BENZEDRINE IN SEA-SICKNESS

BY

JOHN HILL, M.D.

Surgeon, R.M.S. Aquitania

The introduction of benzedrine (beta-phenylisopropylamine) sulphate, with a powerful action more or less sympathicotropic, has naturally suggested its use in sea-sickness, in which there is commonly a predominant vagotonia. The action of the drug is threefold: (1) stimulant to the central nervous system, including the higher cerebral centres; hence it has been used with benefit in narcolepsy and post-encephalitic Parkinsonism, as also in various conditions associated with fatigue, depression, and lethargy; (2) pressor to the vasomotor system, an effect which steadily diminishes with repetition, and may finally disappear; (3) it relaxes smooth muscle in the gastro-intestinal tract, especially in conditions of spasm, whether due to reflex, functional, or organic causes; this property has been utilized to facilitate x-ray investigation of suspected ulcer and other conditions associated with spasm. Contraindications arise from three sources: excitability, nervousness, insomnia; hypertension and coronary or other established heart disease; conditions of gastric or intestinal atony.

Tainter (1933) describes benzedrine as "pseudo-sympathicotropic," the results from its use not being precisely those of sympathetic stimulation. Except in large doses it has little effect on the pupil. Peoples and Guttman (1936) found very slight changes in blood sugar and gastro-intestinal activity. Its action on the stomach and intestine has been fully investigated by Myerson and Ritvo (1936), who found that, although it abolished spasm, it had very little effect on peristalsis; unlike ephedrine, as investigated by Van Liere and others (1936), it relaxed the sphincter and allowed the stomach to empty more rapidly than normally. But their observations seem to have been confined to cases of gastro-intestinal spasm, in which benzedrine was used as an aid to x-ray investigation. That the action on the stomach is at least in part local is suggested by their statement that the effects reach a maximum in fifteen to thirty minutes and begin to diminish in an hour.

Effect of Benzedrine in Health

Twenty adult volunteers—eleven men (average age 35.2) and nine women (average age 37.5)—were given doses of 10 or 20 mg. In some it was repeated after three days or more. Changes in (a) blood pressure, (b) pulse rate, and (c) subjective sensations were recorded at intervals varying from one hour to twenty-four hours afterwards. All cases here recorded were under observation at approximately the same time of day, so that physiological changes due to such causes as food and exercise might be reckoned with and discounted in estimating the final results.

BLOOD PRESSURE

The most consistent change was a rise of blood pressure. The effects of benzedrine are so variable that there has hitherto been some difference of opinion as to the blood-pressure changes which it produces. Myerson (1936) found no rise of pressure after doses of 10 mg. Peoples and Guttman (1936) considered the systolic to be more affected than the diastolic. In the present series the systolic pressure rose in every case after 20 mg., and in 80 per cent. after 10 mg. Absence of diastolic rise was seen in those who showed no increase of systolic pressure. In two others there was no change in diastolic pressure until eleven hours after

the dose, which was 10 mg. in one case and 20 mg. in the other. (It is probably coincidental, but worth noting, that these exceptions were all women.) A definite rise of diastolic pressure was found in all other cases. On the average it was indeed relatively greater than the systolic increase, but occurred later and was longer sustained. The pulse pressure was raised for the first two to two and a half hours, after which it fell and remained below normal during most of the period of observation.

A systolic pressure originally low showed a greater tendency to rise than one which was at first comparatively high; but there was always some rise. To a less extent this seemed true of diastolic pressure; but a high diastolic pressure tended to fall. The rise in pulse pressure was greatest when the first reading was low. The increase in mean readings after 20 mg. (both systolic and diastolic) was surprisingly little more than it was after 10 mg. This suggests that (a) individual sensitivity varies widely, or (b) the effect is reduced by repetition. Both factors are probably operative, but a third possibility is introduced by the fact that (c) it is in states of extreme fatigue that benzedrine usually produces its most dramatic results. This observation should be correlated with the greater increase in conditions of low blood pressure. From the fact that increased arterial pressure was usually accompanied by flushing of the skin it is reasonable to suppose that the essential change is constriction of the splanchnic vessels. A difference much more striking than that dependent upon dosage was the greater susceptibility of males as compared with females, particularly to small doses (10 mg.). It is true that in so few as twenty cases there is room for the confusing irruption of coincidence. The same criticism may well be levelled against all the foregoing observations, which must therefore be accepted with equal reservations.

