THE ACTION OF ANTI-EMETIC DRUGS

by

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INTRODUCTION

In recent years increasing use has been made in clinical practice of anti-emetic drugs. These are drugs which prevent or relieve nausea and vomiting occurring in such conditions as pregnancy and on exposure to motion. Despite the widespread use of these compounds little attention has been paid to methods of evaluating their effectiveness; nor is there any clear understanding of their mode of action. It is with these two problems that this thesis is concerned. The relevant literature is briefly examined in Part 1 of the thesis. Part 2 contains an account of clinical experience with chlorpromazine, the most potent anti-emetic drug available. This is followed by a demonstration of the effectiveness of this drug in preventing sickness induced experimentally by apomorphine in normal men. The remainder of Part 2 contains an account of experiments in human subjects to elucidate the mechanism of this action of chlorpromazine. In the final chapter an attempt is made to coordinate the experimental and clinical findings, and to relate them to previous knowledge of the subject.

Throughout this work I have sought to use the methods of clinical pharmacology, by which I understand controlled observation and experimentation in the human subject, taking into account the factors which influence the response of humans to drugs.

During /

During this work I was attached to the Department of Materia Medica and Therapeutics of the University of Glasgow, and to Stobhill General Hospital, Glasgow.
For part of the time I held a Ciba Research Fellowship in Clinical Pharmacology. I am deeply indebted to Professor Stanley Alstead for his interest and encouragement in my work, and for providing research facilities.
The clinical work, and the earlier experimental studies, were done in collaboration with Dr. J. G. Macarthur.
Mr. J. J. Lewis collaborated in some experiments on motion, and was of great assistance in providing research facilities.
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Above all, however, this work was made possible by the willing and cheerful co-operation of a large band of volunteers - colleagues, students and patients - who acted as subjects in the experiments. It is to them pre-eminently that my thanks are due, and it is for their sake that I express the hope that this work may have made some small contribution to our understanding of a difficult clinical problem.

THE ACTION OF ANTI-EMETIC DRUGS

PART 1

A CRITICAL REVIEW OF THE LITERATURE

Contents

INTRODUCTORY

This thesis consists of an enquiry into how anti-emetic drugs relieve vomiting in man. In this part of the work the relevant literature will be reviewed.

Published studies on anti-emetic drugs in man are concerned very largely with clinical trials of these remedies in a variety of conditions. For experimental work one has to turn to animal investigations, much of which has been devoted to elucidating the mechanism of the vomiting reflex. Recently, extensive screening of compounds for anti-emetic activity has been undertaken, and the pharmacology of such drugs has been studied from many aspects. However very little work has been concerned directly with understanding how anti-emetic drugs act. An important exception is the study by workers in the University of Utah on the action of emetic agents, to which reference will be made.

The review which follows will touch upon research in a number of related fields, which help to shed light on the main problem of the mode of action of anti-emetic drugs in man.

THE PHYSIOLOGY OF VOMITING

The "vomiting centre" is the name given to a group of neurons situated in the dorsal portion of the lateral reticular formation of the lower brain stem in the immediate vicinity of the fasciculus solitarius (1). This area earned its name with the demonstration by Borison and Wang in cats (2) that electrical stimulation strictly confined to the area immediately evoked vomiting which ceased when the stimulus was withdrawn. It was further shown that chronic lesions of the same area in dogs rendered the animals refractory to all emetic agents (3).

These experimental techniques are of course inapplicable to man, so that any description of the control of vomiting must lean heavily on animal experiments. This is the more unfortunate because of pronounced species differences in reaction to pharmacological agents on the vomiting mechanism (4). In the discussion which follows it will be stressed that animal experiments cannot be accepted in explanation of events occurring in man; and the practical value of animal work is to indicate lines of enquiry in man.

Vomiting /

Vomiting is a coordinated sequence of actions which includes fixation of the diaphragm in the position of inspiration, closure of the glottis, contraction of the pyloric portion of the stomach, relaxation of the cardiac portion and contraction of the somatic muscles of the abdominal wall. The vomiting centre regulates and coordinates the actions of the many visceral and somatic structures which are brought into play (5). Vomiting is usually preceded or accompanied by other changes, which include dizziness, salivation, flushing or pallor, sweating and muscle weakness. These accompaniments do not occur after discrete electrical stimulation of the vomiting centre, but they can be evoked by electrical stimulation of nearby structures (2). The vomiting centre lies close to the nucleus of the vestibular nerve, the respiratory centres, the vasomotor centre and the salivatory nuclei. It is surrounded by the bulbar portion of the lateral reticular formation (1). It therefore seems likely that clinical vomiting is often associated with a spreading discharge which affects simultaneously or consecutively a number of neighbouring collections of neurons in the lower brain stem.

NAUSEA

Vomiting in man is often preceded by nausea. Nausea is a characteristic, unpleasant sensation located in the pharynx or the epigastrium, often both; it implies also an apprehensive awareness of impending vomiting and a distaste for or revulsion at food. Nausea is distinct from the changes which often accompany or precede vomiting - dizziness, a sense of "hot and cold", salivation and sweating. The nauseated patient is sensitive to afferent stimuli, such as a sound, a touch, a smell or a movement; and these are often sufficient to provoke vomiting. Nausea often increases in waves and culminates in vomiting by which it is usually relieved. Alternatively nausea may slowly disappear without vomiting occurring.

Physical changes in the tone, motility and secretion of the stomach and bowel have been described as occurring during nausea in man (6 - 9) or as preceding vomiting in experimental animals (10 - 13). These changes are reduction of tone and motility of the stomach, increased tone and contraction of the first and second parts of the duodenum (6, 7) and increased secretion from the jejunum (12). There is however no proof that these changes cause nausea or that they are caused by nausea. They may be absent in the presence of nausea (7) and identical changes can be demonstrated after stimuli which do not cause nausea (6).

The true nature of nausea is undetermined. It is usually tacitly assumed that nausea represents sub-threshold stimulation of the vomiting centre, because of the observation that nausea of mounting intensity usually precedes vomiting. However some familiar features of nausea are not adequately explained on this hypothesis. Nausea often outlasts the evoking stimulus, and this is particularly striking after exposure to motion, when nausea may persist for many hours after stopping the motion (14). Re-exposure to a small amount of motion long after the original stimulus may rapidly bring on nausea again (15). Vomiting often rapidly relieves nausea. Conjectures might be advanced about the possible role of humoral agents in causing nausea and vomiting, but no evidence in support of such a hypothesis is available. Neither the node of evocation of nausea, nor the physical changes of which it is the subjective manifestation, are yet understood.

AFFERENT PATHWAYS IN VOMITING

The vomiting reflex is activated by nervous or chemical stimulation of many peripheral structures. Our knowledge of these is derived from experiments in which the vomiting response of intact animals is observed to electrical or chemical stimulation of appropriate structures, or after the production of lesions of such structures.

Observations /

Observations in man are concerned with the effects of disease and drugs in modifying sensitivity to vomiting. The afferent pathways involved in motion sickness, radiation sickness and in the vomiting due to apomorphine, will be described. Experiments on other forms of vomiting, such as in pregnancy or renal failure, are scanty because of the difficulty of reproducing the sickness in experimental animals.

Motion sickness.

The afferent pathway primarily involved in the genesis of motion sickness is that from the non-auditory labyrinth. Intensive study of this subject, mainly during the second world war (16, 17) established the fact that the prime cause of motion sickness is motion. Two types of motion receptors are involved: the semicircular canals, which perceive angular acceleration, and the utricular maculae (otolith organs), which perceive linear acceleration. Experimentally motion sickness can be produced by either linear or angular acceleration alone, although more readily by the former than by the latter (17). In practice both forms of motion are usually involved, and combined stimulation is more effective than either alone (18, 19). The nervous pathway involved has been demonstrated by ablation studies in dogs.

Destruction /

Destruction of the labyrinth (20, 21) or section of the vestibular nerves (20) renders the animal immune to motion sickness - or at least makes it impossible to cause sickness in response to a procedure which is invariably effective in the intact animal. In addition the following more centrally placed lesions abolished sensitivity to motion:-

Total removal of the cerebellum (22).

Removal of the nodulus, uvula and pyramis (22).

Removal of the nodulus and uvula or of either alone (21).

Ablation of the "chemoreceptor trigger zone" (CT zone) -
See below, p. 18 and reference (23).

Lesions of the following structures on the other hand did not influence susceptibility to motion sickness:-

Removal of the vermis (22).

Removal of the non-vestibular parts of the cerebellum (21).

Removal of the temporal, occipital, frontal or parietal cortex (22).

Total decortication (22).

Unilateral labyrinthectomy diminished but did not abolish emetic sensitivity to motion (21).

On /

On the basis of these results Wang and Chinn (21) proposed a scheme for the nervous pathway of motion sickness in the dog by which impulses from the labyrinth reaching the cerebellum, either directly or via the vestibular nuclei, were conveyed to the CT zone, possibly by humoral transmission. From the CT zone the vomiting centre was activated. Vagal sympathetic afferents and descending impulses from the cortex could modify the response at the level of the emetic centre.

The only evidence in support of a similar mechanism in man is the old observation that patients with complete bilateral disease of the labyrinth are immune to motion sickness (24). No information is available about the central pathways in man.

Another approach to the pathogenesis of motion sickness in man has been to attempt to characterize precisely the form of motion most likely to cause sickness. When the stimulus used was repetitive linear acceleration sickness occurred most readily after wave forms of about 16 cycles per minute with an acceleration of about 0.36 g. (25). Sickness occurred much more readily when, with the body moving in one way, the head was subjected to independent movement in another direction (18, 19, 26). It seems that the /

the vomiting mechanism is not simply overwhelmed by massive vestibular stimulation, but that certain patterns of stimulation are especially prone to cause sickness.

The influence of non-vestibular factors in modifying susceptibility to motion sickness is well recognized; and has been studied quantitatively by exposing men to a standard motion and noting the effect of varying such factors. Manning and Stewart (15) demonstrated that closing the eyes reduced the incidence of swing sickness. Sjoberg (20) noted that when proprioceptive afferent impulses were diminished by immobilizing animals in plaster, susceptibility to motion sickness was reduced. Although quantitative evidence is not available it has been noted that olfactory and auditory stimuli can aggravate motion sickness. It is widely appreciated that psychological influences can markedly influence susceptibility to motion sickness (17). The nervous system as a whole exerts further control over susceptibility to motion sickness by the mechanism of adaptation (27) whereby the response to a given stimulus diminishes after repeated application (28).

Facilitation and inhibition of the emetic effects of motion by non-vestibular afferents and by other nervous mechanisms is an important clue to understanding the control of /

of vomiting. The vestibular system of man is never stimulated in isolation; and abolition of the emetic response to motion by lesions of the vestibular pathway does not prove that stimulation of this pathway alone would necessarily cause motion sickness. A drug which prevents motion sickness does not necessarily impair conduction in the vestibular pathways, but might achieve its effect by blocking facilitating arcs elsewhere in the nervous system.

Radiation sickness.

Radiation sickness occurs in patients after deep X-ray therapy. Our knowledge of the pathogenesis of this condition depends largely on the clinical observations of Court-Brown (29, 30). Court-Brown measured radiation as "integral dose" - the total radiation absorbed by the volume of irradiated tissue. His main findings were that, after therapeutic radiation, nausea and vomiting frequently occurred, with a latency of 1 - 4 hours. The duration of the latent period was inversely proportional to the incidence and severity of symptoms. For a given integral dose the latent period was directly proportional to the surface area of the patient. In other words small patients were made sick more rapidly and more severely than large ones, given the same integral dose of radiation.

From /

From these results it can be deduced that radiation sickness is not due to stimulation of nerve endings in the irradiated tissue, because time always elapses between the conclusion of radiation and the onset of symptoms. Nor is the structure from which vomiting is initiated arranged in a surface layer, because sickness depends on the volume of tissue irradiated rather than on its surface area.

Court-Brown suggests that radiation sickness may be caused by a different non-nervous mechanism. He considers that a chemical substance or substances may be produced by the effects of ionization in cells, and that this then accumulates at some chemoreceptor site. Nausea and vomiting result when a critical concentration of the material is attained. The higher the integral dose of radiation, the more of this substance will be released, and the more rapidly it will accumulate at the receptor. The smaller the patient, the higher will be the concentration of the substance in tissue fluids after a given integral dose. Such a mechanism would explain the observed facts, although the suspected chemical substance has not been identified, nor has the site of its action in man.

No quantitative studies appear to have been made on the influence of nervous factors, such as concurrent vestibular stimulation, on susceptibility to radiation sickness.

Knowledge /

Knowledge of the effectiveness of anti-emetic measures in radiation sickness might provide indirect evidence of the mechanism involved. Few of the many clinical studies allow clear-cut conclusions on the value of a proposed remedy. In brief there is no satisfactory evidence that radiation sickness is prevented or alleviated by antihistamine drugs (31), vitamins (32) and amino-acids (33).

In summary, radiation sickness may be due to stimulation of a chemoreceptor, possibly the CT zone, by a chemical substance liberated from irradiated cells. Direct nervous stimulation plays little or no part in its causation.

Apomorphine.

A very small dose of apomorphine - about 0.1 mg./Kg. in the dog (34) and 0.01 mg./Kg. in man (35) suffices to cause vomiting. Apomorphine is often described as a central emetic agent with a direct action on the vomiting centre. This interpretation was based on the demonstration that apomorphine exerted its full emetic effect in the totally eviscerated animal (36). However, this fact does not exclude a parenteral site of action of apomorphine other than the vomiting centre. Investigations by Borison and Wang and their colleagues (1) have introduced a new view of the mode of action of /

of apomorphine. These workers showed that dogs (3) and cats (1) were rendered immune to the emetic effects of apomorphine by chronic lesions of a small portion of the area postrema extending to the floor of the fourth ventricle. This area was close to, but distinct from, the vomiting centre in the lateral reticular formation; and the operated animals remained normally sensitive to the emetic effects of copper sulphate by stomach tube. Borison and Wang considered that the area on the floor of the fourth ventricle was directly stimulated by apomorphine, and that from it nervous impulses were conveyed to the vomiting centre. They therefore called this area the "chemoreceptor trigger zone" (CT zone). The anatomy of this zone in the cat was described by Borison and Brizzee (37) and by Brizzee and Neal (38) who accepted that certain structures in the area could function as chemoreceptors. Borison, Wang and their colleagues went on to show that animals in whom the CT zone was ablated did not vomit in response to morphine (39), digitalis glycosides (40, 41), ergot alkaloids (39), intravenous injections of copper sulphate (3) and, as already mentioned, motion (23) and radiation (33). Such animals remained sensitive to the emetic action of oral copper sulphate (3), nitrogen mustard (42) and veratrum alkaloids (43).

A number of questions are raised by this conception of the mode of action of apomorphine. What is the chemoreceptor element at the CT zone, how is it activated, and how are impulses conveyed from it to the vomiting centre? Borison and Brizzee (37) and Brizzee and Neal (38) have provided partial answers to these questions by demonstrating in the area postrema of the cat, clusters of glialoid cells with large vascular feet which they think might be the chemoreceptor elements, and from which loose bundles of nerve fibres pass into the lateral reticular formation towards the vomiting centre. How is the thousandfold difference explained of the sensitivity to apomorphine of the dog and cat? Does the CT zone exist in man? Is the CT zone necessary for all the pharmacological effects of apomorphine, or only for its emetic effect? How are vestibular impulses in motion sickness conveyed from the cerebellum to the CT zone? (21). How do environmental factors influence susceptibility to the emetic effects of apomorphine? (44).

These and other questions remain to be answered before Borison and Wang's interpretation of their findings can be unreservedly accepted. However their experiments have added to our knowledge of the central organisation of vomiting, and have suggested possible mechanisms of action of anti-emetic drugs.

<u>Other Drugs.</u> /

Other drugs.

Sickness occurs as a side-effect of many drugs, and experiments to locate the afferent pathways involved will be briefly reviewed.

CT zone.

As stated above, destruction of the CT zone in dogs prevented the emetic effects of apomorphine (3), morphine (39), ergot alkaloids (39) and intravenously injected copper sulphate (3). Vomiting in response to digitalis glycosides was reduced, but not always abolished (41).

Gut denervation.

Combined sympathectomy and vagotomy abolished the emetic effect of oral copper sulphate (3, 45).

Nodose ganglion of vagus. Section of the vagus immediately above this ganglion abolished the emetic effect of veratrum alkaloids, but section immediately below did not do so (43). It was concluded that the emetic effect of veratrum was due to stimulation of a chemoreceptor in the nodose ganglion, from which afferent impulses were conveyed to the vomiting centre.

Cerebral cortex. /

Cerebral cortex.

Chronic extensive decortication abolished vomiting in cats in response to intravenous injection of nitrogen mustard (42).

From the preceding discussion it is seen that many different afferent pathways are involved in the genesis of vomiting, although common central pathways may be utilized. But experiments in which the response to an emetic agent is abolished by lesions of a single structure, do not prove the sole participation of that structure in the vomiting reflex. Emetic responses to different stimuli may all be subject to the modifying influences of other forms of afferent stimulation.

PHARMACOLOGY OF ANTI-EMETIC DRUGS

Clinicians have long appreciated that some drugs protect patients from vomiting, but there was little experimental support for this observation. In the older pharmacological literature are to be found (46) a number of isolated and inconclusive experiments on the ability of various drugs to prevent experimentally-induced vomiting. Quantitative /

Quantitative methods of evaluating anti-emetic activity were introduced by Chen and Ensor in 1950 (34). Their method depended on the reduction by drugs of the frequency of vomiting in dogs after an emetic dose of apomorphine. Similar methods were used by other groups of workers, taking as their index of anti-emetic activity the increase in the threshold dose of apomorphine required to elicit vomiting (47) and the reduction in the number of retching spells after a standard dose of apomorphine (48). Emetic agents other than apomorphine have been used in qualitative studies, but not in the quantitative comparison of anti-emetic drugs.

