Discussion

This study has shown that in man dibenylin is capable of increasing the blood flow through vessels surgically deprived of their sympathetic innervation. The increase in flow after intravenous dibenylin was generally greater in subjects with little or no organic arteriolar narrowing than in those with structural ischaemic change. The volume of blood flowing through any part of the arterial tree is determined by the "perfusing" pressure and by the vascular resistance. In these experiments there was no increase in pressure; on the contrary, the blood pressure generally fell a little with the intravenous infusions of dibenylin. The increased flow was therefore due to a lowering of resistance—that is, to an increase in mean vascular calibre. Since the blood vessels had been denervated the increased flow was not due to any effect of dibenylin on the sympathetic nerves. The vasodilatation could therefore be attributed to an action of the drug at the periphery or to the systemic release of some vasodilator substance by the intravenous dibenylin.

The mechanism was further elucidated by the studies using intra-arterial dibenylin. Dilatation during infusion of the drug into the brachial artery was confined to the corresponding hand. This demonstrated that the vasodilatation with dibenylin can result from a purely peripheral action without involving any systemic or central effect. This peripheral action presumably involves the receptor elements or the contractile muscle of the arterioles.

In subjects with intact vasomotor nerves this action is no doubt reinforced by the effects of the drug (when given orally or intravenously) on the sympathetic nervous system. It has been demonstrated that dibenylin is capable of dilating blood vessels by peripheral action beyond the sympathetic terminals. This is of particular importance in patients in whom the vasomotor nerves have been ablated by surgery or impaired by metabolic or nutritional disorders. Dibenylin is specially indicated in acute ischaemia of an extremity, for it may be infused directly into the artery of any limb to which the vascular disturbance is confined. It is effective in doses that do not influence the blood pressure or systemic circulation.

If two or more limbs are involved the drug may be given intravenously in larger amounts (25–60 mg.). By this route its systemic actions, especially its tendency to lower the blood pressure, may be a disadvantage.

Undesirable effects tend to occur with intravenous doses of over 40 mg. of dibenylin. The most serious of these—tachycardia and hypotension—are related to the widespread vasodilatation produced. The drug is therefore best withheld from people known to have heart disease. After intravenous administration all patients should be kept in bed for 24 to 48 hours, and the heart rate and blood pressure carefully watched. Some drowsiness and lethargy is to be expected during this period, but requires no treatment. Nasal stuffiness due to congestion of the mucosae is common, but rapidly passes off. If dibenylin is given continuously by mouth, especially in daily doses greater than 20 mg., nasal congestion, lethargy, and giddiness may occur, but considerable relief is usually afforded by the use of an amphetamine inhaler and small doses of dexamphetamine sulphate tablets, *B.P.C.*

Summary

It has been shown that dibenylin is capable of increasing the blood flow in the limbs by a peripheral action independent of any effects it may have on the sympathetic nervous system.

The vasodilatation from a single injection is of rapid onset and persists for several hours.

The drug may be of particular value in treating acute ischaemia of a limb, for it is effective when infused intra-arterially in doses (under 0.5 mg. into the brachial

artery) that do not appreciably affect the general circulation.

Dibenylin is effective even in patients in whom the integrity of the vasomotor nerves has been lost.

However, it must always be remembered that the extent to which any blood vessel may dilate with dibenylin or with any other agent is determined ultimately by the degree to which disease has induced structural change in the vessel wall.

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REFERENCES

- Barcroft, H., and Swan, H. J. C. (1953). *Sympathetic Control of Human Blood Vessels*. Arnold, London.
 Duff, R. S. (1952). *J. Physiol. (Lond.)*, **117**, 415.
 Friend, D. G., and Edwards, E. A. (1954). *A.M.A. Arch. intern. Med.*, **93**, 928.
 Green, H. D., Denison, A. B., Williams, W. O., Garvey, A. H., and Tabor, C. G. (1954). *J. Pharmacol.*, **112**, 462.
 Haimovici, H. (1951). *Angiology*, **2**, 531.
 Harvey, S. C., and Nickerson, M. (1954). *J. Pharmacol.*, **112**, 274.
 Landis, E. M., and Gibson, J. H., jun. (1933). *Arch. intern. Med.*, **52**, 785.
 Moser, M., Prandoni, A. G., Orbison, J. A., and Mattingly, T. W. (1953). *Ann. intern. Med.*, **38**, 1245.
 Nickerson, M., Henry, J. W., and Nomaguchi, G. M. (1953). *J. Pharmacol.*, **107**, 300.
 Wertheimer, L., Redisch, W., and Steele, J. M. (1954). *Circulation*, **10**, 366.

