Special Articles

PREVENTION OF SEASICKNESS BY DRUGS *

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THE work described here was undertaken with the object of finding a method of preventing seasickness in troops who are about to land on a hostile shore. In the Navy seasickness is overcome or minimised by adaptation to the motion of the sea; in Army personnel travelling to ports already in friendly hands there is ample opportunity for recovery from the effect of the voyage; but when a landing has to be made in the face of resistance it is easy to see that seasickness might on occasion become a handicap. The seriousness of the problem is probably not so great as might at first be thought, for landings on beaches are not likely to be attempted in a rough sea and in any case the experience of the Navy shows that the excitement of an action tends to banish seasickness. Nevertheless, it is possible that an unfortunate combination of circumstances might necessitate landing seasick troops. Under such conditions there might be some loss of efficiency. It therefore seemed worth while to attempt to find a means of prevention.

Numerous drugs are recommended for the prevention of seasickness. Such recommendations are usually based on somewhat unsubstantial theories, backed by clinical trials under conditions which did not permit of scientific control. The peace-time ship's surgeon is not in a position to treat his patients as experimental subjects. Consequently the only value of the numerous papers which have been published on seasickness is that they provide suggestions as to which drugs are worth a trial. The drugs suggested in this way seem to fall into two main groups: general sedatives and drugs of the belladonna group; in addition 'Benzedrine' (amphetamine) was recommended in the years before the war.

METHODS

In designing these experiments two variables had to be controlled or allowed for: the variability of the causal motion and the variability of the subject's susceptibility. The first might be overcome by a machine capable of reproducing the motion of the sea. An attempt was made to use a swing (to be described elsewhere) for this purpose. Although this swing successfully reproduced the symptoms of seasickness in a proportion of men, it did not enable one to predict with any exactitude which men would be sick on the sea. There was, therefore, no assurance that swing sickness is identical with seasickness, and this implied that any drug found to be successful on the swing would have to be tried again on the sea. For this reason it seemed to us that time would be saved by conducting all trials on the sea from the beginning. Variations in the degree of motion had to be accepted as inevitable, and allowed for by the provision of an approximately equal number of control subjects on all occasions. A further disadvantage which the inconstancy of the sea imposed was that it made comparisons between drugs difficult unless they had been used on the same trips. Finally, dependence on so fickle an element for experimental conditions imposed a considerable strain on the patience of the investigator. Chronic sufferers from seasickness may be astonished to learn that on most days throughout the year an obstinate and baffling calm haunts the waters round this island.

It was only possible to overcome the second difficulty—the great variations in individual susceptibility—by the use of sufficiently large numbers of subjects in treated and control groups, since it was not practicable to obtain the same men for repeated trials. If the treated and control groups were sufficiently large it would be justifiable to assume that each contained its fair share of men of every grade of susceptibility, from the immune to the most susceptible, and that the rate of sickness in the control group was therefore a good indication of what the rate of sickness would have been in the treated group, if no drug had been given. The effects of suggestion were counteracted in the subjects by the use of dummy tablets, and in the observers by leaving ashore the list which recorded which remedy each man had been given.

Accordingly, the following method was worked out and used in all the trials. Whenever there was a prospect of sufficiently rough weather a party of about 70 soldiers was embarked on two motor minesweepers or trawlers. One hour before embarkation each man received either a dummy tablet or one of the drugs being tested. Inspection of the mouth was carried out as a routine in order to discourage attempts to dispose of the tablets by other means than swallowing them. On each trip from 2 to 5 drugs were tested. In the earlier trips, the men were first divided into approximately equal groups, and each group was given either one of the drugs or a dummy tablet, each group being subsequently divided equally between the two ships. With this method of distribution, it seemed possible that groups of friends might receive the same drug and subsequently remain together in a part of the ship exposed to a greater or less degree of motion than the ship as a whole. This would influence the results and this practice was therefore discarded in favour of distributing drugs and dummy tablets in strict rotation.