Many drugs were found by these methods to have the property of antagonising apomorphine, and these included many antihistamine drugs (48, 49), atropine, hyoscine and other anticholinergic agents, and central nervous system depressants (50).

These compounds do not form a homogeneous chemical or pharmacological group. Many are antihistaminic, but not all antihistamines are anti-emetic, and there is no relation between antihistamine potency and effectiveness as an anti-emetic (48). There is a similar lack of correlation between anti-emetic activity and the ability to antagonize acetylcholine, adrenaline /

adrenaline, serotonin and other known or suspected neurohumors (50). An apparent parallelism has been noted between the ability of drugs to prevent vomiting and their activity in relieving muscular rigidity and tremor in Parkinsonism (50). This relationship has not yet been established by quantitative studies.

Because of the universal use of apomorphine to induce vomiting in experimental studies of anti-emetic activity, the term "anti-emetic drug", as used by pharmacologists, has come to mean only that the drug raises the emetic threshold of dogs to apomorphine. Not surprisingly it is found that many drugs with powerful anti-emetic properties as demonstrated experimentally prove of only limited value in clinical practice.

CLINICAL TRIALS OF ANTI-EMETIC DRUGS

It is difficult to establish objectively the clinical value of a drug as an anti-emetic. A properly controlled trial requires attention to the following points:-

1. The various conditions in which the drug is used must be clearly defined, and different reports of its value should be presented for each disease. A drug which is valuable in one disease may not necessarily be effective in another.

2. /

2. The patient should not know that a new drugs is being tested, because sickness can be relieved by suggestion.

3. The criterion of clinical effectiveness to be used in the trial should be defined at the outset and adhered to throughout. Preferably the relief by the drug of nausea and of vomiting should be separately assessed.

4. Whenever it is ethically possible, controls should be introduced into the trial to allow the investigator to estimate the probable outcome of the condition had the anti-emetic drug not been given. When the sickness is of long duration, as for example in uraemia, the patient may be used as his own control, with alternating periods on drug or placebo. With illnesses of short duration patients may be allocated to treatment and control groups, either at random or, preferably, by pairing patients with regard to age, sex, severity and duration of illness.

5. The effects of specific therapy of the disease on the symptom of vomiting must be allowed for.

6. Proper account must be taken of side-effects due to the drugs.

Many /

Many clinical trials on which the reputation of an anti-emetic drug may largely rest, fail to satisfy the rules which have been outlined. Reference will now be made to some particular clinical fields in which assessment of anti-emetic drugs has been attempted.

Motion sickness.

The technique of field trials of motion sickness remedies has reached an acceptable scientific standard. Many of the difficulties of ordinary clinical trials are absent. The use of military personnel allows the organisers to expose a large homogeneous population of fit men to identical conditions. The use of placebos is ethically justifiable, and the attack rates in large groups of untreated subjects can be compared with those in treated ones. In spite of this there is uncertainty in this field too, and different investigators sometimes arrive at conflicting results about the same drugs. Among the reasons for this are the following:-

1. The criteria of effectiveness vary in different trials, according to the symptom whose relief is sought. Vomiting is easier to record than nausea, but it is relief of the latter which is usually required.

There /

There are no agreed criteria for recording or grading nausea. Many investigators speak only of "sickness" or use other unsuitable criteria, such as pallor, sweating or dizziness.

2. Different kinds of motion sickness yield different results, e.g., airsickness, seasickness and swing sickness do not all respond in the same way to drugs (50).

3. The importance of certain environmental factors in influencing results is sometimes overlooked, e.g., in seasickness the position of a man's berth, the nature of his duties, his smoking habits, the amount of head movement, his age, history of previous exposure to motion (51). Randomization often, but not always, overcomes this objection. The study of Gay and Carliner on dramamine (52) has been criticized (17) because the treatment group was berthed in a compartment of the ship where less sick-making motion was experienced than in the compartment where the control group was berthed.

Among the best controlled studies in this field the following should be mentioned:-

1. /

1. The experiments of Glaser and Hervey (53, 54) on the value of hyoscine and other drugs on sickness produced in motor-torpedo boats at sea, and on rubber dinghies in a swimming pool.

2. The studies of Chinn and his collaborators (51, 55-58) on seasickness in American servicemen crossing the Atlantic by troopship

Work of this type allows the "screening" of drugs for activity in preventing motion sickness, and measurement of their comparative effectiveness.

Radiation sickness.

Radiation sickness is caused by an external agency, and the attack rate in a group of cases can be predicted. This makes it a suitable syndrome for evaluating anti-emetic drugs. Nevertheless, many reported trials have been unsatisfactory because of the lack of attention paid to the principles enunciated above. An additional difficulty is that sickness in the course of radiotherapy may be due to the lesion for which treatment is being given, rather than to the treatment itself. The studies of radiation sickness by Court-Brown (29, 30) discussed above, point the way to the correct design for evaluation of anti-emetic drugs in radiation /

radiation sickness. Attention should be paid to the dose of radiation measured as integral dose, to the surface area of the body, to the site irradiated and to the duration of the latent period between irradiation and the appearance of symptoms. No trial of an anti-emetic drug in which these principles have been applied has so far been published, and the findings of many investigators in this field must be rejected as inadequately controlled (59).

Pregnancy sickness.

It is necessary to distinguish between two syndromes which are found in pregnancy, physiological sickness and pernicious vomiting (60). The former refers to nausea and vomiting in the first four months of pregnancy. This syndrome is common, mild and transient. It is difficult to evaluate the effect of drugs, but they appear to be of little value (60). The pernicious form of vomiting, hyperemesis gravidarum,is very often dramatically relieved by admission to hospital and correction of fluid and electrolyte disturbance, without the aid of specific therapy. In cases which do not respond to such measures it is unethical to withold drugs which may save the life of the foetus. It is usually accepted as objective evidence of the /

the value of anti-emetic drugs if the symptoms return when the drug is replaced by a placebo, without the patient's knowledge, and disappear on reintroducing the anti-emetic (61, 62).

Post-anaesthetic sickness.

The evaluation of anti-emetic drugs in post-anaesthetic sickness requires a very large number of cases, a standard anaesthetic procedure, a careful control of variables, and a prolonged and unobtrusive period of post-operative observation of the patient. These objectives were achieved in the study by Knapp and Beecher (63) which gave clear information of quantitative value on the effect of drugs in preventing post-anaesthetic nausea and vomiting. However in this work the anaesthetic used was nitrous oxide and ether, and the sickness rate in the control group was as high as 80%. With anaesthetic techniques currently in favour sickness rates in control groups are very much lower than this, which increases the difficulty of demonstrating a reduction by drugs. Trials are further complicated by the tendency to use a number of drugs in modern anaesthetic techniques, and by the multiple pharmacological actions of many anti-emetic drugs.

An /

An unusual method of evaluating anti-emetic drugs was described by Morris et al (64). They noted that patients under spinal anaesthesia tended to retch or vomit when traction was applied to abdominal viscera during laparotomy. This did not happen in patients who had been treated with chlorpromazine. To confirm this impression seven patients were subjected to "three brisk tugs on the stomach" under spinal anaesthesia, which always induced nausea and retching. Chlorpromazine was then injected intravenously, and the stomach again tugged in the same way. No nausea and retching resulted.

This method of evaluating anti-emetic drugs has limited application.

MODE OF ACTION OF ANTI-EMETIC DRUGS

The experimental part of this thesis is to be devoted to the mode of action of anti-emetic drugs. The subject will be introduced here, but the matter will be restricted to a summary of the experimental findings on how anti-emetic drugs - and in particular the drug chlorpromazine - prevent vomiting induced by apomorphine. Six possible mechanisms will be separately considered, and those are:-

(i) /

(i) Chemical combination of the drug with apomorphine.

(ii) Displacement of apomorphine from a receptor ("competitive inhibition").

(iii) Direct depression of the vomiting centre.

(iv) Depression of the afferent pathway to the vomiting centre.

(v) Depression of facilitating influences on the reflex vomiting mechanism.

(vi) Potentiation of inhibiting influences.

1. Chemical combination with apomorphine.

Impressed by the rapidity and the completeness of the antagonism between apomorphine and chlorpromazine, Wang and Glaviano (39) investigated the admittedly improbable explanation that the two drugs entered into chemical combination. They were able to reject this explanation decisively.

2. Competitive inhibition.

Brand et al. (65) advanced the view that chlorpromazine prevented apomorphine-induced vomiting by successfully competing with apomorphine for attachment to receptors in the CT zone. They based this interpretation on the grounds that, of seven emetic agents which were tested in dogs, three failed to cause vomiting after chlorpromazine. These three emetic agents - apomorphine, morphine and hydergine /

hydergine - had in common the property that the integrity of the CT zone was necessary for them to exert their emetic effect. This purely conjectural explanation is faced with a number of difficulties:-

(a) Chlorpromazine failed to prevent vomiting induced in the dog by intravenously-injected copper sulphate and by the cardiac glycoside, lanatoside-C, although it has been demonstrated that both these drugs require the integrity of the CT zone to exert their emetic effect (3). Brand et al. suggest that there may be more than one type of chemoreceptor in the CT zone, and that specific receptors sensitive to lanatoside-C and copper sulphate are not blocked by chlorpromazine. There is no evidence to support this conjecture.

(b) Chlorpromazine did not prevent the emetic action of apomorphine in the cat, although in this species also integrity of the CT zone is necessary for apomorphine to exert its emetic effect.

(c) Vomiting induced in the cat by pilocarpine was blocked by chlorpromazine, but the integrity of the CT zone is not necessary for this drug to cause emesis.

Glaviano and Wang (47) who obtained similar results to Brand et al. also believed that chlorpromazine exerted its anti-emetic effect by impairing transmission at the CT zone. To explain the ineffectiveness of chlorpromazine against vomiting induced by lanatoside-C and by intravenous copper sulphate they postulated a varying order of affinities for drugs at this receptor site. In their view chlorpromazine might be able to displace apomorphine from receptors, but would fail to displace lanatoside-C or copper sulphate.

This view of the mechanism of the anti-emetic action of chlorpromazine rests on circumstantial evidence and conjecture, and does not adequately explain the observed facts.

3. Depression of the vomiting centre.

Depression of the vomiting centre by anaesthetic drugs or by narcosis prevents vomiting due to apomorphine.(1). It is doubtful if selective depression of the vomiting centre occurs without simultaneous depression of other medullary centres. The selective nature of the anti-emetic action of chlorpromazine makes it unlikely that its anti-emetic action is due to depression of the vomiting centre; because /

because a dose of chlorpromazine sufficient to abolish vomiting induced by apomorphine is ineffective against, say, veratrum alkaloids (65, 66).

Glaviano and Wang, in the paper already quoted (47), refer to the dual mechanism of anti-emetic action of chlorpromazine. When they gave animals chlorpromazine in a dose of 2 mg./Kg. they noted a selective anti-emetic action without signs of depression of the nervous system; and, as already stated, they attributed this effect to an action on the CT zone. They further observed that when the dose of chlorpromazine was 6 mg./Kg. intravenously, a considerable sedative effect was exerted, and furthermore, vomiting after intravenous injection of copper sulphate was now prevented. From this evidence they concluded that the anti-emetic effect of very large doses of chlorpromazine was due to direct depression of the medullary vomiting centre. Again this conclusion is open to criticism. The same high dose of chlorpromazine prevented vomiting caused by morphine in only 50% of animals. Depression of motor activity cannot be taken as evidence of depression of the vomiting centre. Whatever the true explanation of these observations there is certainly no evidence that in therapeutic doses the anti-emetic action of chlorpromazine is due to depression of the vomiting centre.

4,5,6. Blockade of afferent pathways or of facilitating arcs; potentiation of inhibitory arcs.

These possible mechanisms of the anti-emetic action of chlorpromazine are not discussed in the literature despite evidence that chlorpromazine blocks afferent and facilitating nerve pathways in the reticular substance (67). Evidence to be presented in the experimental part of this thesis is in keeping with the view that one or other of these mechanisms is in fact responsible for the anti-emetic action of chlorpromazine, and the subject will be further discussed in chapter 8.

INHIBITION OF DIURESIS

Chapters 5 and 7 of this thesis will be devoted to a study of the inhibition of water diuresis by apomorphine and by vestibular stimulation.

The antidiuretic hormone of the posterior pituitary is released in response to the specific stimulus of a rise in the osmotic pressure of the plasma. Its function is to preserve the osmolarity of the extracellular fluid (68). The hormone is also released in response to a variety of stimuli unrelated to the body's water requirements. These include muscle exercise (69), pain (70), cold (71), fright (72), syncope (73), and the action of many drugs (74).

No /

No adequate explanation of this non-specific activation of the posterior pituitary has been offered. Many stimuli which cause antidiuresis also cause vomiting. It may be suggested that these two phenomena - antidiuresis and vomiting - are non-specific responses of the central nervous system to excessive stimulation. These are only two of many examples in neurology of inappropriate responses to over-stimulation.

While antidiuresis in response to motion and to apomorphine is of no biological value, it is a useful index of the body's reaction to stimulation, and has value as such to the experimentalist.

NYSTAGMUS

Stimulation of the semicircular canals leads to corrective eye movements known as nystagmus. The introduction of new techniques (75 - 78) has led to a degree of accuracy in the quantitative observation of this reflex which is available for the study of few other reflexes in man. It has now been firmly established that the speed at which the eye travels during the slow phase of nystagmus represents the magnitude of the response; and that this response is proportional to the evoking stimulus (75, 76, 79). For example, if a stimulus of /

of angular speed 30°/second is applied to the head by means of a rotating chair, then nystagmus will result, during the slow phase of which the eye will move at a speed somewhat less than 30°/second.

After vestibular stimulation of constant magnitude, the speed of the eye is determined by the intensity and velocity of impulse flow through the vestibulo-ocular reflex arc (80). Impulse passage through this arc is inhibited by adaptation (28, 81) and by certain drugs (82). Very few studies of the effect of drugs have as yet been conducted in animals (82) and none in man. Depression of the response to vestibular stimulation by drugs probably indicates impairment by the drug of interneuronal conduction (80), although other mechanisms are possible. Facilitation of the response by drugs has also been demonstrated (82) and this may represent a release of inhibitory actions or a stimulation of facilitating arcs.

The nystagmic response to vestibular stimulation might be used to demonstrate the effects of drugs on vestibular reflexes, or to illustrate antagonism between stimulant and depressant drugs. It will be seen in chapter 6 of this thesis that this method has been used to yield information on the antagonism between apomorphine and chlorpromazine.

EPILOGUE

In the pages which follow an attempt will be made to understand more fully how drugs cause and prevent vomiting in man. The initial work was devoted to standardizing experimental procedures and to collecting facts about the environmental conditions which influence the occurrence of vomiting. Work was then extended to a consideration of the action of emetic and anti-emetic agents on the supraoptico-hypophyseal system and the control of reflex eye movements. In this way a fuller, and, it is hoped, a more rational picture has been obtained of how drugs prevent vomiting in man.

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THE ACTION OF ANTI-EMETIC DRUGS

PART 2

EXPERIMENTAL

CHAPTER 1.

CLINICAL STUDIES OF CHLORPROMAZINE

In this chapter the clinical evaluation of chlorpromazine as an anti-emetic drug is described. The observations were stopped while they were still incomplete, because of toxic reactions to the drug.

Chlorpromazine [10-(γ-dimethylaminopropyl)-3-chlorphenothiazine] prevents vomiting in dogs induced by apomorphine (1, 2, 3). Clinical reports (4, 5, 6) claimed that chlorpromazine was an effective anti-emetic agent, but some of the claims were based on uncontrolled data. Working with Dr. J. G. Macarthur I used chlorpromazine as an enti-emetic drug in various clinical conditions. Early impressions were favourable, as is illustrated by the following case-notes.

Cerebral tumour.

A man aged 57, suffering from raised intracranial tension, had vomited repeatedly ever since his admission to hospital two weeks previously. All food was immediately regurgitated, /

regurgitated, and retching recurred throughout the day. He was given 50 mg. of chlorpromazine by intramuscular injection, then 50 mg. thrice daily by mouth, until his death nine days later. He did not vomit once after receiving chlorpromazine, and was able to enjoy his food. Necropsy showed a glioma in the frontal and temporal regions.

Acute nitrogen retention.

A girl of 11 had vomited persistently for nine days. The illness, which began with severe diarrhoea, progressed to a state of dehydration, electrolyte imbalance and nitrogen retention. The fluid and electrolyte disorder was corrected by intravenous therapy, but vomiting persisted. She received 25 mg. of chlorpromazine by intramuscular injection, and this was repeated ten hours later. Thereafter she was given 10 mg. eight-hourly by mouth. She vomited swallowed blood from an epistaxis twelve hours after the first injection, but no other vomiting occurred and she was able to take food and fluids by mouth.

Labyrinthine disease. /

Labyrinthine disease.

A woman of 70 suddenly developed herpes of the right auricle, right facial palsy, severe vertigo, tinnitus, nausea and vomiting. These symptoms were uninfluenced by hyoscine, dimenhydrinate and chlorcyclizine. The nausea and vomiting responded immediately to 25 mg. of chlorpromazine by mouth, but the vertigo and tinnitus were unaffected.

In other cases, although the effect of chlorpromazine was not so dramatic, improvement followed its use. Sometimes no benefit was noted. Further experience was as follows:-

Uraemia.

