stimulation in the anaesthetized cat. (2) Inhibition of release of noradrenaline from the spleen on electrical stimulation of the splenic nerve. (3) Reduction of the pressor response to injected tyramine and splenic-nerve stimulation, without effect on pressor response to injected adrenaline and noradrenaline.

(c) *Amine Depletion*.—The noradrenaline content of heart, spleen, and hypothalamus, and the content of adrenaline and nor-