PULSE RATE

By the end of an hour the resting pulse rate had increased in seven cases, with a mean rise of 9.4 per cent. In five cases it was unchanged. In the remaining eight it was slowed, with a mean retardation of 12.6 per cent. Cases with no rise in pulse rate after an hour showed a systolic increase which was slightly less and a diastolic increase considerably more than the average for the whole group. The action of a carotid sinus reflex may be presumed. From the end of the second hour some degree of quickening of the pulse was the rule.

SUBJECTIVE EFFECTS

1. The commonest group of changes reported were gastro-intestinal. Impaired appetite, constipation, and various forms of mild abdominal discomfort occurred in ten cases (50 per cent.). Recovery was complete within twenty-four hours. It is noteworthy that only two out of that number experienced any degree of euphoria.

2. Eight patients (40 per cent.) felt distinctly exhilarated, and this effect was much more pronounced than any of those in the first group. Stimulation of the higher centres was shown in unwonted talkativeness and vivacity. Five of the eight also commented on increased physical energy.

3. In seven others (35 per cent.) there was unmistakable stimulation, but the effect was decidedly disagreeable—flushing and sweating on slight exertion, and sometimes a disconcerting tremulousness. Three patients described all the bodily changes of fear without the corresponding emotion.

4. Six (30 per cent.) complained of insomnia, even twelve hours after taking the drug. Four of these had previously enjoyed pleasant stimulation.

5. Other undesirable effects were: disturbed salivary secretion, thirst, unpleasant taste in the mouth (25 per cent.); cardiac effects, palpitation and evanescent precordial discomfort (20 per cent.). Three patients (15 per cent.) complained of subsequent fatigue and depression, without insomnia; one of these had been slightly stimulated mentally, the other two had experienced only tremor and unpleasant excitement.

6. Three patients felt no change after 10 mg.

EFFECT ON MOOD

The effect of benzedrine on mood varies from time to time in the same person. Conditions of greatest fatigue seem to show the most striking excitation. Wilbur and others (1937) have found that psychoneurotics "who are anxious, highly nervous, and apparently stimulated had their previous condition exaggerated." Stimulation is not always pleasant.

Effects of Benzedrine in Sea-sickness

For various reasons it is not feasible to make accurate records of blood pressure in the sea-sick. The observations here described were therefore confined to changes in pulse rate, the patients' general condition, and the various signs and symptoms of sea-sickness.

Price (1933) has described as one of the clinical signs of low blood pressure "increase in the cardiac rate of more than 10 per minute when the individual assumes the upright posture after lying down." This rule had to be modified according to the limitations imposed by fully developed sea-sickness, the victims of which show a not unnatural reluctance to stand up for any such purpose. The pulse was counted with the patient first recumbent, then sitting up in bed. Ignoring the brief acceleration occasioned by the effort of rising, which ends usually in from 5 to 10 seconds, one finds that the average pulse rate in health increases by roughly 10 per cent. In proportion as the increase in rate exceeds this figure, systolic pressure and pulse pressure are likely to be lower than normal.

For the purposes of this analysis one hundred cases of sea-sickness have been examined. Except in so far as conditions of hypertension, cardiac disease, and any unusual degree of excitability are contraindications to the use of benzedrine, these cases were taken consecutively as they presented themselves, and were not in any other sense selected. As it takes some time to collect data of one hundred sea-sick cases aboard a liner justly famed for her stability, the period of the investigation has allowed of some coming under observation on a second occasion, when previous knowledge of their response to disturbing movement proved of the greatest value and threw light on the possibilities of prevention.

Age and Sex Incidence

The sea-sick group comprised eighty-two women and eighteen men. Their average ages were 36.6 and 33.2 respectively, thus closely approximating to those of the normal cases already described. The decennial age group 25-35 included twenty-seven, and thirty-two were between 35 and 45. That is to say, fifty-nine of the hundred were between 25 and 45, which corresponds to the usual distribution.