Chlorpromazine was given to three patients with advanced renal disease who suffered from persistent nausea and vomiting. In no case was the drug dramatically effective, but in two patients nausea and vomiting diminished while chlorpromazine was being given.

"Cyclical" vomiting. /

"Cyclical" vomiting.

A girl of 10 suffered from so-called "cyclical" vomiting (periodic disease). She was given chlorpromazine first by injection, then by mouth, during one such episode. Vomiting continued, though it was less severe, and it abated about twenty-four hours after treatment was started. The physician in charge did not think that chlorpromazine had influenced the course of the illness.

Hyperemesis gravidarum.

Chlorpromazine was of no value in two of three patients treated. The third patient showed a remarkable response:-

A woman of 39 suffered from hyperemesis gravidarum during her sixth pregnancy. She had had the same condition in three previous pregnancies, one of which was terminated in the third month.

She was three months pregnant when I first saw her. She had already been treated with intravenous fluids, barbiturates and vitamin B preparations without benefit, and termination of the pregnancy was /

was under urgent consideration. She had been vomiting profusely for thirty-six hours before I saw her, and, despite an intravenous infusion, she was dehydrated and had acetonuria. She was given 50 mg. of chlorpromazine by intramuscular injection, and within fifty minutes all vomiting stopped and nausea disappeared. She remained free of vomiting while chlorpromazine treatment by mouth was continued.

Throughout the remainder of this pregnancy bouts of violent vomiting occurred intermittently. The vomiting was always brought under immediate control by chlorpromazine. On four separate occasions injections of saline or inert tablets were given in place of chlorpromazine, unknown to the patient. On every occasion these placebos were quite ineffective, but the symptoms again came under control within one hour of giving chlorpromazine. After more than two months of intermittent therapy the patient was put on a maintenance dose of chlorpromazine for the remainder of her pregnancy. Vomiting occurred about twice per week, but the violent bouts of persistent vomiting did not recur.

A /

A barium meal examination at the beginning of the pregnancy showed no abnormality. A second one four months later showed a diaphragmatic hernia.

The cause of vomiting in the patient is uncertain. There seemed no doubt that chlorpromazine had a powerful anti-emetic effect.

Hiatus hernia.

A woman of 54 with an oesophageal hiatus hernia said that she had vomited several times daily for many months. A record was kept of her behaviour in hospital, and she was seen to vomit from four to six times daily. After one week of observation she was given inert tablets which, she was told, were "for her sickness". The rate of vomiting fell to twice daily. After a second week chlorpromazine was substituted for the inert tablets, but the patient did not know of the change. She continued to vomit an average of two times daily. No specific anti-emetic effect could be assigned to chlorpromazine in this patient.

Sickness due to drugs. /

Sickness due to drugs.

Chlorpromazine was used in sickness which occurred during treatment by morphine, diamorphine, pethidine, digitalis, stilboestrol, chlortetracycline, veratrum viride and mustine hydrochloride.

Morphine, diamorphine, pethidine.

Three patients with carcinomatosis vomited occasionally while receiving these drugs for the control of pain. Chlorpromazine reduced the required dose of analgesic and greatly reduced sickness.

Digitalis.

In two patients with advanced congestive cardiac failure adequate treatment with digitalis was impossible because of the severe nausea which this drug caused. In both patients administration of chlorpromazine allowed digitalis to be given in adequate amount without sickness.

Stilboestrol.

Two patients were given chlorpromazine for vomiting during large-dose oestrogen therapy for metastatic breast cancer. Chlorpromazine seemed to be of help in one of these patients.

Chlortetracycline. /

Chlortetracycline.

One patient who was nauseated during chlortetracycline therapy improved when chlorpromazine was given.

Mustine hydrochloride.

Chlorpromazine was given to three patients before the intravenous infusion of mustine hydrochloride in malignant conditions. Two patients had the expected nausea and vomiting, and one had no unpleasant symptoms.

Veratrum viride.

An opportunity for the assessment of the value of chlorpromazine in vomiting due to veratrum viride was afforded by the case of a women aged 48 who suffered from renal hypertension. It was known that nervous stress in this patient often provoked attacks of severe headache accompanied by acute rise of blood pressure. (A diagnosis of phaeochromocytoma had been excluded) One such attack was treated by the intramuscular injection of 2 mg. of "veriloid" (a preparation of veratrum alkaloids). The blood pressure fell rapidly to normal levels, but the patient vomited violently and repeatedly (see Fig. 1.1).

Some /

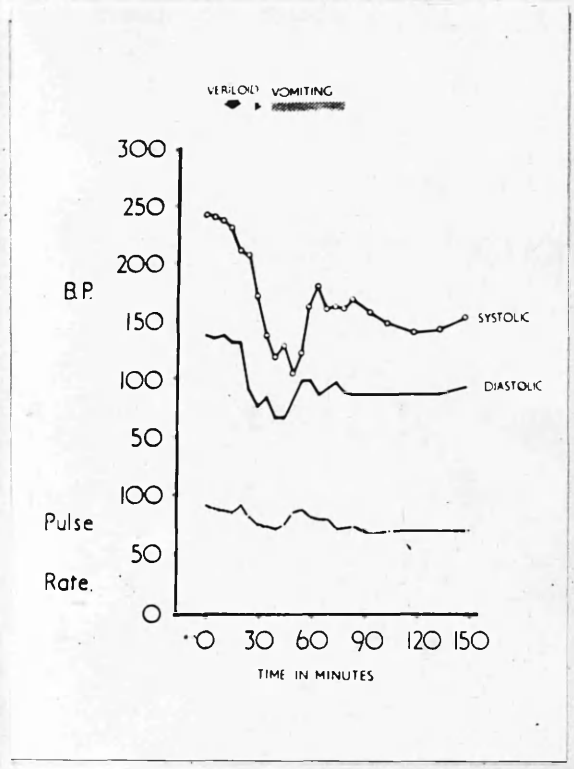

Fig. 1.1.

Effect of intramuscular injection of 2 mg. of veriloid on blood pressure, pulse rate and sickness.

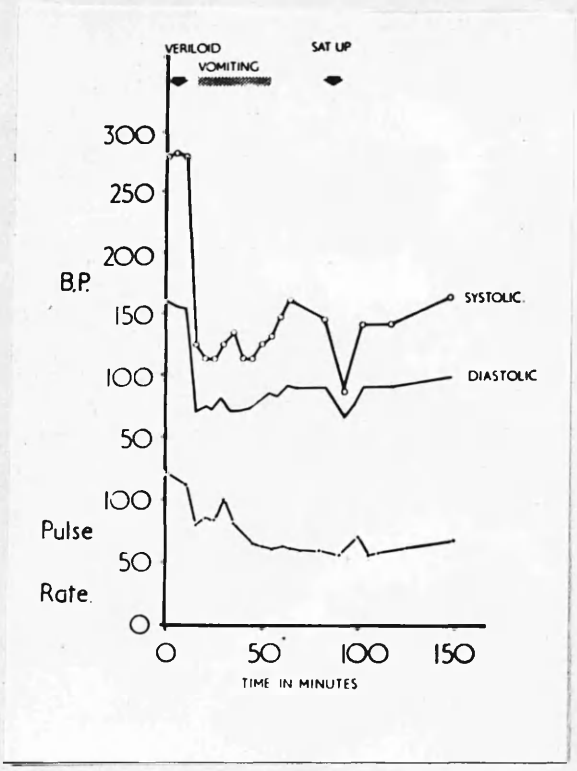

Fig. 1.2.

Effect of same dose of veriloid in same patient four hours after 50 mg. of chlorpromazine.

Some days later the patient was given 50 mg. of chlorpromazine by mouth for its "tranquillizing" effect four hours before intravenous pyelography. While she was awaiting the injection of radio-opaque medium she became agitated and the blood pressure was found to be 260+/160 mm.Hg. She was given an injection of 2 mg. of veriloid intramuscularly. The blood pressure fell rapidly, but vomiting was severe and prolonged (Fig. 1.2). It was later demonstrated in this patient that 50 mg. of chlorpromazine given four hours before an injection of apomorphine prevented vomiting due to the latter.

Details of this case were reported by Isaacs and Macarthur (7). Chlorpromazine was ineffective in this patient in preventing vomiting due to veriloid.

Radiation sickness.

There was evident need for a controlled trial of the anti-emetic effect of chlorpromazine. In consultation with Dr. R.K. Turnbull it was agreed that suitable material for such a trial might be found in patients under treatment for cancer of the breast. It was the practice to give these patients

a /

a two-week course of deep X-ray therapy before operation and an identical course after operation. It was planned that patients would be given 25mg. of chlorpromazine thrice daily during one of these courses, and inert tablets during the other. The incidence of nausea and vomiting would be compared during the two courses. Neither the patient nor the observer would know what drug was being given, and the order in which the two courses were administered would vary in different patients. Dr. Turnbull predicted a sickness rate of not more than 10% in the control group, so that a large number of patients would be required before a significant effect of chlorpromazine might be detectable. Eight patients were treated; sickness occurred in three of these after inert tablets and in three after chlorpromazine. Dr. Turnbull attributed this high sickness rate to the interest which the trial had inevitably aroused among the patients, and at his request the experiment was terminated.

This study gave no evidence that chlorpromazine was effective in the prevention of radiation sickness.

Chlorpromazine and jaundice.

The usefulness of chlorpromazine as an anti-emetic agent is limited by its toxicity. Chlorpromazine caused mild toxic effects in several patients, which did not interfere with its use. However five patients developed jaundice, and three of these died, though it was not certain that chlorpromazine was the cause of death. These cases have been described elsewhere in detail, and their implications discussed. (8, 9, 10).

The threat of liver damage was often too high a price to pay for the possible symptomatic benefits to be expected from chlorpromazine. It was therefore decided to confine the use of chlorpromazine as an anti-emetic agent only to specially selected cases, and a full-scale clinical evaluation of the drug was not pursued.

Our clinical experience with chlorpromazine as an anti-emetic is summarized in Table 1.1.

Summary. /

Table 1.1 Summary of clinical experience with chlorpromazine

Condition	Number of patients treated	Number of cases in which chlorpromazine appeared to be:-		
		Effective	Ineffective	Of Doubtful Value
Cerebral tumour	1	1	-	-
Acute nitrogen retention	1	1	-	-
Vestibular neuronitis	1	1	-	-
Hyperemesis gravidarum	3	1	2	-
"Cyclical vomiting"	1	-	-	1
Hiatus hernia	1	-	1	-
Chronic nitrogen retention	3	-	1	2
Radiation sickness	12	-	12	-
Drugs:- Morphine) Diamorphine) Pethidine)	3	3	-	-
Digitalis	2	2	-	-
Oestrogens	3	1	2	-
Chlortetracycline	1	1	-	-
Veratrum	1	-	1	-
Mustine hydrochloride	3	1	2	-

Summary.

Chlorpromazine was used in the prevention and treatment of vomiting due to cerebral tumour, renal disease, hyperemesis gravidarum, hiatus hernia and vestibular disease; and to the administration of various drugs and X-rays. Jaundice occurred as a complication of treatment in some cases, and this limited the extent of the observations. Chlorpromazine seemed to have a valuable anti-emetic effect in single cases of cerebral tumour, hyperemesis gravidarum and vestibular disease. It was of help in relieving sickness caused by morphine and digitalis. Chlorpromazine did not appear to be of value in preventing sickness caused by uraemia, by radiation therapy or by veratrum viride.

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CHAPTER 2.

THE USE OF APOMORPHINE AS AN EMETIC AGENT

Clinical experience indicated that chlorpromazine had anti-emetic properties, but not whether it was superior to other anti-emetic drugs. This could be determined quantitatively only in controlled experimental conditions. It was decided to study the influence of chlorpromazine and other anti-emetic drugs in preventing sickness induced experimentally in normal human subjects by the injection of apomorphine. Apomorphine was used as the emetic stimulus because it caused sickness in a high proportion of subjects safely, rapidly and with minimal after-effects.

Colleagues and medical students volunteered to act as subjects in these tests, and I am very grateful to them for their participation.

The first steps were to determine a suitable dose of apomorphine, to adopt criteria for measuring the response, and to arrange suitable control of the environmental conditions. Experience indicated that 1 mg. of apomorphine hydrochloride by subcutaneous injection caused vomiting in about half of all subjects tested, and this dose was adopted as a standard.

About /

About five minutes after such an injection symptoms began with drowsiness and a sense of detachment from the environment. The face and ears began to flush; there was often lacrimation, yawning and difficulty in focussing the eyes. A few minutes later nausea first appeared as a sensation of discomfort located at the back of the throat, then in the epigastrium. The nausea came in waves, lasting ten or twenty seconds, with brief intermissions. The waves of nausea were sometimes brought on by a sound or a touch. There was increasing drowsiness and mental depression. The subject salivated, felt very warm, and perspired profusely. Fifteen to twenty minutes after the injection, and usually quite suddenly, the subject vomited. The vomiting was repeated after two or three minutes until the stomach was empty. Vomiting relieved all symptoms except drowsiness, and the subject was glad to lie down. He rested for fifteen to twenty minutes after the test, as though asleep, but the mind received impressions and there was a free and dreamlike flow of ideas. Quite suddenly this dreamy state ceased, and the subject rose, none the worse of the experience.

There /

There was wide variation in the severity of the reaction and in the march of symptoms. Some subjects experienced no symptoms, or only a little drowsiness. In some severe vomiting occurred within five minutes of the injection. Often nausea appeared, reached a maximum after twenty minutes, then regressed without vomiting having occurred. Some subjects vomited very suddenly without premonitory or accompanying symptoms. Drowsiness was sometimes the dominant symptom, and became overpowering. Tinnitus, vertigo, muscle weakness, paraesthesiae in the limbs and call to stool were among other symptoms complained of.

The response to an injection of apomorphine was classified into one of three grades:-

Vomiting:- Regurgitation of recognisable gastric contents including milk or milk curds.

Nausea:- A complaint of nausea, irrespective of severity, which was either spontaneous or which was elicited in response to the question "Have you any symptoms?" Retching and regurgitation of mucus were classed as "nausea".

No sickness:- A negative reply to the question, "Do you feel sick?" When subjects complained of flushing, dizziness, /

dizziness, lacrimation and other symptoms, but denied feeling sick, their responses were classified as "no sickness".

As experience with apomorphine increased it became apparent that the response to an injection was influenced by many environmental factors. The most important of these were the head and body position, and the state of the stomach. The influence of the first of these was analyzed in detail (Isaacs, 1957; see ch.4). During experiments with anti-emetic drugs the subjects remained seated for twenty or twenty-five minutes after receiving the injection, or until vomiting occurred; only then were they allowed to lie down. While sitting they were allowed to move their heads freely and to keep their eyes open; and they were encouraged to write, read or talk to distract their attention.

In preliminary experiments the impression was gained that vomiting after apomorphine occurred more readily when the stomach was full than when it was empty. All later tests were conducted with the subjects fasting, that is, at least three hours after food. On arrival at the laboratory, and before receiving the injection of apomorphine, they were given 250 ml. of milk to drink.

Not /

Not only environmental factors affected the severity of the response to an injection of apomorphine. Subjects varied in their susceptibility, so that 1 mg. of apomorphine might cause violent bouts of vomiting in one person and no symptoms at all in another. This made it desirable in comparative experiments with apomorphine to use each subject as his own control.

The variability in susceptibility to apomorphine could not be correlated with body weight, or with susceptibility to motion sickness as determined roughly by questioning. The reason for it is unknown.

Variation in the response of the same person to repeated injections of apomorphine was also observed. Possible explanations of this were physical tolerance to apomorphine, or psychological adaptation to the experimental procedure. It was possible to examine this question in the course of the experiments on anti-emetic drugs to be reported in chapter 3. In these two studies forty-eight subjects each received 1 mg. of apomorphine on four occasions at intervals of one week. In two of these tests anti-emetic drugs were given as well as apomorphine, but in the other two only inert tablets preceded the injection. The order of these /

these tests varied in different subjects, all twenty-four possible permutations of four being used. The results were thus available of ninety-six tests in which apomorphine alone was given. Twenty-four of these tests were the first in the sequence of four tests which the subject underwent, twenty-four were second tests, twenty-four were third tests and twenty-four were fourth tests. The results of these ninety-six tests are given in Table 2.1 and are shown graphically in Fig. 2.1. It is seen that nausea and vomiting occurred more often in first tests than they did in subsequent tests. There was no difference between the responses to second, third and fourth tests.

If physical tolerance to apomorphine had developed during this sequence of four tests, a steady diminution in the frequency of severe symptoms would have been expected. The fact that the observed diminution in severity occurred entirely after the first test suggests that the process was one of psychological adaptation after the first exposure to the experimental procedure.

Conclusion. /

Table 2. 1. Influence of previous experience of the experimental procedure on the response of 48 subjects to the injection of 1 mg. of apomorphine.