The trips were of 2 to 6 hours' duration, the return to port being made when up to 40% of the men on board were affected. The men brought the usual Army haversack rations and ate them as soon as they got on board. They usually remained on deck and their movements were not restricted. One observer sailed in each ship. He noted the time of onset of rough water and of re-entering smooth water. During the trip he moved around the ship, talking to the men individually and observing the onset of symptoms. On returning to harbour every man was asked if he had had any symptoms; in this way occasional cases of vomiting or nausea which had gone undetected at the time were brought to light. Since the ships were small very few cases of sickness can have escaped observation.

On the whole the men enjoyed the trips. As far as could be judged from their remarks there was little apprehension of sickness before the trip started, and there were few instances of sickness unless the sea was at least moderately rough. In an explanatory talk before each trip the men were told that the object of the trip was to find which was the best of several seasickness remedies and it was also pointed out that the trip was to serve as an exercise in using their equipment at sea against a possible enemy air attack. The men's opinion of the remedies varied; some men thought that the pills had been given to them with the idea of making them more prone to sickness, and others that the remedies were very effective. It was interesting to note that some of the men believed firmly in the efficacy of the dummy tablets.

RESULTS

Table I shows the results obtained with all the drugs tested. As used in this table the term "sick" includes men who were nauseated as well as men who actually vomited. The diagnosis of nausea rested mainly on the man's own statement, but could often be confirmed by a glance at his face. On short trips such as these, nausea appears to be as incapacitating as vomiting; the fact that the majority of those nauseated had vomited by the end of the trip suggests that vomiting may be regarded as an incidental symptom likely to occur sooner or later in every nauseated subject. It is of course true that on long voyages vomiting is likely to become a disadvantage per se, on account of the loss of food and fluids and consequent exhaustion.

The final column in table I, headed "susceptibles protected %," is intended to be an estimate of the number whom the drug saved from sickness, expressed as a percentage of the total number who would have been sick if no drug had been given. Thus in the trips in which the effect of giving 0·6 mg. of hyoscine was determined 47% of the controls were sick, but only 20% of those treated with hyoscine. It has been assumed, therefore, that 27% (i.e., 47%—20%) of all the men

* This work was undertaken on behalf of the Medical Research Council with the collaboration of the Directors General of the three Medical Services.

receiving hyoscine were protected, and that 57% (i.e., $\frac{27}{47} \times 100$) of those who would otherwise have been sick were afforded protection. The figures in this final column have been obtained by the formula :

$$\frac{(\%\text{ sick in control group}) - (\%\text{ sick in treated group})}{(\%\text{ sick in control group})} \times 100$$

This formula enables a rough comparison to be made between drugs used on different trips, but it must be remembered that such a comparison would be invalidated if it were shown that the efficacy of a drug (expressed as "susceptibles protected %") varied with the roughness of the sea (estimated by the percentage sick in the control group). These figures should be taken as an indication of the order of efficacy of the drug, rather than as an exact statement.

Some proprietary remedies.—Three of the more popular proprietary remedies (remedies A, B, C_1 and C_2 of table I) were chosen for investigation as being fairly representative of the large assortment available to the traveller. With two of the remedies (A and B) there was no significant difference between the sickness-rates in the treated and control groups, although the directions

TABLE I

Drug	Trips	No. of controls	Sick (%)	No. of treated	Sick (%)	Susceptibles protected (%)
Remedy A *	1–7	83	22	78	22	0
Remedy B *	1–7	83	22	75	25	0
Remedy C_1 *	1–10	141	34	129	16	53
Remedy C_2 *	13–17	86	38	91	37	3
Methedrine 8 mg.	1–7	83	22	77	22	0
Phenobarbitone gr. 1	6–10	84	39	78	32	18
Hexobarbitone gr. 10	4 & 5	18	61	14	64	0
Sodium hydantoinate 0·2 g.	27	16	38	14	35	8
d-Hyoscyamine 2 mg.	23 & 26	38	55	34	41	25
Homatropine 2 mg.	23 & 26	38	55	32	41	25
Atropine 1 mg.	13–17	86	38	88	23	40
l-Hyoscyamine 0·96 mg.	18–22	88	51	85	31	40
Hyoscine 0·6 mg.	13–23, and 26	212	47	218	20	57
Hyoscine 1·2 mg.	18–22	88	51	84	14	73

* Stated composition of proprietary remedies :—

Remedy A { Chlorbutol (chloretone) .. .. 0·52 g. ; Caffeine .. .. 0·13 g.