The ratio of eighty-two women to eighteen men should not be taken as a true index of the sex incidence of sea-sickness. By one of the oddities of human nature men will often conceal it if they can.

Classification of Results

The classification of results was necessarily somewhat arbitrary. They were grouped in three categories: (1) satisfactory results, (2) doubtful results, (3) failures.

(1) *Satisfactory results* were obtained in thirty-nine cases, in all of which the improvement was unequivocal, every likely fallacy having been carefully excluded. Those responding to benzedrine alone showed a mean pulse rate of 69 recumbent, increasing by 18 per cent. on sitting up; in the group of failures the corresponding figures were

77 and 11 per cent.—that is to say, a tendency to vagotonia predominated in the first group. It is doubtless in the vagotonic variety of sea-sickness that benzedrine finds its greatest usefulness. In its mode of onset this sickness reproduces in slow motion the prologue to an attack of syncope, especially that attributed by Gilchrist (1937) to a hypersensitive carotid sinus: an uneasy sense of helpless weakness, a light-headed feeling of dizziness, cold sweats, and vague abdominal unrest, accompanied by slowing of the heart-beat and an abrupt fall of vasomotor tone. The clinical signs point to a disturbance of the stabilizing control of the circulation whereby the effects of low arterial pressure are neutralized by tachycardia, and vice versa. Hence the predilection of the patient for the horizontal position.

(2) *Doubtful cases* numbered forty. This group comprised not only those of whom it was doubtful if they had improved but also those concerning whom there was any room for doubt as to how improvement had been brought about. The following factors were taken into account:

(a) *Age of Patient*.—Experience shows that sea-sick patients in their teens usually recover, with or without treatment, sooner than those ten or twenty years older. All patients under 20 have therefore been relegated to the "doubtful" class, whatever spectacular results ensued. It may be mentioned here that for young children even very small doses of benzedrine seem to be unsuitable, while in the elderly its pressor effect is a definite contraindication.

(b) *Duration of the Attack*.—Another of the lessons of experience is that natural recovery occurs in the majority of cases after about the third day. This may be due to adaptation to the movement, but on the other hand it is exceptional for consistently bad weather to continue for more than three days. Cases with a history of three days or more were therefore likewise classed as "doubtful."

(c) Any evidence of spontaneous improvement before treatment was begun was also assumed to prove that any benefit observed might be due to a natural tendency to recovery.

(d) The vagaries of Atlantic weather further confused the issue in some cases. The ordinarily sea-sick person is apt to be indifferent to minor changes of weather, but there are times when the improvement must be manifest to all but the moribund.

(e) Undesirable side-effects of the drug, such as abdominal discomfort, thirst, flushing, sweating, palpitation, and insomnia, sometimes spoiled an otherwise satisfactory result.

(f) In some cases recovery was only partial, as, for example, when headache and vertigo disappeared but nausea remained. At other times benzedrine seemed to produce or aggravate headache. Occasionally vomiting stopped but a sense of nausea persisted.

(g) The influence of other drugs previously taken by the patient, and still likely to be capable of producing some effect, was a further source of confusion which made some results appear very doubtful indeed. This difficulty applied particularly to proprietary and other remedies of unknown composition.

(h) Ailments other than sea-sickness were present in some cases; such were asthma (which may be a vagotonic manifestation), pre-existing gastric disorder, and the morning sickness of early pregnancy.

Finally, intrusive psychological factors had to be reckoned with. It does not require much experience of sea-sickness to recognize the type of patient who is fatalistically expectant and whose expectations are therefore seldom wrong. These cases present a problem which is more than therapeutic in the ordinary sense. (Certain cases in the "doubtful" category may have been partial failures because one has neglected to pay due attention to the ever-present psychological factor; but the primary aim of the investigation was the action of benzedrine.)