CARDIOVASCULAR COLLAPSE DURING APOMORPHINE TREATMENT

BY

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Apomorphine treatment for alcoholism is being used on an increasingly large scale, and published reports suggest that it is effective and safe. In principle, the method, which was introduced by Dent in 1934, consists in giving drinks of alcohol together with subcutaneous or intramuscular injections of apomorphine repeatedly over a few days. There has recently been a trend, expounded chiefly by Feldmann (1952), of Geneva, towards long and intensive courses of treatment, such as apomorphine 1/10 gr. (6.5 mg.) by injection and alcohol by mouth, two-hourly day and night for six to ten days, during which time other foods and fluids are absolutely withheld.

In view of the safety claimed for this treatment, it is thought worth publishing the following observations on a patient who showed an anomalous and dangerous reaction to apomorphine. In spite of his experiences under therapy, he generously volunteered to have further doses of the drug experimentally, and thereby made it possible for the nature of this unusual reaction to be more accurately defined.

Case History

The patient, a man of 32, was of markedly asthenic physique and had a thoracic kyphoscoliosis. He had a history of repeated attacks of intestinal colic, which had not been cured by a reconstruction operation carried out on the hypothesis that an aberrant mesenteric vessel might be responsible. He came under psychiatric treatment because of a confusional state provoked by drugs and alcohol. The most notable feature in his drug-taking history was the injection of pethidine in doses up to 2,500 mg. daily, intermittently

over nine months with periods of freedom from the drug of up to three weeks. In addition, he had on rare occasions taken intravenous thiopentone in such dosage as 0.5 g. His drinking history was less remarkable, amounting to frequent symptomatic excess rather than confirmed and continuous addiction, his daily intake being of the order of 3 pints (1.7 litres) of beer and nine whiskies. His confusion cleared before admission.

Before starting on apomorphine treatment, a course of modified insulin was given to improve his general physical condition. He proved to have a high insulin tolerance, taking as many as 440 units without losing consciousness.

Treatment by apomorphine was started on the 57th day after admission. The patient, who was anxious and apprehensive, had a B.P. of 120/60 and a pulse rate of 96 a minute. In accordance with the method of Feldmann (1952), he was then given an initial dose of 1/10 gr. (6.5 mg.) of apomorphine subcutaneously, with 20 oz. (570 ml.) of beer. After 10 minutes he experienced nausea, and after 15 minutes he vomited copiously, whilst his pulse rose to 126. Twenty minutes after the injection he suddenly became pale and cyanosed. Profound cardiovascular collapse followed, with cessation of respiration, absence of radial pulse, loss of consciousness, and an appearance of extreme prostration. Artificial respiration and oxygen were given and the return of shallow irregular respiration and of a slow pulse was accompanied by generalized clonic jerks. He recovered consciousness within a minute or so, but with some transient confusion. He was then restless and agitated, but within 15 minutes of the collapse his physical condition no longer gave cause for concern.

In view of this severe and dangerous collapse the treatment was withheld for a week. During this time an E.E.G. showed mild bilateral dysrhythmia of constitutional type, but no evidence of epilepsy. An E.C.G. revealed a sinus bradycardia of 50 a minute, with flat P waves in all leads, but the curves were considered to be within normal limits. The bradycardia was an isolated finding, his usual pulse rate being 70 to 80. It was decided to proceed cautiously with the treatment. He was watched very closely after each dose of the drug and means of immediate resuscitation were kept at hand. His reactions to subsequent doses are summarized in the Table.

Reactions to Apomorphine

Days after Admission	Time	Dose of Apomorphine	Vomiting	Cardiovascular Effects
64	6.55 p.m.	gr. mg. 1/40 1.6	After 5 mins.	Nil
64	9.05 "	1/30 2.2	" 5 "	(1) Fall of pulse from 84 to 48 after 10 mins. (2) Malaise, shock, pallor, cyanosis after 15 minutes. B.P. 70 systolic. Nikethamide 5 ml. given i.m. (3) Improving 20 minutes after injection. Pulse 84. B.P. 95/50
65	10 a.m.	1/60 1.1	Nil	Nil (difficulty in focusing after 5 mins.)
65	12 noon	1/50 1.3	Nausea only after 6 mins.	Nil
65	1.30 p.m.	1/40 1.6	Nil	"
65	3 "	1/30 2.2	Nausea after 6 mins. (retching)	Yawning and fall of B.P. from 110/75 to 90/50 after 20 mins. Nil else. Pulse steady
65	4.10 "	1/20 3.2	After 5 mins.	Malaise and fall of B.P. to 95/60 after 13 mins. Pulse steady
65	8.08 "	1/20 3.2	" 5 "	Pulse 46 after 10 mins. Pallor and collapse after 12 mins. requiring oxygen and nikethamide
66	10 a.m.	1/30 2.2	Nil (nausea after 5 mins.)	Nil significant (facial flush and blurred vision after 15 minutes)

Because of its manifest hazards in this case, apomorphine treatment was abandoned. The patient agreed, however, to have further doses of the drug under experimental conditions so that electrocardiographic recordings could be made.