Response to:-	Number of subjects who showed:-		
	No sickness	Nausea	Vomiting
First experiments	2	7	15
Second experiments	6	7	11
Third experiments	6	7	11
Fourth experiments	10	4	10

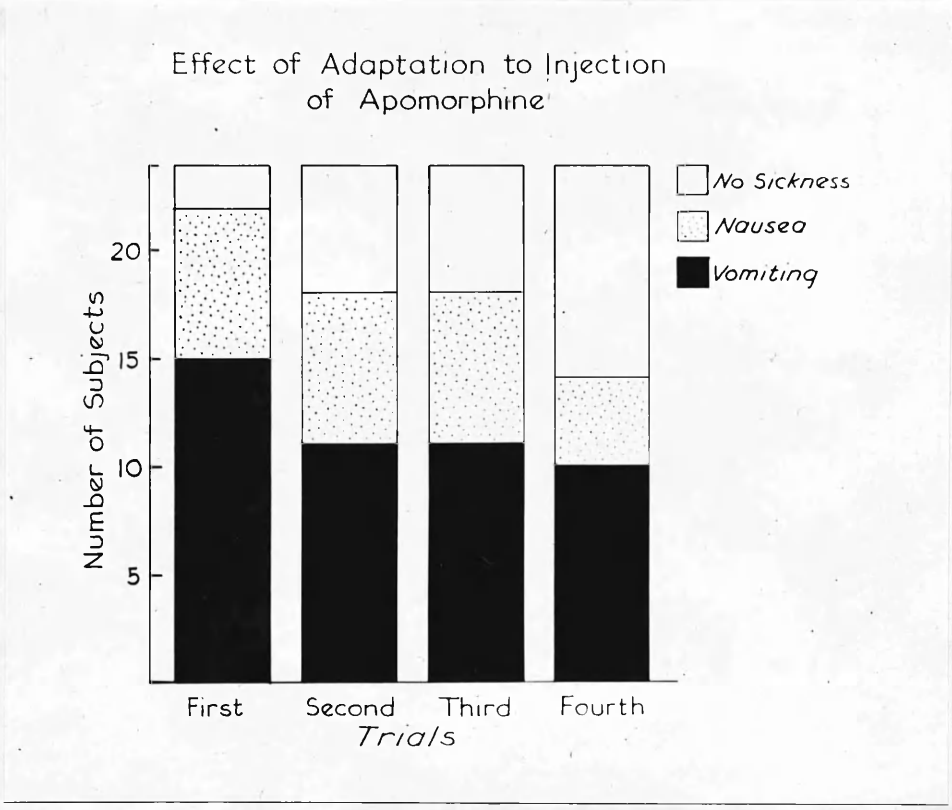

Effect of Adaptation to Injection of Apomorphine
No Sickness
Nausea
Vomiting
Number of Subjects
20
15
10
5
First
Second
Third
Fourth
Trials

Fig. 2.1.

Conclusion.

When the response to apomorphine is used as an indication of the action of anti-emetic drugs the experimental design should ensure that:-

1. Many subjects participate.
2. The subjects are of similar age.
3. The environmental conditions are standardized, especially as regards head and body position and stomach contents.
4. The subject does not know what drugs he has received.
5. Each subject acts as his own control in a sequence of tests.
6. The order in which various drugs are given varies for each subject.

These precautions have been observed in the experiments on anti-emetic drugs to be described in chapter 3.

Summary. /

Summary.

A subcutaneous injection of 1 mg. of apomorphine is a suitable agent in the experimental evaluation of anti-emetic drugs in man. Its effects vary from no symptoms at all to violent bouts of vomiting. The variability of response depends on variations in individual susceptibility to the drug and environmental influences. The experimental evaluation of anti-emetic drugs using apomorphine as an emetic agent requires careful standardization of the conditions, the participation of many subjects and a cross-over experimental design.

CHAPTER 3.

EXPERIMENTAL EVALUATION OF ANTI-EMETIC DRUGS

In this section experiments are described which were designed to determine whether chlorpromazine prevented vomiting induced experimentally by injection of apomorphine in man. Chlorpromazine was compared with other anti-emetic drugs - promethazine, hyoscine and atropine. The findings have been reported elsewhere (1, 2).

It was decided to compare chlorpromazine first with promethazine, which was chosen for the following reasons:-

(i) Promethazine resembles chlorpromazine chemically (Fig. 3.1).

(ii) The absorption and fate of the two drugs is similar (3, 4).

(iii) Promethazine is an effective anti-emetic agent (5 -11).

(iv) Promethazine is a powerful anti-histamine agent: chlorpromazine is not (12 - 14).

It /

It was hoped to obtain evidence on the relation between antihistamine and anti-emetic activity. It was decided to observe the effects of 50 mg. of each of these drugs, given two hours before the injection, on the response to 1 mg. of apomorphine.

Methods.

Twenty-four healthy males, whose ages ranged from 19 to 30 years, volunteered as subjects. Each subject underwent 4 tests at intervals of one week. In each test, not less than one hour after a light meal, the subject swallowed two tablets. Two hours later he came to the laboratory and drank 250 ml. of milk. He then received a subcutaneous injection. The subject was told that the tablets "might or might not be anti-emetic drugs" and that the injection "might or might not be an emetic agent". In fact, all injections were 1 mg. of apomorphine hydrochloride.

After the injection the subject sat at a table and copied from a book. He reported symptoms to an observer. After twenty minutes, or after the occurrence of vomiting, whichever was shorter, the observation period was terminated and the subject allowed to lie down. After resting he left the laboratory.

The /

The symptoms were classified as "no sickness", "nausea" and "vomiting" according to the definitions in chapter 2.

The four sets of tablets used were referred to as:-

A - Two inert tablets.

B - Two tablets each of 25mg. of chlorpromazine hydrochloride.

C - Two inert tablets.

D - Two tablets each of 25 mg. of promethazine hydrochloride.

The inert tablets were indistinguishable from the active ones. On joining the experiment each subject was given at random a coding formed by the letters A, B, C, D in one of their twenty-four possible permutations. This determined the order in which each received the four sets of tablets.

Results.

These are set out in Table 3.1 and are illustrated in Figs. 3.2 and 3.3.

In /

Table 3.1 Results of the first anti-emetic experiment

Subject		Response to apomorphine after:-			
No	Sequence of tablets	A (inert)	B (chlorpro-:mazine)	C (inert)	D (prometh-:azine)
1	A B C D	V	O	N	V
2	A B D C	V	N	N	V
3	A C B D	N	O	V	N
4	A C D B	N	O	N	O
5	A D B C	V	O	V	V
6	A D C B	V	O	N	N
7	B A C D	V	O	V	N
8	B A D C	N	O	V	N
9	B C A D	V	O	N	N
10	B C D A	V	V	V	V
11	B D A C	V	O	O	O
12	B D C A	O	O	O	O
13	C A B D	V	O	V	V
14	C A D B	O	O	N	O
15	C B A D	V	O	V	V
16	C B D A	V	O	V	O
17	C D A B	N	N	V	O
18	C D B A	V	O	V	O
19	D A B C	N	O	O	N
20	D A C B	N	N	N	N
21	D B A C	V	O	V	V
22	D B C A	O	O	N	N
23	D C A B	N	O	N	N
24	D C B A	O	O	O	N
Totals	O	4	20	4	7
	N	7	3	9	10
	V	13	1	11	7

O = No sickness
N = Nausea
V = Vomiting

Dose of chlorpromazine and promethazine was 50 mg.

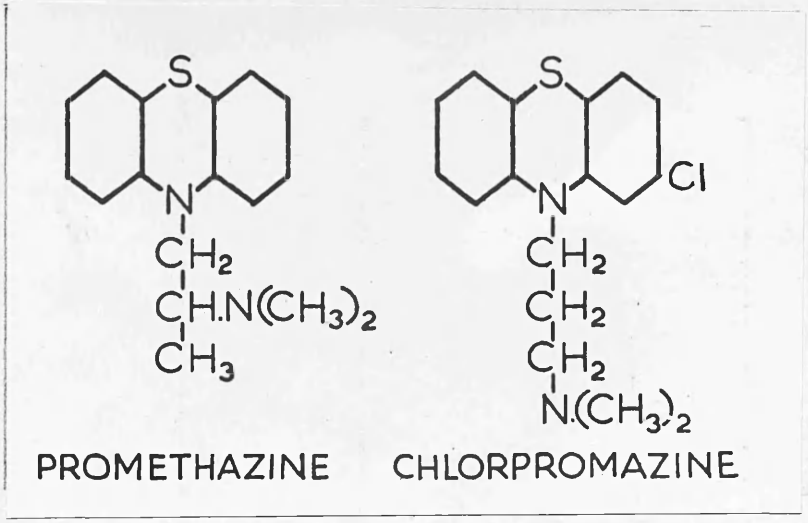
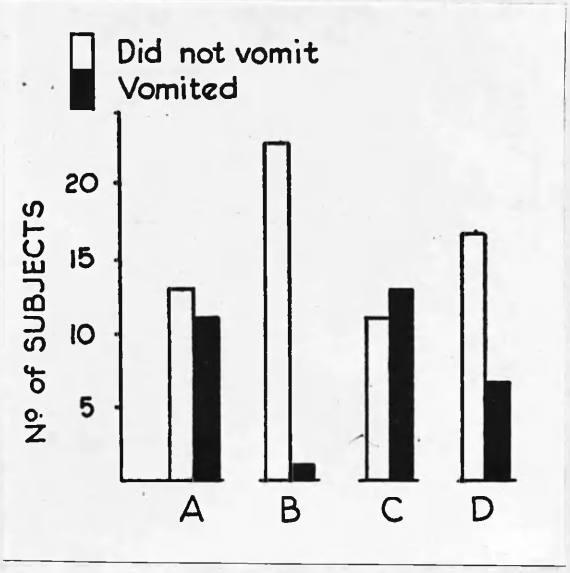
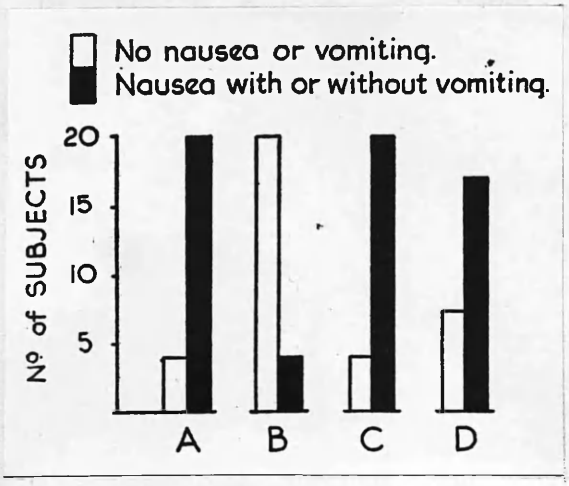


Fig. 3.1.

Chemical formulae of chlorpromazine and promethazine.





Figs. 3.2 and 3.3.

Results in 24 subjects after:-

A and C - Inert tablets
B - Chlorpromazine
C - Promethazine

In response to 1 mg. of apomorphine thirteen of twenty-four subjects vomited after inert tablets A and eleven of twenty-four after inert tablets C. The men who vomited after A were not necessarily the same as those who vomited after C, but the distribution of responses within these groups was similar. This supports the validity of the experimental design.

After taking chlorpromazine only one of twenty-four subjects vomited in response to apomorphine, and three others complained of nausea. The remaining twenty subjects experienced no sickness. After promethazine seven of twenty-four subjects vomited in response to apomorphine and ten others complained of nausea. The nausea in these ten subjects was more severe on the average than it was in subjects who received apomorphine alone.

After chlorpromazine a few men complained of drowsiness and of dryness of the mouth. After promethazine many complained of drowsiness, and they slept soundly after the injection.

Statistical analysis of the results shows that there was no significant difference in the distribution of the responses between the two control groups, A and C. The difference between chlorpromazine and the controls was highly significant ($p < 0.001$). Chlorpromazine also differed /

differed significantly from promethazine ($p < 0.001$). The difference between promethazine and the controls failed to reach the 5% level of significance.

These results demonstrate that chlorpromazine almost entirely prevented nausea and vomiting induced by apomorphine. The antagonism between the two drugs was often so complete that the subjects did not suspect that they had been given an injection of an emetic agent. After promethazine the incidence of vomiting in response to apomorphine was less than it was after inert tablets. This reduction of the incidence of sickness was not statistically significant, but it should be mentioned that, with the incidence of sickness in the control groups of this experiment, it would be necessary for the number who vomited after an anti-emetic drug to fall to six of twenty-four before a significant reduction of the incidence of vomiting could be claimed. It seems justifiable to conclude that promethazine reduced the frequency of vomiting after apomorphine, but that it was much less effective than chlorpromazine.

Influence of atropine and hyoscine on apomorphine vomiting.

Chlorpromazine was next compared with hyoscine, in its ability to prevent apomorphine-vomiting, for the following reasons:-

1. Hyoscine has been used as an anti-emetic probably for longer than any other drug.

2. Hyoscine differs widely from chlorpromazine in chemical structure.

3. Hyoscine is a powerful anticholinergic drug: chlorpromazine is not (13, 14). It was of interest to study the relation between anti-emetic activity and anticholinergic potency.

The action of atropine on apomorphine-vomiting was studied in the same experiment. Less is known about the anti-emetic properties of atropine than of hyoscine. It is of interest to compare these two drugs which differ in their central but not in their peripheral actions.

This trial differed from the previous one only in the following respects. A further twenty-four medical students acted as subjects: ten of these were females.

The /

The tablets were taken one hour before the injections, instead of two hours, because of the more rapid onset of action of these drugs. After the injection the subjects read but did not write. The observation period after the injection was twenty-five minutes rather than twenty minutes. The tablets used were:-

E - Inert.

F - Atropine sulphate 0.75 mg.

G - Inert.

H - Hyoscine hydrobromide 0.75 mg.

The tablets were tasteless and indistinguishable.

Results.

These are given in Table 3.2 and illustrated in Fig. 3.4.

The results in the control groups E and G were similar to one another and to the results in the control groups A and C. Twelve of twenty-four subjects vomited in response to 1 mg. of apomorphine after inert tablet E, and eleven of twenty-four after inert tablet G. Eight of twenty-four subjects vomited in response to apomorphine after 0.75 mg. of atropine and five others complained of nausea but did not vomit. Eleven subjects experienced no sickness. After hyoscine four of twenty-four subjects

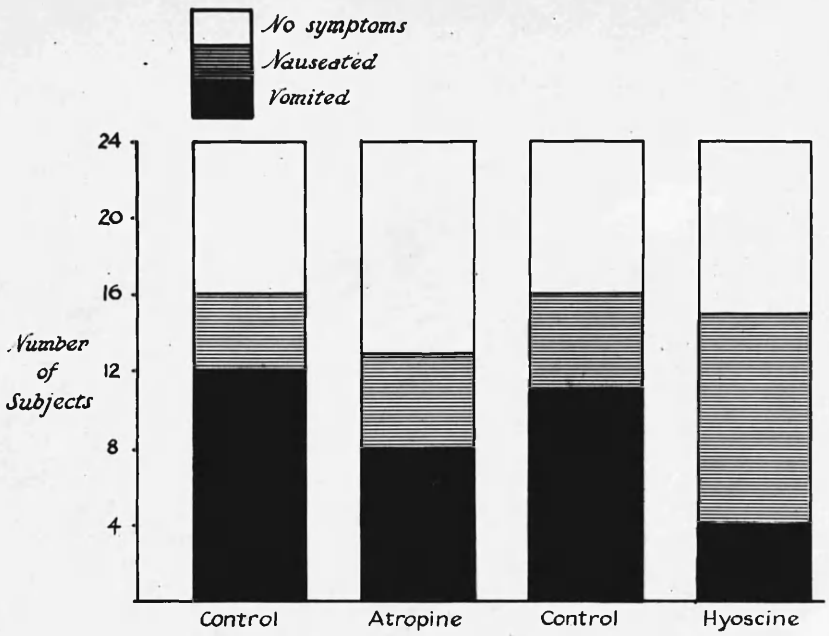
vomited /

Table 3. 2. Results of second anti-emetic experiment

Subject			Response to apomorphine after:-			
No	Sex	Sequence of tablets	E (inert)	F (atropine)	G (inert)	H (hyoscine)
1	M	E F G H	O	O	O	O
2	F	E F H G	V	V	V	N
3	M	E G F H	V	O	V	N
4	M	E G H F	V	V	V	V
5	M	E H F G	V	N	O	N
6	F	E H G F	V	V	V	O
7	M	F E G H	O	O	V	N
8	F	F E H G	V	V	V	V
9	M	F G E H	V	V	V	O
10	M	F G H E	N	O	O	O
11	F	F H E G	V	O	O	O
12	M	F H G E	V	V	V	N
13	M	G E F H	N	O	V	O
14	F	G E H F	V	N	N	N
15	M	G F E H	O	O	N	N
16	F	G F H E	O	O	N	O
17	M	G H E F	O	V	N	O
18	F	G H F E	N	N	O	O
19	F	H E F G	V	V	V	V
20	F	H E G F	V	N	V	N
21	M	H F E G	N	N	N	N
22	M	H F G E	O	O	O	N
23	F	H G E F	O	O	O	N
24	M	H G F E	O	O	O	V
Totals		O	8	11	8	9
		N	4	5	5	11
		V	12	8	11	4

O = No sickness
N = Nausea
V = Vomiting

Dose of atropine sulphate and hyoscine hydrobromide was 0.75 mg.



Incidence of Nausea and Vomiting in 24 subjects in response to Apomorphine preceded by various drugs.

Fig. 3.4.

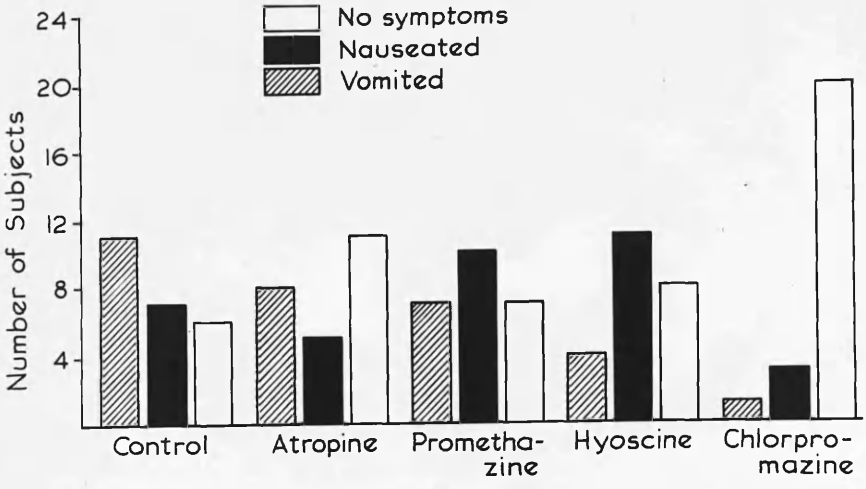


Fig. 3.5.