Another difficulty which is mainly psychological arises with patients unable to converse in English. Even with the aid of an accomplished interpreter it is usually impossible to evaluate changes in mood and general sense of well-being. Psychological influences may be helpful rather than harmful, but such cases also have had to be excluded from records of successful benzedrine treatment. Instances of these are the patient who has on a previous voyage derived benefit from benzedrine and swallows it with an access of confidence, and the other who, expecting some sort of sedative, quietly turns over and falls asleep.

3. *Failures.*—There is more to be learned from a critical study of the causes of failure than from the complacent contemplation of success. Analysis of the twenty-one cases which failed to respond satisfactorily to benzedrine yields the following conclusions:

(i) Most cases of sea-sickness being amphotonic—that is, combining both vagotonic and sympathicotonic elements—benzedrine alone, even in the presence of definite signs of vagotonia, is apt to swing the balance towards the other extreme. It is best given in suitable combination.

(ii) In some cases of extreme vagotonia, accompanied probably by high sympathetic threshold, the dosage (usually 10 to 20 mg.) was apparently not adequate. In others there was definite improvement which lasted but two or three hours, and might well have been maintained had the dose been repeated.

(iii) Insufficient attention was paid to the influence of associated disorders, chief among which in this series was constipation, a condition interfering very definitely with the process of adaptation. Contrary to the findings of Myerson and Ritvo (1936)—in different conditions—most of the cases at present under review appeared to have peristaltic activity either suppressed or delayed.

(iv) Resistance to the effects of benzedrine was encountered in only one case, that of a woman of 50. Vomiting stopped after 20 mg., but no other objective or subjective changes were apparent; nausea and vertigo persisted. These symptoms finally disappeared after two further doses of 30 mg. each, when the first complaint of headache was recorded and there was slight interference with sleep. Twelve hours later no evidence of any benzedrine action could be found, and the patient appeared to have made a spontaneous recovery. It is fortunate, in dealing with such cases, that even if the effects of benzedrine are wholly bad they are not long continued. From laboratory investigations reported through the courtesy of the manufacturers, Messrs. Smith, Kline, and French (1937), it appears that the drug is fairly readily destroyed in the body.

(v) In ten cases the results were unsatisfactory, but none of the above causes supplied any explanation. The average age of these cases was 46, exactly ten years more than the average for the series. Although the circulatory changes could not be distinguished clinically from those of the remainder, it may be that after 45 there is a tendency for undesirable pressor or other effects to be produced.

General Commentary

A study of the data provided by the cases here described yields two interesting generalizations regarding the action of benzedrine. (1) When euphoria has resulted the subsequent depression is insignificant in degree and duration compared with the preceding exaltation; probably the reaction coincides with the period of sleep. (2) The effects appear very rapidly, but are long-continued, as if a succession of interdependent physiological changes had been initiated by the action of the drug. The rapid effect on gastric spasm, suggesting a local action, is obviously of great value in sea-sickness. It is certainly remarkable how seldom benzedrine is vomited, even by patients who have openly despaired of being able to retain it.

Enthusiasm for a new drug must be tempered with sound scepticism and the results scrutinized with care. These conditions granted, there is still reliable evidence that benzedrine is a valuable aid in the treatment of certain types of sea-sickness. It is not a rival to old-established methods, but a useful ally. The effect is greater and more lasting when benzedrine is combined with other remedies, because cases of sea-sickness seldom fit conveniently into the twin pigeon-holes of vagotonia and sympathicotonia: the majority show features characteristic of each. Further, the effect is augmented by the vagus-inhibiting properties of belladonna *et hoc genus omne*, while in the presence of concomitant sympathetic activity bromides or barbiturates prevent unpleasant restlessness and insomnia without, apparently, interfering with the gastro-intestinal or circulatory effects of benzedrine.

For the suppression of sympathetic activity, especially that associated with dread of sea-sickness, bromides rank high. Combined with chloral hydrate they produce results not yet surpassed by any of the more elegant products of the modern pharmaceutical laboratory. An effective method of administration, favouring retention and absorption, is:

Sodium bromide	...	...	...	60 grains
Chloral hydrate	...	...	...	30 grains
Spirit of chloroform	...	...	...	q.s.
Water to one ounce.				