Remedy B { Dimethyl propanalester of tropic acid 0·4 g. ; Dioxydiethylpiperidine .. .. 0·2 g.

Remedy C_1 and C_2 { Hyoscyamine camph. .. .. 0·8 mg. ; Hyoscine camph. .. .. .. 0·2 mg. ; Sod. bicarb. .. .. .. 400·0 mg.

of the manufacturers were followed. The third proprietary remedy was found to be effective when first tested (C_1), but a second supply (C_2) from the makers was found to be without effect (table II). Biological tests on samples of this second batch suggested that its potency was less than indicated on the label, but it was not possible to carry out similar tests on samples from the first batch.

Miscellaneous drugs.—Other drugs found to be without appreciable effect were methedrine, 8 mg. (pharmacologically similar to 10 mg. benzedrine), sodium hydantoinate, 0·2 g., and the barbiturates hexobarbitone, gr. 10 and phenobarbitone, gr. 1.

In the present investigation the use of a drug was stopped as soon as it became evident that other drugs were more effective. In some cases, therefore, the number of subjects used was too few for a definite statement that the drug had no effect on seasickness.

Drugs of the belladonna group.—Atropine, hyoscyamine, and hyoscine were shown to have a significant effect on seasickness. All these drugs belong to the belladonna group. The figures given in table I suggest that hyoscine, even in the smaller dose used (0·6 mg.), caused a greater reduction in seasickness than did any other drug. Hyoscine (0·6 mg.) was used in the same series of trips as atropine and *l*-hyoscyamine, and a direct comparison of these drugs with hyoscine is therefore possible (table IIIA and B).

Though atropine and *l*-hyoscyamine seem to be less effective than hyoscine the difference is not statistically significant even if the combined figures for the two drugs are compared with those for hyoscine (0·6 mg.) on trips

TABLE II

Drug	Trips	Total men	Nauseated	Vomited	Total affected	Difference in % affected and standard error	Susceptibles protected (%)
Dummy tablets	1–10	141	8 (6%)	40 (28%)	48 (34%)		
Remedy C_1		129	5 (4%)	16 (12%	21(16%)	18 ±5·15	53
Dummy tablets	13–17	86	2 (2%)	31 (36%)	33 (38%)	..	..
Remedy C_2		91	2 (2%)	32 (35%)	34 (37%)	..	0

13–22 (difference = 6 ± 4·5). The larger dose of hyoscine (1·2 mg.) gave consistently better results than *l*-hyoscyamine on each of 5 trips (18–22) and the difference between the percentages affected is statistically significant (17 ± 6·4). Atropine, being used in different trips, cannot be directly compared.

It will be seen from table I that atropine (1·0 mg.) and *l*-hyoscyamine (0·96 mg.) appear to be of the same order of efficacy. It might be thought from this that, since 1·0 mg. of atropine contains only half this quantity of *l*-hyoscyamine, the other isomer (*d*-hyoscyamine) was exerting an effect. It is doubtful, however, whether the evidence will bear this interpretation since *l*-hyoscyamine and atropine were not used in the same trips. Moreover, some direct evidence on this point is available in that it was shown, although only in a small number of subjects, that *d*-hyoscyamine in doses of 2 mg. had no very striking effect (table IIIC). It is unlikely, therefore, that the 0·5 mg. of this substance, which was present in the dose of atropine used, could have had a detectable effect.

From table IV it will be seen that the effectiveness of hyoscine (0·6 mg.) as a seasickness remedy is firmly established. Table IIIA suggests that 1·2 mg. is even more effective than 0·6 mg., though the difference is not statistically significant (10 ± 5·9). Before recommending hyoscine as the most successful remedy of the series tried, however, it is necessary to consider the possibility of unwelcome side-effects.