Summary of results of trials of four anti-emetic drugs.

vomited in response to apomorphine. Eleven others experienced nausea and nine had no sickness. Nausea after hyoscine was often severe and prolonged, and many subjects wanted to vomit but were unable to do so.

More subjects in E and G had "no sickness" than in A and C. It cannot be said whether this was due to the slight difference in procedure, or whether the second group contained by chance more people who were relatively insusceptible to apomorphine. The second explanation is more likely.

Some subjects complained of dry mouth and blurring of vision after hyoscine and atropine, but no one complained of drowsiness.

On statistical analysis of these results no significant difference was found between the control groups. Hyoscine differed significantly from the controls ($p < 0.05$). The difference between atropine and the control group did not reach the 5% level of significance.

Direct comparison between chlorpromazine and promethazine on the one hand and atropine and hyoscine on the other is not entirely valid, because different subjects were used in the two studies and the experimental conditions were not identical. However, the distribution of responses to the control /

control injections in the two groups was similar, and only a slight error in the comparison is therefore likely. When chlorpromazine and hyoscine were compared in this way the difference between the responses to them was highly significant ($p < 0.01$). Hyoscine differed from chlorpromazine not only in protecting fewer people from vomiting but also in giving little or no protection against nausea. Chlorpromazine differed significantly also from atropine and from promethazine. These results are summarized graphically in Fig. 3.5. (See also Table 3.4).

Effect of larger doses of atropine and hyoscine.

A third experiment was conducted, along similar lines to the two previous ones, to test the effect of larger doses of atropine and hyoscine on vomiting induced by apomorphine. It was thought possible that a larger dose of hyoscine might yield results closer to what was found after chlorpromazine. Twelve students took part in this experiment, ten of them males. The same method as before was used except that each student was given three injections of 1 mg. of apomorphine, preceded by:-

E_2 - Two inert tablets.

F_2 - Atropine sulphate 1.5 mg.

G_2 - Hyoscine hydrobromide 1.5 mg.

The /

Table 3. 3. Results of third anti-emetic experiment

Subject			Response to apomorphine after:-		
No	Sex	Sequence of tablets	E_2 (inert)	F_2 (atropine)	H_2 (hyoscine)
1	F	E F H	N	N	N
2	M	E H F	N	N	N
3	M	F E H	O	O	N
4	M	F H E	V	V	V
5	M	H E F	O	O	O
6	M	H F E	O	O	V
7	F	E F H	O	V	O
8	M	E H F	V	V	V
9	M	F E H	V	O	O
10	M	F H E	O	N	O
11	M	H E F	N	N	O
12	M	H F E	W I T H D R A W N		

Doses of atropine sulphate and of hyoscine hydrobromide were 1.5 mg.

The results of this experiment are recorded in Table 3.3. One subject was withdrawn from the experiment because he developed syncope after his first injection of apomorphine: this had been preceded by hyoscine. Of the remaining eleven students in the control group E_2, three vomited in response to apomorphine alone. Three vomited in response to apomorphine after 1.5 mg. atropine and three after 1.5 mg. of hyoscine. Side-effects due to the anti-emetic drugs were common, and this prevented the inclusion of more subjects. Complaints included dry mouth, blurring of vision, drowsiness and mental detachment. These occurred in eight subjects after hyoscine and were also noted after atropine.

It was surprising that only three of eleven subjects vomited after the control injection of apomorphine. This makes it impossible to ascribe any anti-emetic activity to the drugs in this trial. Many more subjects would have been required to determine differences between the effects of the two doses of atropine and hyoscine used. It can be said that no evidence was obtained that 1.5 mg. of hyoscine was more effective in preventing apomorphine-vomiting than was 0.75 mg. of the same drug.

Discussion. /

Discussion.

All the drugs tested in this study reduced the incidence of vomiting after apomorphine. Only chlorpromazine, however, and, to a much smaller extent, atropine, increased the number who were relieved of both nausea and vomiting. Hyoscine prevented two-thirds of susceptible subjects from vomiting, but they experienced severe nausea instead. This is quite unlike the action of chlorpromazine which relieved both nausea and vomiting. Hyoscine differed also from atropine, for the latter drug reduced the number who vomited, and affected but little the number who had nausea, thus increasing the number who had "no sickness".

The main difference between chlorpromazine and hyoscine was that chlorpromazine prevented both nausea and vomiting, whereas hyoscine greatly reduced the incidence of vomiting but did not affect the occurrence of nausea. It seems that the prevention of vomiting and the prevention of nausea are not merely quantitatively different aspects of the same pharmacological action. It may be that hyoscine depressed the activity of the vomiting centre, but did not significantly interrupt the action of apomorphine; whereas chlorpromazine blocked the action

of /

of apomorphine at a more proximal site, apart from any depressant action it may have exerted on the vomiting centre. This is conjecture at present, but evidence will be presented later which will allow development of this idea.

These experiments also throw light on the relation of anti-emetic activity and anti-histamine and anticholinergic properties. Promethazine is 100 times more powerful an antagonist of histamine than is chlorpromazine (13, 14), but is a much less effective anti-emetic. The same workers showed that promethazine was also 8 times more powerful than chlorpromazine as an antagonist of acetylcholine; and this indicates that anti-emetic activity does not depend on anticholinergic potency. This is further borne out by the inferiority of atropine and hyoscine to chlorpromazine as antagonists of acetylcholine. Chinn and Smith (15) reviewed the literature on motion sickness remedies and concluded that, although many effective drugs were antihistaminic or anticholinergic, their anti-emetic effect did not depend on either of these properties.

It is concluded that chlorpromazine was by far the most effective of the four drugs studied in preventing nausea /

nausea and vomiting induced by apomorphine. Atropine, promethazine and especially hyoscine all reduced the incidence of vomiting with little effect on the incidence of nausea. There was a qualitative and not merely a quantitative difference between the action of chlorpromazine and the other drugs studied. This may depend on a specific antagonism of apomorphine by chlorpromazine and the antagonism may occur elsewhere than at the vomiting centre itself. The anti-emetic actions of the four drugs studied is independent of their power to antagonise acetylcholine and histamine.

Summary.

Three experiments were conducted, using sixty normal subjects, in which the ability of drugs to prevent apomorphine-vomiting was studied. The drugs tested were chlorpromazine 50 mg., promethazine 50 mg., atropine 0.75 mg. and 1.5 mg. and hyoscine 0.75 mg. and 1.5 mg. Chlorpromazine was highly effective in preventing nausea and vomiting. Hyoscine greatly reduced the incidence of vomiting but did not reduce the incidence of nausea. Atropine and promethazine also reduced the incidence of vomiting. Anti-emetic action does not depend on antihistamine or anti-acetylcholine effects. Chlorpromazine exerts an action different not only in degree but also in kind from that of hyoscine and the other drugs.

References. /

Table 3.4

Effects of various drugs in preventing apomorphine sickness: analysis.

The table shows the probability (p) that the observed difference in the response to any pair of drugs was due to chance.

Drugs	Control	Atropine	Promethazine	Hyoscine
Atropine	$0.2>p>0.1$			
Promethazine	$0.2>p>0.1$	0.3		
Hyoscine	$0.02>p>0.01$	$0.2>p>0.1$	>0.5	
Chlorpromazine	$p<0.001$	$0.02>p>0.01$	<0.01	<0.01

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CHAPTER 4.

THE INFLUENCE OF ENVIRONMENTAL FACTORS ON THE EMETIC ACTION OF APOMORPHINE

It was suggested in the last chapter that the mode of action of chlorpromazine in preventing apomorphine vomiting might be antagonism at some site other than the vomiting centre. Further explanation of this possibility requires knowledge of the pathways of the action of apomorphine. Although much experimental work has been devoted to this subject in cats and dogs (1, 2), little evidence is available about the action of apomorphine in man. In this chapter experiments will be described which were designed to elucidate the mechanism of the emetic action of apomorphine in man. The experimental approach used was a study of the influence of certain environmental factors on the response of groups of subjects to injections of apomorphine. These experiments have been reported elsewhere (3).

In the preliminary experiments with apomorphine it was observed that the symptoms which followed the injection were relieved if the subject lay down. Experiments were therefore directed first to determining the degree and nature of the protective effect of recumbency.

Methods. /

Methods.

In the experiments described in this chapter forty-seven healthy medical students participated. There were forty males and seven females, and each underwent four tests at intervals of one week. In each test the subject's response to an injection of apomorphine was observed while he maintained an arranged position, and was classified in one of the three grades - No sickness, nausea or vomited. A different position was adopted in each test, and the order varied in each subject. The procedure resembled that described in chapter 3. Two hours after a light meal the subject was given a tablet which, he was told, "might or might not be an anti-emetic agent", but in fact all the tablets were inert. One hour later he received 250 ml. of milk, followed by an injection, which, he was told, "might or might not be an emetic agent". The injection was always of apomorphine hydrochloride, and the dose was 1 mg. unless otherwise stated. For twenty-five minutes after the injection, or until vomiting occurred, whichever was less, the subject maintained an arranged position. Thereafter he was allowed to rest.

Results. /

Results.

Effects of recumbency.

In the experiments described in chapter 3 the response to 1 mg. of apomorphine in the sitting position with free head movement was observed in one-hundred-and-seven tests. In the present series twenty-one more subjects received 1 mg. of apomorphine while they remained seated with head held upright and still and eyes closed. Taking these one-hundred-and-twenty-eight tests together, vomiting occurred in sixty-four tests (50%), nausea in thirty-two (25%) and no sickness in 32 (25%). Forty-three subjects received 1 mg. of apomorphine and remained supine with head still after the injection. The eyes were open in nineteen and closed in twenty-four. Only five of these subjects (12%) vomited, ten (23%) complained of nausea, and twenty-eight (65%) had no sickness. The difference between the distribution of responses in these groups is highly significant ($p < 0.001$) (Table 4.1). It is concluded that recumbency conferred a high degree of protection against the emetic effect of apomorphine.

The protective effect of recumbency might have been associated with the horizontal position of the head, or the supine /

Table 4.1 Influence of recumbency on the emetic effect of apomorphine.

Experiment	Body position	Number of tests	Number who experienced:		
			No sickness	Nausea	Vomiting
First anti-emetic trial	Seated, free head movement, eyes open	48	8	16	24
Second anti-emetic trial	Seated, free head movement, eyes open	48	16	9	23
Third anti-emetic trial	Seated, free head movement, eyes open	11	5	3	3
Present experiment	Seated, head still, eyes closed	21	3	4	14
Total	Seated	128	32	32	64
Present experiment	Supine, head horizontal, eyes open	19	14	4	1
Present experiment	Supine, head horizontal, eyes closed	24	14	6	4
Total	Recumbent	43	28	10	5

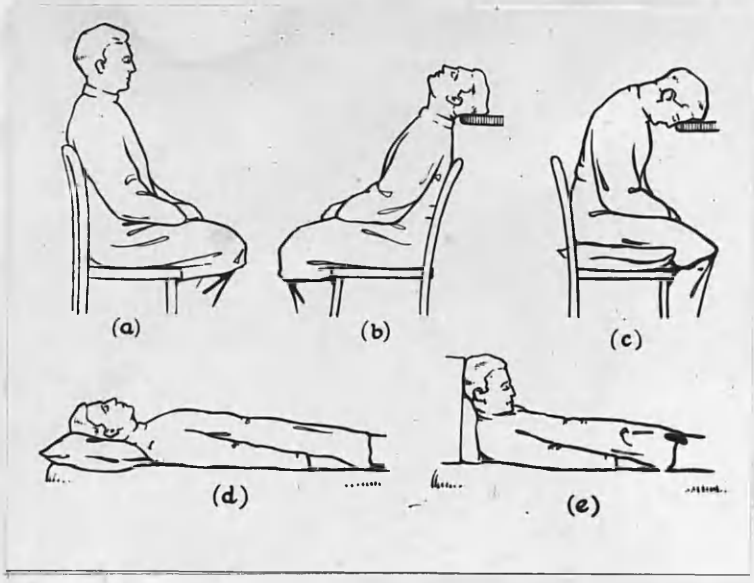

Fig. 4.1.

Positions of the head and body employed in the study.

Fig. 4.2.

The subject lay supine and compressed a spring with his feet.

Table 4.2 Influence of head and body position on response to 1 mg. of apomorphine.

Position of:		Number of tests	Number of responses classified as:		
Head	Body		No sickness	Nausea	Vomited
Vertical	Seated	21	3	4	14
Horizontal	Seated	6	1	1	4
Vertical	Recumbent	24	12	9	3
Horizontal	Recumbent	24	14	6	4

supine position of the trunk. To examine this point tests were carried out in which the subjects adopted positions illustrated in Fig. 4.1. In position (a) the subjects lay supine, but the head was flexed into the vertical position as in sitting. In position (b) they sat but the head was extended backward and rested on a table in the position occupied in recumbency. The results of these tests are shown in Table 4.2.
With the trunk supine the response to apomorphine remained the same whether the head was horizontal or vertical.
With the subject seated, the response to apomorphine was the same whether the head was vertical or horizontal. Only six tests were carried out with the subject seated and the head extended backward, because the position was difficult to maintain and severe symptoms occurred. It is concluded that the protective effect of recumbency was associated with the supine position of the trunk itself, and was little influenced by the position of the head.

When free head movement was allowed in the earlier tests, the subjects often voluntarily flexed their heads forward, and noted that this partly relieved nausea. In the next group of tests, therefore, the response to apomorphine was tested /

Table 4.3 Influence of head position on response of seated subjects to apomorphine.

Position	Dose of apomorphine	Number of tests	Number of responses classified as:		
			No sickness	Nausea	Vomited
Seated, head upright	1.0 mg.	21	3	4	14
do.	0.75 mg.	16	8	5	3
do.	0.5 mg.	11	7	2	2
Seated, head flexed forward	1.0 mg.	6	1	2	3
do.	0.75 mg.	10	5	5	0
do.	0.5 mg.	10	9	1	0

tested in subjects who sat with the head flexed forward and with the brow resting on a table (Fig.4.1 (c)). The group tested with 1 mg. of apomorphine was small, because the symptoms were severe, and so tests were also conducted with doses of 0.5 mg. and 0.75 mg. of apomorphine. The results of these tests are shown in Table 4.3. Nausea and vomiting occurred less frequently when the head was flexed forward than it did in the upright position. The differences were not statistically significant, but they suggested that forward flexion of the head conferred some protection against the emetic effect of apomorphine.

Influence of muscle tone.

The protective effect of recumbency might have been due to the diminished muscle tone in this position. To examine this possibility the experiment illustrated in Fig. 4.2 was conducted in seven subjects. They lay supine with head horizontal and eyes closed, and they compressed with their feet a spring of 42 lbs. tension. This increased tone in the muscles of the legs, pelvis, trunk and shoulder girdle. An injection of 1 mg. of apomorphine was given and the compression was maintained for twenty-five minutes. One of the seven subjects vomited,

one /

one other experienced nausea, and five had no sickness. The distribution of responses was thus similar to what occurred in ordinary recumbency. It was concluded that the protective effect of recumbency was not due to a general reduction of muscle activity.

Effect of vestibular stimulation.

In another group of tests the influence of stimulation of the vestibules was studied. The subjects remained supine with eyes closed and received an injection of 1 mg. of apomorphine. They were then subjected to regular motion on either the horizontal or the vertical swing. These appliances are described in Appendix 3. On both swings the rate of motion was 18 cycles per minute and its amplitude 1 metre. The results are given in Table 4.4. When apomorphine and vestibular stimulation were applied together sickness occurred frequently. Vestibular stimulation alone, as applied in this test, caused no symptoms.

In an additional group of ten subjects an injection of apomorphine was combined with caloric stimulation of the vestibule. In this experiment, which was originally a study of the influence of apomorphine on vestibular /

Table 4.4 Effect of apomorphine and vestibular stimulation.

Vestibular stimulation	Dose of apomorphine	Number of tests	Number of responses classified as:		
			No sickness	Nausea	Vomited
Horizontal swinging	1 mg.	16	2	5	9
Vertical swinging	1 mg.	12	1	6	5
Caloric stimulation	0.25 mg.	10	6	3	1

vestibular reflexes, only 0.25 mg. of apomorphine was injected. The left ear was irrigated with water at 30°C for forty seconds, fifteen minutes and five minutes before the injection and ten minutes and twenty minutes after the injection. One subject vomited and three others complained of nausea. Neither 0.25 mg. of apomorphine alone nor caloric stimulation alone caused symptoms.

It was concluded that the effects of apomorphine and of vestibular stimulation were additive.

Influence of vision.

The influence of vision on the emetic action of apomorphine was examined by giving injections of apomorphine in the seated and recumbent positions. After the injections the subjects either remained with eyes closed, or looked steadily at the wall or ceiling. The results of these tests are set out in Table 4.5. The incidence of vomiting was higher, but not significantly so, in both positions, when the eyes were closed than when the eyes were open.

Discussion. /

Table 4.5 Influence of vision on the emetic action of apomorphine.