Experimental Observations

The patient was given a series of injections of apomorphine, each on a different day. Tracings were taken as indicated by a Cambridge Electrite cardiograph, lead II being used throughout. In the following summaries of the observations made, the times noted refer to the interval after injection, and letters A-F to the series of E.C.G. tracings (Fig. 2) corresponding to the points on the pulse chart (Fig. 1) for the third experiment.

First Experiment (71 days after admission).—Resting E.C.G. normal. Pulse 75, regular. Apomorphine 1/40 gr. (1.6 mg.) subcutaneously. 9 minutes, slight malaise. 13 minutes, yawning. No vomiting. No significant change in E.C.G.

Second Experiment (78 days after admission).—Resting E.C.G. normal. Pulse 88, regular. Apomorphine 1/25 gr. (2.6 mg.) subcutaneously. 9½ minutes, vomiting followed by malaise. No significant change in E.C.G., pulse, or blood pressure.

Third Experiment (83 days after admission).—Resting pulse 97. B.P. 120/70. (A.) Apomorphine 1/20 gr. (3.2 mg.) intramuscularly. 4 minutes, subjective flushing. 7½ minutes, vomiting. 8-9 minutes, rapid fluctuations in size of pupils. 10 minutes, onset of malaise. 15 minutes, slight conjunctival injection. 16 minutes, further vomiting; pupils reacting briskly to light, sluggishly to accommodation. 18 minutes, inability to focus; much more severe malaise; a floating feeling. 19 minutes, increasing malaise, restlessness, and pallor. 20 minutes, onset of severe collapse. (B.) 21-26 minutes, cyanosis and profound collapse; oxygen and nikethamide given. (C. D. E.) 29 minutes, rapidly improving; B.P. 110/50. 30 minutes onwards, steady and uninterrupted recovery. (F.) 45 minutes, hiccuping and drowsiness; B.P. 115/60.

FIG. 1.—Pulse chart showing third experiment. A-F refer to times at which the electrocardiographic tracings shown in Fig. 2 were taken.

The urgent need for resuscitative measures made it impossible to take blood-pressure readings while he was collapsed, and the state of the pupils was also neglected. For similar technical reasons, there were short breaks in the E.C.G. tracing between points B and C, and C and D. Fig. 1 shows the changes in pulse rate. Representative sections of the E.C.G. are reproduced in Fig. 2.

This series of electrocardiographic changes supports the clinical diagnosis of a severe vasovagal syndrome, the gravity of which is well illustrated by the tracings C and D. The rapid return of the E.C.G. to normal is regarded as evidence against the possibility of a direct toxic action of apomorphine on the heart.

Discussion

The pharmacology of apomorphine was extensively reviewed by Sumwalt (1943), while, of the standard works of reference, those of Drill (1954) and of Goodman and Gilman (1955) give comprehensive accounts of the drug's actions. Apomorphine is, of course, a central emetic which acts

selectively (according to Borison and Wang, 1953) on a chemoreceptor trigger zone in the floor of the fourth ventricle, separate from the emetic centre in the fasciculus solitarius. Vomiting occurs 5 to 15 minutes after a dose of 2 to 8 mg. in most adults. Emesis is not the only excitatory effect of the drug; restlessness, tremor, polypnoea, and even convulsions have occasionally been reported. There is, in addition, a central depressive action, manifest usually by

FIG. 2.—Electrocardiographic findings (third examination). A. (Time zero.) Normal E.C.G.; rate 97; P-R interval 0.16 second. B. (20 minutes.) Rapidly increasing bradycardia; rate regular, 75-50; P-R interval 0.12 second. QRS complex normal. C. (21½ minutes.) Extreme slowing and irregularity; rate 26; P-R interval 0.12 second; QRS complex normal. D. (23¼ minutes.) Regular bradycardia; rate 39; all P wave activity suppressed; idioventricular rhythm; QRS complex normal. E. (26 minutes.) Regular bradycardia; rate 52; normal P wave re-established; P-R interval 0.12 second; QRS normal. F. (30 minutes.) Normal curves; rate 71; P-R interval 0.14-0.16 second.

fatigue and somnolence after vomiting. According to Drill, central depression of vasomotor tone, causing momentary syncope, occurs in 1 to 5% of patients having the drug, and in rare cases there is fatal cardiovascular collapse. No reference to E.C.G. changes in humans has been found, but Crittenden (1932) reported cardiographic evidence of heart block and cardiac arrest in unanaesthetized animals given subcutaneous apomorphine. The wide range of variation in individual susceptibility to apomorphine has been generally stressed.