Of this the dose is one teaspoonful every half-hour. Before there is any possibility of overdosage the patient drops off to sleep and thereby lengthens the intervals. Coincident vagal activity may be controlled by belladonna or counteracted by the sympathicotonic action of benzedrine, of which 10 or 20 mg. may be incorporated in the first ounce of mixture. Thereafter the dosage and intervals should be adjusted to meet the needs of the case. Benzedrine is best omitted in the late afternoon or evening, as its stimulant effect is usually prolonged; even 60 grains of bromide will sometimes fail to prevent insomnia. The slow elimination of bromides is sometimes quoted as a drawback to their use. But in the not infrequent case of sea-sickness where unpleasant after-effects are apt to continue for a time on land this objection may be discounted. Even in protracted sea-sickness it is exceedingly unlikely for bromism to develop. If the patient fails to respond to the treatment suggested above, the case should be carefully reviewed before any other sedative drugs are given.

Advantages and Disadvantages of Barbiturates

The main advantages of barbiturates are that they are more palatable and convenient, and more rapidly excreted. The latter property is advantageous in short crossings where only a brief action is desired. Those members of the group which find favour as hypnotics are eliminated more rapidly than those used as general nervous sedatives. The action of sodium amytal, for example, is usually too evanescent for the ordinary case of sea-sickness. The same is true of its isomer, nembutal, and of evipan and pentothal. A more prolonged effect follows the use of dial. Luminal is excreted still more slowly. Elimination of barbitone itself (veronal) is slower than that of any of those mentioned. It is not free from the danger of cumulative action. In common with most, if not all, of its derivatives barbitone in repeated doses is apt to produce toxic effects on liver and kidneys. In view of the liability to ketosis in sea-sickness this is a danger to be carefully considered. When barbiturates are given for the control of motor excitability possibly aggravated by benze-

drine it is well to remember that this action is more marked (Hale-White, 1935) in those which have the ethyl group, C_2H_5 , replaced by phenyl, C_6H_5 ; examples of this molecular construction are luminal, prominal, and nirvanol. It might be desirable in certain cases to combine a quick-acting sedative with one more slowly absorbed but having a more prolonged action. In this connexion it should be recalled that luminal sodium is incompatible with chloral hydrate or any salt of ammonium.

Two disadvantages of barbiturates are (1) the occasional occurrence of idiosyncrasy, and (2) the narrow margin of safety with full doses. Mutch (1934) gives the following ratio M.L.D./M.Th.D.: for luminal, 1.3; barbitone, 1.6; soneryl, nembutal, and phanodorm, all 2.4; dial, 2.5; evipan, 5.

Addiction to Benzedrine

Recent publicity has given prominence to the fear that some may learn to partake too freely of benzedrine. But Guttman and Sargent (1937) and Wilbur and others (1937) have shown that the ecstasies fade with repetition. It is the unstable neurotics who need to be kept from drugs of addiction. These unfortunates, being at discord with life, crave one thing above all others—oblivion. The fact that benzedrine robs them of sleep will quickly make it unpopular.

Summary

1. The clinical effects of benzedrine (beta-phenylisopropylamine) sulphate on twenty adults in normal health have been studied, with special reference to changes in pulse rate, blood pressure, and subjective sensations.

2. One hundred cases of sea-sickness treated with benzedrine, alone or combined, are classified according to results.

3. Benzedrine has great possibilities of usefulness in certain cases of sea-sickness in which there are signs of excessive vagus activity.

My thanks are due to Sister Hilda M. Smith for much valuable help in collecting data for this paper.