Side-effects of hyoscine.—At sea the only unpleasant side-effect noticed with the use of the larger dose of hyoscine was the occasional complaint that dryness of the mouth made mastication difficult. The men were not drowsy and did not complain of eye symptoms. For military purposes, however, this was not considered adequate evidence of the absence of side-effects. Major

TABLE III

Drug	Trips	Total men	Nauseated	Vomited	Total affected	Difference in % affected and standard error	Susceptibles protected (%)
A							
Dummy tablets	18–22	88	5(6%)	40(45%)	45(51%)	..	..
Hyoscine (1·2 mg.)		84	3(4%)	9(10%)	12(14%)	37 ±6·6	73
Hyoscine (0·6 mg.)		88	6(7%)	15(17%)	21(24%)	27 ±7·0	53
l-Hyoscyamine (0·96 mg.)		85	3(4%)	23(27%)	26(31%)	20 ±7·3	39
B							
Dummy tablets	13–17	86	2(2%)	31(36%)	33(38%)	..	..
Atropine (1 mg.)		88	7(8%)	13(15%)	20(23%)	15 ±6·6	40
Hyoscine (0·6 mg.)		94	7(7%)	11(12%)	18(19%)	19 ±6·9	50
C							
Dummy tablets	23 & 26	38	2(5%)	19(50%)	21(55%)	..	..
Hyoscine (0·6 mg.)		35	0	5(14%)	5(14%)	41 ± 10·0	75
d-Hyoscyamine (2·0 mg.)		34	1(3%)	13(38%)	14(41%)	14 ± 11·7	25
Homatropine (2·0 mg.)		32	3(10%	10(31%)	13(41%)	14 ± 11·9	25

C. Wilson, RAMC, therefore, made observations on the effect of hyoscine and *l*-hyoscyamine on men carrying out a strenuous military exercise. His observations were made some two hours after the ingestion of the drugs in order that their effects should be at a maximum. He found that although hyoscine (1·2 mg.) and *l*-hyoscyamine (0·96 mg.) caused more unpleasant dryness of the mouth after severe exercise than appeared in control subjects, the drugs had no obvious effect on physical performance, ability to shoot, or on near vision. Our personal experience was that the mouth dryness caused by hyoscine (1·2 mg.) was unpleasant but preferable to seasickness, whereas the dryness caused by hyoscine (0·6 mg.) was only just detectable.

TABLE IV

Drug	Trips	Total men	Nauseated	Vomited	Total affected	Difference in % affected and standard error	Susceptibles protected (%)
Dummy tablets	13–23 & 26	212	9(4%)	90 (42·5%)	99 (46·5%)	..	..
Hyoscine (0·6 mg.)		218	13(6%)	31(14%)	44(20%)	26·5 ± 4·4	57

It is evident from Major Wilson's experiment that hyoscine did not dangerously diminish sweating in men undergoing severe exertion in this country. In a small series of experiments in which two subjects took exercise in a hot chamber we found that the sweat output was somewhat less, and the rise in rectal temperature somewhat greater, when hyoscine (0·6 or 1·2 mg.) had been taken. The differences were, however, small and probably insufficient to be of practical importance. Our observations have since been repeated in Australia for the 0·6 mg. dose, with similar results. Hyoscine is therefore unlikely to have any deleterious effects, unless given to men on the borderline of heatstroke.

It must be pointed out that all our evidence on the unimportance of side-effects was derived from young male subjects, and has no reference to what might happen in the female, the very young, or the very old.

Repeated doses of hyoscine.—The evidence so far presented has been solely concerned with the effects of single doses of drugs in trips of 4–6 hours' duration. With the object of securing evidence of the effects of repeated doses of hyoscine and atropine during a longer period we made some observations during a voyage on a troopship. This experiment proved to be full of unexpected difficulties and no reliable evidence of the effectiveness of either drug was obtained. This experience showed, however, that, after an initial dose of 0·6 mg., hyoscine could be repeated in doses of 0·3 mg. at intervals of 6 hours for 48 hours without the appearance of obvious side-effects. Since there can be no doubt that hyoscine prevents seasickness in a proportion of men on short trips it seems reasonable to suppose that it would also be to some extent effective if given in this way on longer trips.