Apart from the uses to which it has been put by psychiatrists, apomorphine has few therapeutic applications. It is recommended, traditionally but with great caution, as an emetic in alcoholic intoxication and other instances of acute poisoning, and as a remedy for paroxysmal tachycardia (Finkle, 1939). Apomorphine has less often and with doubtful effect been tried as an analgesic in obstetrics, as premedication for emergency operations in delirious patients, and to reduce tremor in Parkinsonism. In experimental pharmacology it has been found useful in the evaluation of anti-emetic substances.

The apparent efficacy of apomorphine in the treatment of alcoholics depends, in part, on the production of conditioned aversion to alcohol. Psychodynamic processes such as expiation of guilt by submitting to such unpleasant treatment may also be important. There is, however, some evidence that the main action of the drug is not in effecting psychological changes in these ways, but in correcting physiological abnormalities causally underlying the alcoholism. Feldmann (1955), who has treated over 3,400 patients (not all alcoholics) with apomorphine, inclines to this last view.

Feldmann (1955) carries out preliminary physical assessment in every case, but says that apomorphine treatment given for alcoholism by his rigorous technique has "absolutely no contraindication." He and Dent, in personal communications, regard the case here reported as quite exceptional (as do we, from our much smaller experience of the method at the Atkinson Morley Hospital). In Feldmann's clinic,

apomorphine treatment has been given without mishap to cases of severe cardiovascular degeneration, including six patients with bundle-branch block. It would, however, be unfortunate if the confidence felt in such a large and well-staffed clinic was casually assumed and misapplied elsewhere.

As to the dangerous idiosyncrasy exhibited to apomorphine by our patient, it might be postulated that he possessed inherently abnormal autonomic lability. The rapid fluctuations in pupillary size following injection would support this hypothesis, as would the history of attacks of intestinal colic. On the other hand, anomalous responsiveness to other drugs was shown by the high pethidine and insulin tolerance (the latter being a common incidental finding in psychiatric patients). A year after these experiments he developed minimal but definite signs of thyrotoxicosis in the inexplicable presence of a blood cholesterol of 405 mg. per 100 ml.

Aside from such speculations, the clinical and electrocardiographic observations in this case leave no doubt that apomorphine is a potentially dangerous drug in certain individuals. Whenever it is given, the patient should be under very close observation for at least 30 minutes after each dose. It is best to start with a small dose, such as 1/30 gr. (2.2 mg.) in case of idiosyncrasy, and oxygen and restoratives should be at hand for immediate use. Malaise and restlessness after vomiting (instead of the usual nauseated drowsiness and relaxation) are danger signals. Syringes should be sterilized by boiling, since alcohol destroys apomorphine, perhaps making it more difficult to judge dosage. Finally, if any green coloration is seen in the prepared injection it should be discarded and fresh supplies obtained.

Summary

The case is described of a man of 32 who showed profound and dangerous cardiovascular collapse with therapeutic doses of apomorphine. Electrocardiographic findings following experimental administration of the drug to the same patient are described and illustrated. It is suggested that the traditional caution of pharmacologists and physicians in the use of apomorphine should not be disregarded now that the drug is finding a new and promising application to psychiatric problems.

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REFERENCES

- Borison, H. L., and Wang, S. C. (1953). *Pharmacol. Rev.*, 5, 193.
- Crittenden, P. J. (1932). *Amer. J. Physiol.*, 101, 26.
- Dent, J. Y. (1934). *Brit. J. Inebr.*, 32, 65.
- Drill, V. A. (1954). *Pharmacology in Medicine*, Chap. 17, p. 8; Chap. 45, p. 11.
- Feldmann, H. (1952). *Praxis*, 41, 871.
- (1955). *Brit. J. Addict.*, 52, 7.
- Finkle, G. E. (1939). *J. Kans. med. Soc.*, 40, 372.
- Goodman, L. S., and Gilman, A. (1955). *Pharmacological Basis of Therapeutics*, 2nd ed., p. 1064. New York.
- Sumwalt, M. (1943). *Publ. Hlth Rep. Wash.*, Suppl. No. 165.

In his report for the second quarter of 1956 the city analyst of Birmingham, Mr. H. H. BAGNALL, reports that "an ointment and medicine prescribed by another of the pseudo-medical geniuses with whom the country appears to be infested were, as usual, the cheap common articles that one has come to expect in such cases." The patient treated by this person (at 3 guineas for a consultation and 13s. 6d. a month for medicines) was said to be suffering from spinal injury and gravel on the kidney. The ointment was kaolin poultice and the medicine a dilute laxative syrup. The cost of the two specimens would be less than 1s., reports Mr. Bagnall, and he remarks on "the apparent ease with which effrontery of this kind is able to impose on a certain section of the population."