REFERENCES

- Gilchrist, A. R. (1937). *British Medical Journal*, 1, 204.
 Guttman, E., and Sargent, W. (1937). *Ibid.*, 1, 1013.
 Hale-White, W. (1935). *Materia Medica*, twenty-second edition, London.
 Mutch, N. (1934). *British Medical Journal*, 1, 321 (quoted by Martindale, *Extra Pharmacopoeia*, 1936).
 Myerson, A. (1936). *Arch. Neurol. Psychiat.*, 36, 816.
 — and Ritvo, M. (1936). *J. Amer. med. Ass.*, 107, 24.
 Peoples, S. A., and Guttman, E. (1936). *Lancet*, 1, 1107.
 Price, F. W. (1933). *Practice of Medicine*, fourth edition, p. 1043, London.
 Smith, Kline, and French Laboratories, Philadelphia, Pa., U.S.A. Personal communication (1937).
 Tainter, M. L. (1933). *Arch. internat. Pharm.*, 46, 192.
 Van Lier, E. J., Lough, D. H., and Sleeth, C. K. (1936). *J. Amer. med. Ass.*, 106, 535.
 Wilbur, D. L., MacLean, A. R., and Allen, E. V. (1937). *Ibid.*, 109, 549.

G. Ferrari (*Rif. med.*, August 14, 1937) states that though the risks of pneumoperitoneum are almost negligible provided proper precautions are taken, a number of serious cases have been recorded in which infection of the peritoneum, haemorrhage, puncture of the intestine, emphysema, and embolism have taken place. He records one case of a man, aged 31, who suffered from bronchiectasis complicated by haemoptysis. Pneumoperitoneum was carried out as a haemostatic measure, and the haemorrhage, which had been refractory to drug treatment, ceased. Four days later, however, the patient developed lobar pneumonia complicated by a pulmonary abscess.

A CRITICAL SURVEY OF 349 CASES OF BREECH DELIVERY*

BY

C. H. G. MACAFEE, M.B., F.R.C.S.Eng., F.R.C.S.I.,
F.C.O.G.

AND

H. I. McCLURE, M.B., B.Sc., F.R.C.S.Ed., M.C.O.G.

In reading the published results of breech delivery from a variety of sources we have been struck with the marked disparity in the foetal mortality rates. The recorded figures are so much at variance and some of them are so alarming that we decided to investigate a series of consecutive breech deliveries occurring in the Royal Maternity Hospital, Belfast, during the years 1932–6. This paper is based on a review of 349 consecutive cases. These cases represent a frequency of 6.03 per cent. of all deliveries occurring in the hospital over the same period. In reviewing 638 of our own private cases we found the frequency to be 2.5 per cent. Of the 349 cases 305 were primary breech presentations. Three hundred and thirty-two mothers were delivered of 349 babies—that is, there were seventeen cases of twins in which each child was delivered as a breech. The mothers have been classified into four groups, as shown in Table I.

TABLE I.—Classification of the 332 Cases

					Primigravidae	Multigravidae
Ante-natal	..	..	..	..	67	135
Emergency	..	..	..	..	48	82
					<hr/> 115	<hr/> 217

With the exception of three cases in which Caesarean section was performed delivery was effected by the classical methods. We wish, however, to draw attention to the fact that the deliveries were carried out by various members of our resident medical staff, and do not represent the results which might be obtained in a series of cases dealt with by an individual obstetrician.

In assessing the results of breech delivery, in our opinion undue stress has been laid on the so-called “complicated breech.” In this paper we define a complicated breech as one where there exists an additional risk to the life of the foetus—for example, placenta praevia, contracted pelvis, or marked prematurity. Provided that adequate management is available we do not regard extension of the limbs as a complication. Extension of the legs, in our experience, is the rule in primigravidae. We at once admit that extension of the limbs adds to the difficulties of delivery, especially in a primigravida; but a mother must be a primigravida at some stage in her career, and therefore the term “breech with extended legs in a primigravida” cannot, in our opinion, be regarded as a complicated breech. Published statistics of foetal mortality in breech presentation vary from 30 per cent. to 8.6 per cent. in primigravidae—for example, Gibberd (1931) gives a gross mortality of 30 per cent. and a corrected mortality of 28 per cent. The gross uncorrected foetal mortality in our series was as follows:

TABLE II.—Gross Foetal Mortality

	Babies Born	Babies Born Dead	Percentage
All cases	349	118	33.8
Primigravidae	118	28	23.72
Multigravidae	231	90	38.96

* Read in the Section of Obstetrics and Gynaecology at the Annual Meeting of the British Medical Association, Belfast, 1937.