Position	State of eyes	Dose of apomorphine	Number of tests	Number of responses classified as:		
				No sickness	Nausea	Vomited
Seated, head upright	Closed	0.75 mg.	16	8	5	3
Seated, head upright	Open	0.75 mg.	6	1	5	0
Recumbent, head horizontal	Closed	1 mg.	24	14	6	4
Recumbent, head horizontal	Open	1 mg.	19	14	4	1

Discussion.

Because of individual variation in the susceptibility to apomorphine, the influence of environmental factors should be compared by noting the response of a large group of subjects exposed successively to different conditions in a cross-over type of experiment. The present study was executed partly along these lines, but many comparisons had to be made between small and heterogeneous groups. It was then not possible to examine the differences between groups statistically; but in many experiments the trend of the results was clear. The detection of small differences between groups requires very large numbers of subjects, and it is not practicable to conduct such large experiments.

The emetic effect of apomorphine was prevented by lying down. This suggests that apomorphine does not directly stimulate a central emetic mechanism, but that its action depends on the flow of afferent impulses to the brain. Vestibular impulses might be concerned, because vestibular stimulation causes motion sickness (4) which resembles the symptoms caused by apomorphine; and vestibular stimulation and apomorphine together caused severe sickness. Recumbency might /

might then protect against apomorphine, as it is believed to do against motion, by reducing the vestibular inflow. In experiments where no head movement took place the vestibular inflow was confined to the resting discharge from the vestibules (5). This depends on the position of the head in space. It is least when the head is flexed forward, and in this position sickness after apomorphine was found not to depend on the position of the head in space. It is concluded that apomorphine does not ordinarily cause vomiting by facilitating vestibular impulses, but that apomorphine and vestibular stimulation may have an additive effect in causing sickness.

The reduction in impulses from the muscles and ligaments of the trunk and limbs in the supine position did not determine protection against apomorphine, since increasing these impulses by pressing against resistance did not change the response to apomorphine. Impulses from the neck may have been more important. In sitting, the head is supported by the muscles and ligaments of the neck, which send proprioceptive impulses to the brain. In recumbency the head rested on a couch, the neck was relaxed, and the proprioceptive inflow was less. In the former case vomiting was frequent, in the latter infrequent. /

infrequent. If the state of the neck influenced susceptibility to apomorphine, sickness would occur when the neck was stretched and not when it was relaxed. This tendency was found, for when the subjects sat with the head extended and the neck stretched sickness was severe; and when the head was flexed and supported and the neck relaxed, less sickness occurred. In recumbency the head was supported both when it was extended and when it was flexed: in the latter case the occiput rested against an upright support. In both these positions the incidence of sickness was low. However, while this factor may have played some part, it would not explain all the observed differences; nor is there any quantitative information on the proprioceptive inflow from neck structures in different positions. The part played by impulses from the neck in influencing the emetic action of apomorphine remains uncertain.

The recumbent position of the trunk itself was associated with a low incidence of sickness in response to apomorphine, irrespective of the position of the head and the state of the muscles. The upright position of the trunk was associated with a high incidence of sickness. It is possible that susceptibility to apomorphine was influenced by impulses from structures /

structures within the thorax and abdomen, such as the diaphragm, the mesentery and the stomach wall, and that such impulses differed in the upright position and in the supine position. At present there is no other experimental support for this conjecture.

There is no evidence that the protective effect of recumbency was mediated by haemodynamic factors. The diminished susceptibility to apomorphine on lying down may have been due in part to the enhanced feeling of security in the recumbent position. The finding that sickness was rather more common when the eyes were closed than it was when they were open recalls a similar observation of Manning and Stewart (6) in experimental motion sickness, and illustrates how the higher centres can influence the activity of the emetic mechanism.

This study has demonstrated the protective effect of recumbency against the emetic action of apomorphine in man. Indications are given of the possible role in apomorphine vomiting of afferent impulses from the vestibules, the neck and thoracic or abdominal structures. Hatcher and Weiss (7) believed, from experiments in dogs and cats, that apomorphine caused vomiting by facilitating the influence /

influence of afferent impulses on the central emetic mechanism. More recent experimental work by Wang and Borison (8) has shown that apomorphine causes vomiting in dogs and cats only when a small receptor area in the medulla remains intact. They call this area, which is distinct from the vomiting centre, the "chemoreceptor trigger zone" and they declare that apomorphine acts solely at this site. It is not known whether the chemoreceptor trigger zone occurs in man. But even if this structure is the sole receptor site for the emetic action of apomorphine in man, it remains necessary to take into account the influence of environmental factors in determining the response of the central emetic mechanism to the effect of apomorphine.

Since the recumbent position prevents apomorphine from causing vomiting by limiting the afferent inflow, any drug which exerted a similar effect might prevent apomorphine from causing nausea and vomiting without acting on the vomiting centre itself. This suggests an approach to an understanding of the mode of action of chlorpromazine which will be discussed more fully later.

Summary. /

Summary.

The influence of environmental factors on the response to apomorphine was studied by giving injections of the drug while the subjects maintained various positions. It was found that the supine position conferred a high degree of protection against the emetic effect of apomorphine. The protective effect of recumbency depended on the supine position of the trunk, and was little influenced by the position of the head.
It is considered that apomorphine may cause vomiting by sensitising the central emetic mechanism to afferent impulses from the vestibules, the neck and other parts. The findings are discussed in relation to a possible mode of action of anti-emetic drugs.

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THE ANTIDIURETIC ACTION OF APOMORPHINE

It was shown in the previous chapter that the emetic action of apomorphine depended on the flow of afferent impulses to the brain. When these impulses were reduced by lying down apomorphine failed to provoke vomiting. The action of chlorpromazine in preventing apomorphine-induced vomiting was attributed to blockade of afferent impulses destined for the vomiting centre, and not to depression of the latter. Support for this hypothesis was next sought by examining the influence of body position and of chlorpromazine on other effects of apomorphine. In this chapter it will be shown that sub-emetic doses of apomorphine inhibited water diuresis in man. This inhibition of water diuresis was prevented by recumbency and by previous administration of chlorpromazine. Chlorpromazine thus prevented in a similar way both the emetic and the antidiuretic effects of apomorphine.

Methods.

The influence of apomorphine on water diuresis was studied in medical students and colleagues who were asked to take part in a sequence of tests at intervals of one week. In each test the subject attended the laboratory two hours after /

after a light meal. He refrained from smoking for two hours before the test and during it. At the beginning of the test he emptied his bladder and then drank one litre of water in ten minutes. Thereafter he emptied his bladder every fifteen minutes, and recorded the volume of the specimen. Forty-five minutes after beginning the test he was given an injection of apomorphine, and for twenty-five minutes thereafter he maintained one of the following positions (except when passing urine fifteen minutes after the injection):-

(a) Seated, head vertical and still, eyes closed.

(b) Supine, head horizontal and still, eyes closed.

(c) Supine, head vertical, eyes closed.

(d) Seated, head extended backward, eyes closed (one test only).

Urine specimens were collected every fifteen minutes until the water load had been excreted. The subject was otherwise allowed to adopt any desired position after the period in a fixed position, and often chose to lie down.

When water diuresis was not inhibited the fifteen-minute volumes of urine increased steadily, reached a maximum after one to one-and-a-half hours, and declined to resting levels after two to three hours. When water diuresis was inhibited a first peak of diuresis occurred at one hour or one-and-a-quarter hours. The fifteen-minute volumes then declined, remained low /

low for a variable time, rose again to reach a second peak, and declined again. The duration of antidiuresis was expressed as the time between the two peaks of diuresis. In these experiments the second peak of diuresis was defined as the time when the largest fifteen-minute volume of urine was passed, or a preceding volume which was more than 90% of the largest.

In some tests chlorpromazine was given by mouth one hour and a quarter before the water load, that is, two hours before apomorphine.

When antidiuresis is due solely to liberation of antidiuretic hormone (ADH) the "peak-to-peak time" measured in this way is related to the amount of antidiuretic hormone released (1). From the data of Burn and Grewal (1) a peak-to-peak time of one hour corresponds to the release of about 50 mU of ADH, and a peak-to-peak time of two hours to about 200 mU.

Results.

These are summarized in Table 5.1 and typical experiments are illustrated in Fig. 5.1.

Five men were given 0.5 mg. of apomorphine in the sitting position and water diuresis was inhibited in three of /

Table 5.1 Influence of apomorphine on water diuresis

Subject	Dose of apomorphine (mg.)	Head and body position	Measurement of anti-diuresis peak-to-peak time in minutes Method A.	Symptoms
J.J.L.	0.25	Subject seated, head upright.	0	Mild nausea.
J.J.L.	0.5		60	Moderate nausea.
B.I.	0.5		0	Mild nausea.
B.I.	1.0		165	Severe nausea.
B.W.	0.5		0	No symptoms.
A.J.	0.5		75	No symptoms.
F.L.	0.5		150	Severe nausea.
A.Z.	0.5	Subject recumbent, head back.	0	No symptoms.
A.J.	0.5		0	No symptoms.
F.L.	0.5		0	No symptoms.
B.W.	0.5		0	No symptoms.
G.R.Y.	0.5		75	No symptoms.
B.I.	0.75		0	Mild nausea.
B.I.	1.0		75	Mild nausea.
B.I.	1.0		90	Mild nausea.
A.Z.	0.5	Subject recumbent, head vertical.	0	Mild nausea.
B.W.	0.5		0	No symptoms.
F.L.	0.5		60	No symptoms.
A.J.	0.5		150	Mild nausea.
B.I.	1.0		105	Mild nausea.
B.I.	1.0		0	Mild nausea.

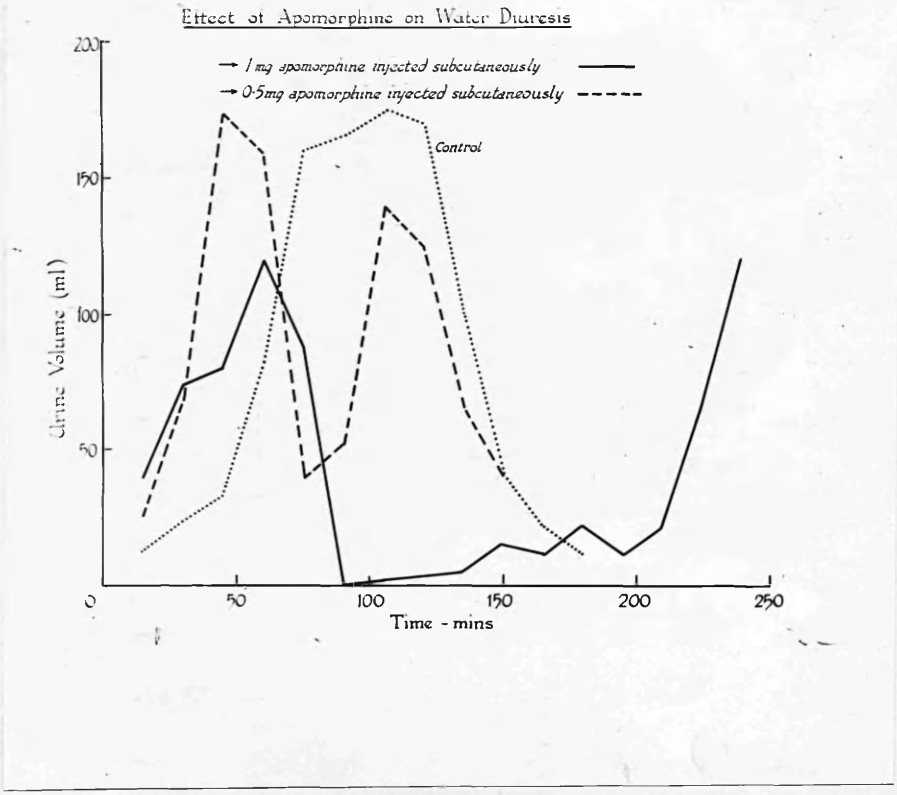


Fig. 5.1.

The results of three tests are shown. In each test the subject drank 1000 ml. of water at zero time. Forty-five minutes later he received an injection of apomorphine (0.5 mg. and 1 mg.) or of inert material. Each point on the graphs represents the volume of a 15-minute sample of urine.

of these, the peak-to-peak time being from 60 to 150 minutes. One of the two men who showedno inhibition after 0.5 mg. of apomorphine received, on another occasion, 1 mg.; diuresis was inhibited for 165 minutes.

Five men received 0.5 mg. of apomorphine in the recumbent position, and in only one was diuresis inhibited, with a peak-to-peak time of seventy-five minutes. One other man had no inhibition after 0.75 mg. of apomorphine in the supine position, but diuresis was inhibited for seventy-five minutes after 1 mg. The recumbent position thus reduced or abolished the antidiuretic effect of apomorphine.

In a further small group of tests to determine the part played by the position of the head and trunk in preventing apomorphine antidiuresis, four men received 0.5 mg. of apomorphine while they lay supine with head vertical. Inhibition occurred in two men, lasting for 60 and 150 minutes respectively. One man was given 1 mg. of apomorphine whilt sitting with head extended back. Water diuresis was inhibited for ninety minutes.

Effect of chlorpromazine.

Chlorpromazine was given before apomorphine in three tests in the sitting position. One man received 50 mg. of chlorpromazine followed two hours later by 1 mg. of apomorphine /

apomorphine, and the other two received 25 mg. of chlorpromazine followed by 0.5 mg. of apomorphine. In no case was water diuresis inhibited.

Relationship to nausea.

Vomiting did not occur in any test in this group, but several men experienced nausea. Severe nausea was usually accompanied by prolonged inhibition of water diuresis, and when water diuresis was not inhibited nausea was usually absent. It might therefore be thought that in these experiments antidiuresis was caused by nausea; and that prevention of the antidiuretic effect by recumbency and by chlorpromazine was due to the absence of nausea. This explanation is possible, but Table 5.1 shows that the relationship between nausea and antidiuresis was not strict. Mild nausea occurred in five tests when water diuresis was not inhibited, while in three tests diuresis was inhibited for periods up to 120 minutes in the absence of nausea. Another more probable explanation of the relationship is that nausea and antidiuresis are independent effects of apomorphine, which generally appear together at about the same dose-level of the drug, but which can occur independently after a small dose.

Mechanism /

Mechanism of the antidiuresis.

Giarman and Condouris (2) showed that apomorphine inhibited water diuresis in rats by releasing antidiuretic hormone from the posterior pituitary. Antidiuresis due to apomorphine has not hitherto been demonstrated in man. In the tests described here inhibition of diuresis began twenty to thirty minutes after the subcutaneous injection of apomorphine. The rate of urine flow fell in some cases to about 1 ml./min. representing 10% of the control rate, and continued at this level for up to two hours. In other cases the urine flow never reached this low rate, or at least did not remain there throughout a full collection period. After the antidiuresis the rate of urine flow returned exponentially to its control level. These findings are consistent with the hypothesis that antidiuresis caused by apomorphine was due to release of ADH.
More direct evidence was sought in further tests in which three normal men drank a water load of 1,500 ml.
Every fifteen minutes thereafter they passed urine and drank more water equal to the volume of urine passed plus 1 ml./min. to allow for insensible water loss. Three successive control urine specimens were collected during a constant rate of urine flow of more than 10 ml./min.
The subjects were then given a subcutaneous injection of 0.5 mg. /

0.5 mg. of apomorphine, and remained sitting still with head upright and eyes closed for twenty-five minutes, except for rising to pass urine. The bladder was emptied ten minutes after the injection and the specimen discarded, though water was drunk as usual. The urine specimens were collected, with water replacement, twenty-five, forty and fifty-five minutes after the injection. The urine passed before and after the tests was examined for total osmotically active solutes, creatinine and sodium as described in Appendix 2. The results of one test are presented in Table 5.2 and similar figures were obtained in the other two. A marked fall in urine output occurred in specimens 5 and 6. This was accompanied by an increase in the concentration of creatinine, sodium, and total osmotically active solutes. The rate of excretion of creatinine, which is a satisfactory measure of the glomerular filtration rate (3), was virtually unchanged. The excretion of sodium and of total solutes fell slightly. These changes are identical with those which occur after liberation of ADH (4 - 6) or after administration of exogenous pitressin (5 - 10; see also Chapter 7).

Additional evidence that the antidiuresis of apomorphine was caused by liberation of ADH was sought by /

Table 5.2 Influence of apomorphine on renal function

Specimen No.	Urine		Total osmotically active solutes		Creatinine		Sodium	
	Volume ml.	Flow ml./min.	Concentration mM/l.	Rate of excretion mM/min.	Concentration mg./ml.	Rate of excretion mg./min.	Concentration mEq./l.	Rate of excretion µEq./min.
1	195	13.0	92	1.20	0.106	1.38	18.4	239
2	213	14.2	86	1.22	0.096	1.36	15.0	213
3	225	15.0	76	1.14	0.090	1.35	14.7	221
4	122	8.1	102	0.83	0.144	1.17	18.6	151
5	12	0.8	618	0.49	1.50	1.20	151	121
6	16	1.1	600	0.64	1.22	1.30	132	141

0.5 mg. of apomorphine was injected subcutaneously 10 minutes before the start of period 4.