Further experiments.—In view of the unpleasant dryness of the mouth caused by hyoscine, it might be profitable to explore other related compounds in the hope of finding one which would be as effective against seasickness but which would not inhibit salivation. A start was made in this direction by testing homatropine and *d*-hyoscyamine. In the small doses used these drugs had only a doubtful effect on seasickness (table IIIC), but as considerably larger doses can be taken without discomfort it was hoped to make further trials. We also intended to try benzoyloscine and benzoyltropine, as both these atropine-like drugs are without much effect on salivation. Circumstances, however, prevented further investigations.

The search for more effective drugs would be greatly assisted if the mode of action of hyoscine in preventing seasickness could be discovered. The necessarily expedient nature of war-time research does not encourage investigations of this type.

SUMMARY

A number of drugs have been examined for their ability to prevent seasickness in troops. Hyoscine (0·6 mg. and 1·2 mg.) appears to be the most generally useful.

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MEDICINE AND THE LAW

Simultaneous or Consecutive?

To decide the devolution of property and the incidence of death duties a court is sometimes called upon to declare the order in which two or more persons, the victims of some common catastrophe, met their end. Were the deaths simultaneous or consecutive? Some eighty years ago Lord Cranworth observed that it was highly unlikely that two people died at exactly the same moment of time. That was in the days before high explosive rained down sudden death at random from the skies. He was thinking perhaps of shipwrecked survivors on a raft in mid ocean or of persons injured in a coaching or railway accident. The law demanded definite proof, not mere guesswork. The consequent uncertainty was shown to be inconvenient in Wing *v.* Angrave in 1862, where the court refused to accept any presumption of survivorship. To get over this difficulty a clause was included in the Birkenhead reforms of the law of property. Section 184 of the Act of 1925 enacts that, where two or more people die in circumstances rendering it uncertain which of them died first, then (subject to any order of the court) the deaths will, for all purposes affecting the title to property, be presumed to have occurred in order of seniority, the younger being deemed to have survived the older. The words "subject to any order of the court" were construed to mean that the court could receive evidence and act upon it in displacement of the new statutory presumption.

Last month the Court of Appeal took a non-technical view of deaths which had occurred in an air-raid; it refused to worry over split seconds. "Metaphysically speaking," said the Master of the Rolls, "time is infinitely divisible; but the law proceeds on a basis of common sense"—a reassuring statement. The case was *re* Grosvenor deceased. Two brothers, Dr. Randolph Grosvenor and Mr. Edward Grosvenor, were killed with other people when a bomb fell on a house in Chelsea in September, 1940. Dr. Grosvenor, the elder of the two, had left his estate to be divided among any of his brothers living at his death. The younger brother had left one third of his estate to Dr. Grosvenor. One brother, Mr. Robert Grosvenor, remained. It was necessary to decide at the outset whether the brothers Randolph and Edward died simultaneously, in which event Robert Grosvenor would be entitled to the whole of Dr. Grosvenor's estate. Mr. Justice Cohen, following a judgment by the late Mr. Justice Bennett in the Lindop case of 1942, held that, in the absence of proof, the statutory presumption must apply. Bennett, J., had used the phrase that time was infinitely divisible and had cited Lord Cranworth's dictum on the improbability of simultaneous death, even though there was medical evidence that the deaths of Mr. and Mrs. Lindop must have been simultaneous. Mr. Lindop was ten years older than his wife; they lived in the same room in a house in Torquay and lost their lives in the same air-raid in May, 1941, their bodies being found on the ground floor underneath their bedroom, suffering from multiple injuries. In the absence of exact proof the judge ruled that it must be presumed that the husband, being older, died "some brief moment" before his wife, in spite of the medical evidence that death from the blast would have been instantaneous. Now the Court of Appeal takes the "common sense" view which happens to coincide with the medical evidence. But it was a majority judgment of two lords justices to one; Lord Justice Luxmoore, in the minority, maintained that the circumstances of the deaths still furnished the element of uncertainty for which the statutory presumption was created to provide. Leave to appeal to the House of Lords has been granted; thus at last the attempt of Parliament to remove uncertainty will come