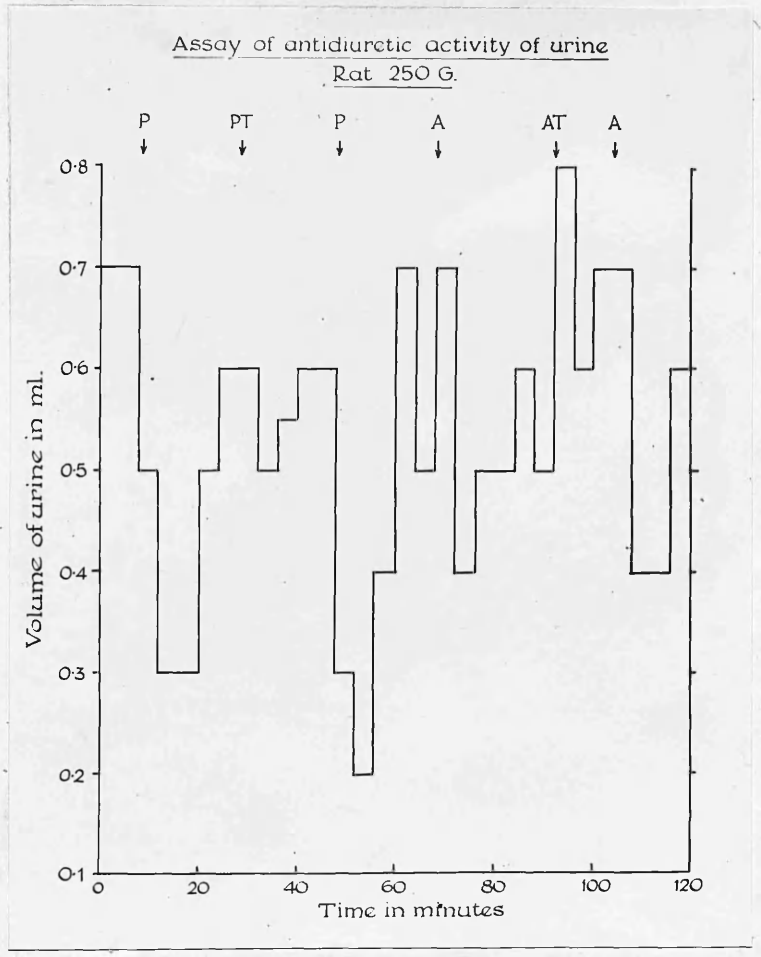


Fig. 5.2.

The figure shows the rate of urine flow in a water-loaded rat, and the influence of the following substances injected intravenously at the times indicated:-

P - 40 microunits of pitressin.
PT - 40 microunits of pitressin after treatment with sodium thioglycollate solution.
A - 0.5 ml. of a urine sample passed by a subject during the period 30-45 minutes after the injection of apomorphine.
AT - 0.5 ml. of same specimen of urine after treatment with sodium thioglycollate solution.

The urine sample had an antidiuretic effect similar to that of the pitressin. The activity of both the pitressin and the urine sample was destroyed by treatment with sodium thioglycollate.

by injecting the urine obtained, before and after administration of apomorphine to man, into water-loaded rats under alcohol anaesthesia. These tests were made by my colleague Miss Fay Johnston, and the method is described in detail in Appendix 4.
The urine obtained in the control period had no effect, while that obtaining during antidiuresis after apomorphine caused temporary inhibition of water diuresis in the rats. This inhibitory effect of the urine was destroyed by treatment for fifteen minutes with sodium thioglycollate solution, which specifically inactivates ADH (11). A typical experiment is illustrated in Fig 5.2. Strong circumstantial evidence is thus available that the inhibition of water diuresis caused by apomorphine was due to release of ADH. Final proof would require the demonstration that inhibition of diuresis did not occur after an adequate dose of apomorphine in a patient with diabetes insipidus insensitive to hypertonic saline (12) and to nicotine (13). A suitable patient has not been available. It remains possible that an antidiuretic mechanism other than the posterior pituitary one may also be involved in the antidiuretic action of apomorphine, but such a mechanism would play, at most, a minor part.

Effects /

Effects of the recumbent position on water diuresis.

While antidiuresis in the sitting position is due to release of ADH, the altered response in recumbency might be mediated in part by local vascular or venous changes in the kidney; for it is known that the urine flow during passive standing may be only 50% of that in recumbency (14, 15). However, the sitting position of the present tests is not comparable to the passive upright posture used in the experiments quoted. The changes in urine flow during standing coincide with the change in position, but in the present tests antidiuresis was not established until the end of the twenty-five minute period of fixed position, and continued during the period of free movement thereafter, although the subject often chose to lie down. During the antidiuresis of passive standing the glomerular filtration rate falls and the excretion of sodium is reduced proportional to the fall in water excretion (16), and these changes did not occur in the present tests. As additional evidence that the effect of position was not due to local factors six control tests were conducted in which the influence of maintaining the sitting or lying positions was observed

on /

on the course of a water diuresis, in the same conditions as in the tests with apomorphine, except that no drugs were administered. The course of the water diuresis was not appreciably different in the sitting and lying positions. It may therefore be concluded that the different responses to apomorphine in sitting and in lying were not due to local effects of body position on the kidney.

Similar arguments apply to the influence of chlorpromazine. This drug exerts no appreciable effect on the rate of urine flow, the glomerular filtration rate and the renal plasma flow in normal men (17). In the present tests four additional control experiments were done in which the course of a water diuresis was followed after administration of 50 mg. of chlorpromazine. The maximum rate of urine flow in these tests was rather higher than in similar tests when chlorpromazine was not given, but the increase was about 10%, and this could not have accounted for more than a small part of the effect of chlorpromazine on the antidiuresis due to apomorphine. The mechanism of this effect was further studied (18) and no evidence was obtained that chlorpromazine influenced the normal secretion of ADH.

It remained necessary to investigate the possibility that chlorpromazine and recumbency prevented the antidiuretic effect of apomorphine by interrupting the action of circulating ADH on the renal tubules. This was tested by determining their influence on the antidiuretic effect of pitressin administered during a water diuresis. After 100 mU of pitressin injected in the sitting position three men had inhibition of diuresis which lasted for 165, 135 and 135 minutes respectively. In the recumbent position in response to the same dose antidiuresis lasted for 105, 135 and 165 minutes respectively; and after 50 mg. of chlorpromazine, for 105, 135 and more than 105 minutes respectively. It was concluded that neither recumbency nor chlorpromazine influenced the action of ADH on the renal tubules.

The foregoing evidence points to the conclusion that both the recumbent position and chlorpromazine acted by preventing apomorphine from releasing ADH from the posterior pituitary. It is not known how apomorphine causes release of ADH, but two possible mechanisms may be considered:-

1. It may act directly on the cells of the supraoptic nucleus.

2. /

2. It may stimulate or facilitate an afferent pathway or pathways going to or relaying at the supraoptic nucleus.

Duke, Pickford and Watt (19) have produced evidence that morphine may act directly on the cells of the supraoptic nucleus, but their findings are not necessarily applicable to apomorphine in man. The effect of body position on the response to the drug, which was not studied by Duke, Pickford and Watt, is more in keeping with the second explanation offered. Indirect evidence on this point was sought in further experiments by studying the influence of body position and of chlorpromazine on the antidiuretic effect of nicotine. The site of the antidiuretic action of nicotine is not known with certainty, but it has been suggested that nicotine is a direct stimulant of the cells of the supraoptic nucleus, although firm evidence of this is not available (20).

Effect of nicotine.

Convalescent male patients from a dermatological ward volunteered as subjects in tests of the influence of body position and of chlorpromazine on the antidiuretic effect /

Table 5.3 Influence of recumbency and of chlorpromazine on the antidiuretic effect of nicotine.

Subject	Number of cigarettes smoked	Duration of inhibition of diuresis (minutes):-		
		Seated	Recumbent	After 50 mg. chlorpromazine
W.H.	1	75	-	60
J.McG.	1	120	60	135
W.F.	2	60	-	60
J.M.	2	45	-	75
C.M.	2	75	60	75
J.B.	2	90	-	-
J.K.	2	75	45	-

effect of nicotine. Their ages ranged from 19 to 35, and all were habitual smokers. Antidiuresis was induced by the smoking of one or two cigarettes in fifteen minutes. The subjects remained seated or supine with head still and eyes closed during smoking and for fifteen minutes afterwards. The procedure was otherwise the same as in the apomorphine experiments. The results are presented in Table 5.3.
After smoking one or two cigarettes seven men all showed inhibition of diuresis lasting for from 45 to 120 minutes. In three men tested in the supine position diuresis was inhibited for 45 to 60 minutes. Five men were tested after taking 50 mg. of chlorpromazine, and inhibition of diuresis ensued, lasting for from 60 to 135 minutes. It was concluded that body position and chlorpromazine did not influence the antidiuretic action of nicotine.

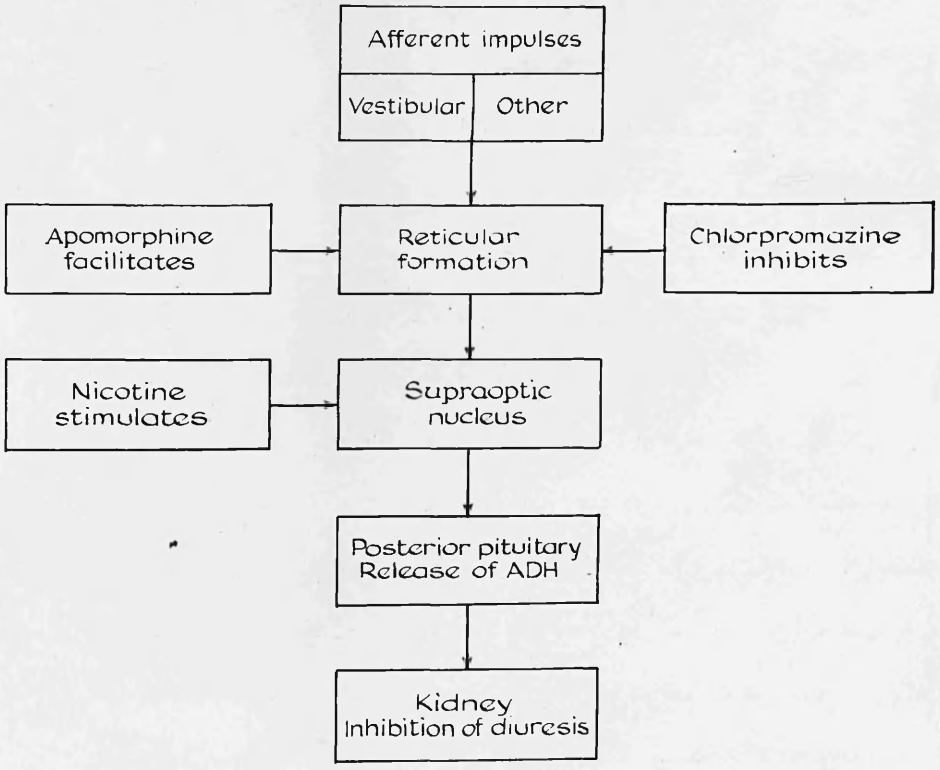
Discussion.

There was thus a clear difference between the antidiuretic action of nicotine and that of apomorphine. If we accept that the former acts by direct stimulation of the supraoptic nucleus, then the supine position and chlorpromazine must influence the antidiuretic effect of apomorphine at some point distal to the supraoptico-hypophyseal /

supraoptico-hypophyseal system. It cannot yet be said how or where this antagonism takes place. Analogy with the influence of recumbency, and of chlorpromazine, on the emetic effect of apomorphine, discussed in the previous chapter, suggests that apomorphine may facilitate afferent impulses which are potentially capable of provoking the release of ADH, but which do not ordinarily do so unless they are present in excess. This raises the question of what afferent impulses might be involved. It was not possible in this section to analyze the contribution of different afferent stimuli to the antidiuretic effect of apomorphine, as was done in chapter 4 in the analysis of its emetic effect. The effects of vestibular stimulation, and the influence of apomorphine and of chlorpromazine, will therefore be studied further in the two following chapters. Thereafter a return will be made to the discussion of the mechanism of the antidiuretic effect of apomorphine in man, and its prevention by recumbency and by chlorpromazine.

A scheme of the possible action of apomorphine, nicotine and chlorpromazine on water diuresis, is shown in Fig. 5.3.

Summary. /



Scheme of the suggested effect of drugs on water diuresis.

Fig. 5.3.

Summary.

When subemetic doses of apomorphine were injected into normal men who remained sitting, water diuresis was inhibited. This was usually but not always accompanied by nausea, but was not due to nausea. The antidiuretic effect of apomorphine did not occur if the subject remained supine. It was also prevented by chlorpromazine. The antidiuresis was due to release of antidiuretic hormone from the posterior pituitary. The antidiuretic effect of pitressin and of nicotine was not prevented by recumbency or by chlorpromazine. Apomorphine probably caused inhibition of water diuresis by facilitating the effects of vestibular and other afferent impulses on the supraoptico-hypophyseal system.

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CHAPTER 6

THE INFLUENCE OF APOMORPHINE AND OF CHLORPROMAZINE ON VESTIBULAR NYSTAGMUS

It has been shown that chlorpromazine prevented vomiting and antidiuresis induced by injection of apomorphine. These effects were tentatively attributed to blockade by chlorpromazine of facilitating actions of apomorphine on the afferent components of reflex arcs. It would be of value to demonstrate antagonism between chlorpromazine and other effects of apomorphine. In this chapter the action of these drugs on vestibular nystagmus will be discussed. When nystagmus was induced in normal people by angular acceleration, the magnitude of the response to a given stimulus was increased by apomorphine and unaffected by chlorpromazine. Chlorpromazine given before apomorphine, however, prevented the latter from exerting its usual effect.

Principle of the method.

The semicircular canals of man are stimulated by angular acceleration, which causes a flow of endolymph relative to the head. This endolymph current displaces the cupula from its position of rest, by an amount proportional to the stimulus (1 - 3). Displacement of the cupula causes an increase in the flow of impulses in the vestibular nerve, which is proportional to the degree of its displacement (4 - 6). These impulses reflexly /

reflexly initiate nystagmus. After application of a single acceleratory stimulus the cupula soon reaches its position of maximum displacement, and corresponding to this, nystagmus rapidly becomes maximum. The nystagmus then slowly declines and becomes imperceptible in the period of 20 - 40 seconds required for the elastic cupula to resume its position of rest (7).

The intensity of the nystagmus, when this is suitably measured, is directly proportional to the stimulus. Recent work has firmly established that the appropriate measure of the nystagmus response is the velocity of the eye during the slow phase of the nystagmus - the "vestibular eye speed" - rather than the amplitude or duration of the nystagmus (7 - 9). Techniques have been introduced to allow the accurate measurement of this velocity (8, 10 - 13) and one such method was used in the present study. Accurate methods have also been introduced for applying angular accelerations (3, 12, 14 - 16), and the method introduced by van Egmond in his work on cupulometry (14) has been followed in this study.

Method. /

Method.

A subject seated in a rotating chair was accelerated from rest with a uniform acceleration of less than 0.5°/second until a desired angular velocity was attained. This rate of acceleration lay below the minimum perceptible acceleration and did not stimulate the vestibular organ (2, 16, 17). After a period of rotation for one minute at constant velocity the chair was braked and brought to rest within one second. The effect was to apply to the subject a single deceleratory stimulus, equal to the velocity of the chair at the time of stopping. This stimulus caused nystagmus, which rapidly reached a maximum value, then gradually declined. The eye movements were recorded during the period of rotation at constant velocity and for thirty seconds after stopping the chair. The velocity of the slow phase of the nystagmus was calculated from the tracing of the eye movements. The maximum vestibular eye speed was attained 1 - 3 seconds after stopping the chair, and was related to the velocity of the chair at the time of stopping.

The stimulus was applied by means of an electrically-operated hydraulically controlled rotating chair. The movements of the eyes were obtained from a continuous tracing of the changes in the electrical potential between the cornea and the retina which occurred when the position of the eyes changed. The apparatus and techniques are described in detail in Appendices 3 and 5.

Preliminary experiments. /

Preliminary experiments.

Experiments were conducted in fifteen normal people, six males and nine females, whose ages ranged from 17 to 32. They were exposed to a series of tests in which eye movements were recorded as described after the application of a stimulus which ranged from 24°/second to 42°/second. In most tests a stimulus of 36°/second was used. The stimulus caused a sensation of rotation lasting fifteen to thirty seconds, but no other symptoms were noted. In each test the vestibular eye speed was determined, and the ratio of this to the speed of the chair - the "eye/chair ratio" was calculated.

This ratio was studied previously by Henriksson (9). He found that its value in thirty normal people lay usually between 0.5 and 1.0, although a few values as low as 0.25 and as high as 1.50 were obtained. The ratio was independent of the duration and speed of turning. Large differences were found in the ratios of different people. The values obtained in different tests on the same person also varied, though to a less extent. The eye/chair ratio represented the sensitivity of the vestibulo-ocular reflex.

In the present study of fifteen subjects the eye/chair ratio on first testing ranged from 0.48 to 0.86 (mean 0.65). No relation was noted between the ratio and the age or sex

of /

of the subject. The ratio was independent of the stimulus between the range of 24° and 42° per second.

When the same person was repeatedly tested the ratio fell steadily to reach a fairly constant value of between 0.1 and 0.2. This fall was complete after 10 - 20 tests, and occurred independently of the interval between tests. Once the decline in response had occurred the original sensitivity did not return, even after an interval of several weeks.

This decline in the response to repeated vestibular stimulation has been observed in previous studies (18 - 22), and has been critically analyzed by Hallpike and Hood (21). The response is one of "central elimination or inhibition of an unnecessary response to an abnormal but not harmful stimulus" (22). The phenomenon concerns us here by demonstrating that the effect of drugs on the vestibulo-ocular reflex should be studied in subjects who respond consistently to repeated stimulation. In interpreting the results of such experiments, the effects of adaptation must be taken into account.

Effect of drugs. /

Effect of drugs.

The influence of apomorphine and chlorpromazine on vestibular nystagmus was studied in four subjects who had become adapted to the experimental procedure. Each person had undergone at least ten previous tests without drugs, and the eye/chair ratio had become consistently less than 0.25 in the five preceding tests. Two control tests were run with a stimulus of about 36°/second. Apomorphine 0.25 mg. was then injected subcutaneously, and twenty minutes after the injection a third test was conducted with the same stimulus. In one subject 0.5 mg. of apomorphine was also given. No symptoms were caused by the injection of 0.25 mg. of apomorphine, but after 0.5 mg. the subject vomited one minute after stopping the chair.

In other tests chlorpromazine 25 mg. was given by mouth, and rotation was applied at intervals up to six hours after the drug. The influence of chlorpromazine on apomorphine was tested by giving the former two hours before the latter.

Results. /

Table 6.1 Influence of apomorphine on vestibular nystagmus

Subject No.	Dose of apomorphine mg. subcutaneously	"eye/chair" ratio	
		Before apomorphine (mean of two tests)	20 minutes after injection of apomorphine
1	0.25	0.19	0.34
	0.5	0.21	0.45
2	0.25	0.16	0.27
3	0.25	0.19	0.31
4	0.25	0.22	0.41

Table 6.2 Influence of chlorpromazine and of chlorpromazine and apomorphine on vestibular nystagmus.

Subject No.	Dose in mg. of:-		Eye/chair ratio	
	Chlorpromazine oral	Apomorphine subcutaneously	Two hours after chlorpromazine (mean of 2 tests)	20 minutes after apomorphine, given 2 hr. after chlorpromazine
1	25	0.25	0.23	0.19
2	25	0.25	0.18	0.24
3	25	0.25	0.17	0.20
4	25	0.25	0.24	0.19

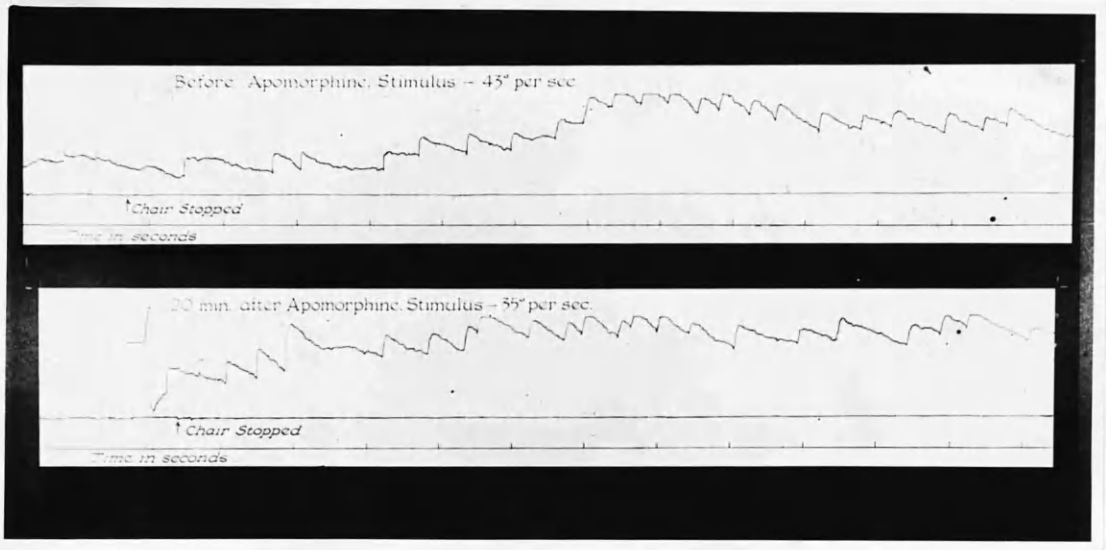

Fig. 6.1.

Post-rotatory nystagmus.
The upper trace represents the eye movements, an upward deflection corresponding to a movement to the right. During rotation at constant velocity (left-hand part of trace) only small random eye movements occur. When the chair is brought to rest, nystagmus movements begin after one second. The slow phase of the nystagmus is represented by the downward deflection, the slope of which corresponds to the speed of the eyes ("vestibular eye speed"). The eye speed gradually declines over a period of about 20 seconds.

The middle trace represents the chair speed, every deflection of the pen corresponding to 30° of rotation.

The bottom trace gives time in seconds.

Fig. 6.2.

Tracing from the same subject in the same experiment 20 minutes after the subcutaneous injection of 0.25 mg. of apomorphine. Although a smaller stimulus was used the eye-speed was much faster than in the control record.

Results.

These are shown in Tables 6.1 and 6.2 and a typical experiment is shown in Figs. 6.1 and 6.2. After 0.25 mg. of apomorphine the eye/chair ratio rose in adapted subjects by 50 to 100%, and after 0.5 mg. of apomorphine by 150%. In one unadapted subject apomorphine similarly increased the ratio. When 25 mg. of chlorpromazine was given two hours before 0.25 mg. of apomorphine, no change in the ratio was noted. Chlorpromazine alone caused no change in the ratio.

Additional results, not strictly related to the present problem, were that the ratio was markedly increased by nicotine. This effect of nicotine was not prevented by chlorpromazine. Hyoscine had no effect on the ratio.

Discussion.

Apomorphine increased the eye speed in post-rotatory nystagmus after a single vestibular stimulus. This effect was prevented by previously giving chlorpromazine. The literature on the effects of drugs on vestibular nystagmus is fragmentary. Longo and Napolitano attempted a systematic investigation of the subject (23, 24), but for the following reasons their results are not comparable with the present ones:-

(a) /

(a) They used rabbits and not men as their test subjects;

(b) They used a quite unphysiological stimulus of 360°/second, the response to which could be expected to be irregular;

(c) They measured as the effect of vestibular stimulation the amplitude and duration of the nystagmus, rather than the speed of the slow phase;

(d) They made no allowance for the effects of adaptation.

Their main finding was that post-rotatory nystagmus was reduced or abolished by mephenesin and other so-called "internuncial-neurone blocking agents". They concluded that this was due to inhibition by these drugs of conduction in internuncial neurones in the bulb and midbrain, and accepted this as evidence that such neurones participated in the vestibulo-ocular reflex. These interesting results cannot be accepted unreservedly in the present context.

The /

The effect of drugs on vestibular nystagmus has been briefly studied in man. Gutner et al. (25) found that morphine, and also pethidine and methadone, lengthened the duration of caloric nystagmus. Rubin and Winston (26) thought that morphine reduced the duration of caloric and post-rotatory nystagmus. Neither group studied the effect of apomorphine. These contradictory results may be attributed to the use of unsuitable techniques.

There are three ways in which apomorphine might influence vestibular nystagmus:-

(i) Stimulation of the vestibular neurone.

If so it might be expected to lower the threshold of vestibular sensitivity, and there is no evidence that it does so.

(ii) Stimulation of the neurones of the third, fourth and sixth nerves.

It might then be expected to affect spontaneous eye movements, as for example, in reading, and it does not do so.

(iii) /

(iii) Facilitation of the reflex arc between the nuclei of the eighth and third nerves.

This last is the likely mode of action of apomorphine. The pathway involved is not certainly known, but the vestibulo-ocular pathway is believed to run through the mesencephalon and brainstem, in the reticular substance adjacent to the posterior longitudinal bundle (27, 28).

It is apparent that in a dose far below that required to cause nausea and vomiting, apomorphine is yet able to enhance the effects of vestibular stimulation.

A clue to the mechanism of action of chlorpromazine which emerges from this study is that the compound blocks the facilitating action of apomorphine in a dose which does not interfere with the normal passage of vestibulo-ocular impulses.

Summary. /

Summary.

A method is described for studying the effects of drugs on vestibular nystagmus in man. A single vestibular stimulus was applied by abruptly bringing a subject to rest after rotation at constant velocity in a special chair. The resulting nystagmus was recorded by amplifying the changes of corneo-retinal potential. From the resulting tracing it was possible to calculate the maximum speed of the eye in the slow phase of the nystagmus. The ratio of this eye-speed to the speed of the chair measured the sensitivity of the reflex. The values of this ratio were determined in fifteen normal people, and it was found that on repeated testing the response declined until a stable level of adaptation or habituation had been attained. In adapted subjects small doses of apomorphine increased the sensitivity of the reflex. This effect of apomorphine was prevented by giving chlorpromazine beforehand, although in the dose used, the latter had itself no effect on the sensitivity of the reflex. This action of apomorphine was probably due to facilitation of interneuronal conduction in the reticular substance of the mid brain and brainstem.

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CHAPTER 7

THE INFLUENCE OF MOTION ON WATER DIURESIS

It was shown in chapter 5 that apomorphine inhibited water diuresis in seated but not in recumbent subjects. This led to the suggestion that afferent impulses were concerned in the antidiuretic action of apomorphine, and that these afferent impulses were more prominent in the sitting position than in recumbency. A possible origin of such impulses is the vestibular system. In this chapter experiments will be described in which the influence of vestibular stimulation on water diuresis was examined by subjecting human volunteers to motion in the course of a diuresis.

The aims of these experiments were:-

1. To determine whether inhibition of water diuresis occurred during experimental motion sickness.
2. To determine the effect of different types of motion and different positions of the body in influencing the antidiuretic response to motion.
3. To study the relation between antidiuresis and the symptoms of motion sickness.

4. /

4. To study the physiological mechanism of the antidiuresis.
5. To investigate the influence of chlorpromazine on the antidiuresis produced by motion.

The principal findings to be presented are:-

1. Profound inhibition of water diuresis occurred during motion sickness.
2. Inhibition of water diuresis sometimes occurred after exposure to motion which was insufficient to cause symptoms, but more often inhibition of diuresis was accompanied by nausea.
3. The inhibition of diuresis was probably due to liberation of the antidiuretic hormone of the posterior pituitary.
4. The inhibition of diuresis induced by motion was diminished or abolished by chlorpromazine.

Methods.

Male medical students and convalescent hospital patients were the subjects of these studies. Their ages ranged from 19 to 47, most of them being under 25. The hospital patients were all free from disease of the kidneys, ears or nervous system and were not receiving drugs. Water diuresis was induced by three different standardized procedures, and the influence /

influence of various kinds of motion applied for various times was observed. In all tests the bladder was emptied voluntarily and men who experienced difficulty in emptying the bladder were excluded.

Procedures for inducing water diuresis.

Method A.

This was the method used in the experiments of chapter 5. The subject did not eat or smoke for two hours before the test or during it. He emptied his bladder, then drank one litre of water in five to fifteen minutes. Thereafter he passed urine every fifteen minutes precisely and noted the volume. Forty-five minutes after beginning the test he was exposed to motion. After the motion he emptied his bladder again and continued to do so every fifteen minutes until the water load had been excreted. The degree of antidiuresis was expressed by the "peak to peak time" (chapter 5).

Method B.

The effect of the procedure in delaying an expected diuresis was studied. The subject drank no fluid and did not smoke after 1 p.m. on the day preceding the test. On the morning of the test he remained fasting; he emptied his bladder and drank a water load of 15 ml./Kg. body weight in five to fifteen minutes. He was then exposed to motion. He emptied his bladder after the motion, and every fifteen minutes precisely for three hours. The /

The degree of antidiuresis was expressed in terms of the time which elapsed from beginning the experiment until the largest fifteen-minute specimen of urine was passed, or any preceding specimen which was more than 90% of the volume of the largest specimen. This period was called the "peak time" and its use is discussed below.

Method C.

The subject drank a water load equal to 20 ml./Kg. body weight in thirty minutes. Thereafter he emptied his bladder every fifteen minutes, and at the same time drank more water equal to the volume of urine passed, with a supplement of 1 ml./min. to allow for insensible water loss. This was continued until three successive specimens were passed, each more than 150 ml. and differing little in volume. The subject was then exposed to motion. One to five minutes after the motion he emptied his bladder. This specimen was rejected, but water was drunk as usual to maintain the water load. Three more specimens of urine were then obtained at fifteen-minute intervals, with water replacement. The degree of antidiuresis was measured by calculating the ratio of the volume of urine passed in forty-five minutes after motion to the volume in forty-five minutes before motion.

Types of motion. /

Types of motion.

1. Vertical motion.

The subject sat upright with eyes closed, head vertical and held still on the vertical swing. (This, and the other machines used, are described in Appendix 3) In some experiments the subject lay supine with head horizontal, or with head held vertical, as in the experiments described in chapter 5. The swing was moved by hand up and down through an amplitude of 1 metre at a rate of 18 complete cycles per minute. The motion was of simple harmonic type.

2. Horizontal motion.

The subject sat upright or lay supine on the horizontal swing which was moved by hand through an amplitude of 1 metre at a rate of 18 cycles per minute.

3. Rotation with sagittal head movement.

The subject sat with eyes closed in a chair which was rotated mechanically at a constant rate of 10 revolutions per minute for five minutes. During one revolution he voluntarily flexed his head forward through a right angle on to his chest, the movement taking one to two seconds. During the next revolution he brought the head back into the vertical plane. This alternate flexion and extension movement of the head was continued for the duration of the motion.

4. Irregular motion. /

4. Irregular motion.

The subject sat or lay on the horizontal swing which was moved irregularly forwards, backwards and sideways while the subject altered the position of his head.

Results.

An experiment in which irregular motion was applied for fifteen minutes during the course of a water diuresis induced by method A is illustrated in Fig. 7.1. Following exposure to motion diuresis was profoundly inhibited, and urine flow continued at a very low rate for two hours. Subsequently water diuresis recommenced, and a second peak of urine output occurred 165 minutes after the first peak. In this experiment the subject complained of severe nausea, salivation, colic, sweating, weakness of limbs and depression, and he was strikingly pale. The symptoms passed off thirty minutes after the motion.

Horizontal and vertical motion.

The results of experiments in which diuresis was induced by method A are presented in Table 7.1. In the sitting position exposure to vertical motion for fifteen to twenty minutes caused inhibition of diuresis in two of four men tested. Exposure to horizontal motion with the subject seated upright caused inhibition of diuresis in four of five men tested. In the supine position horizontal motion for fifteen to thirty minutes failed to cause antidiuresis in three men.

Usually /

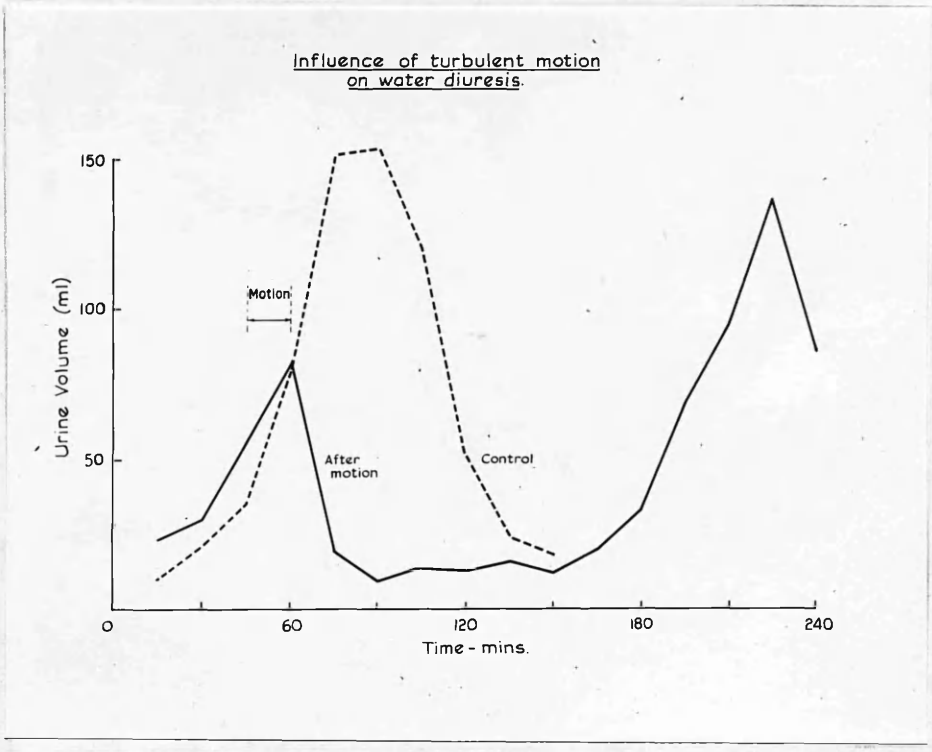

Fig. 7.1.

1000 ml. of water was drunk at zero time. Each point on the graph represents the volume of urine passed in 15 minutes. The broken line shows the response when no stimulus was applied.

Table 7.1 Influence of motion on water diuresis

Type of Motion	Subject	Duration of motion (mins.)	Duration of antidiuresis Peak-to-peak time (mins.)	Symptoms
Vertical motion - subject seated upright.	J.C.D.	15	75	None
	B.I.	15	70	Moderate nausea
	R.D.G.	20	0	None
	R.M.Q.	20	0	None
Horizontal motion - subject seated upright.	J.B.	5	105	Mild nausea
	A.P.	10	0	None
	B.I.	10	105	Moderate nausea
	J.J.L.	15	95	Mild nausea
	R.E.L.	15	75	Mild nausea
Horizontal motion - subject supine	C.N.G.	15	0	None
	J.J.L.	15	0	None
	B.I.	30	0	None

Table 7.2

Effect of vertical motion for different periods of time on water diuresis in one subject

Duration of motion (mins.)	Antidiuresis peak-to-peak time (mins.)	Symptoms
5	0	None
10	0	None
15	70	Moderate nausea
20	105	Moderate nausea
25	150	Severe nausea
30	150	Moderate nausea

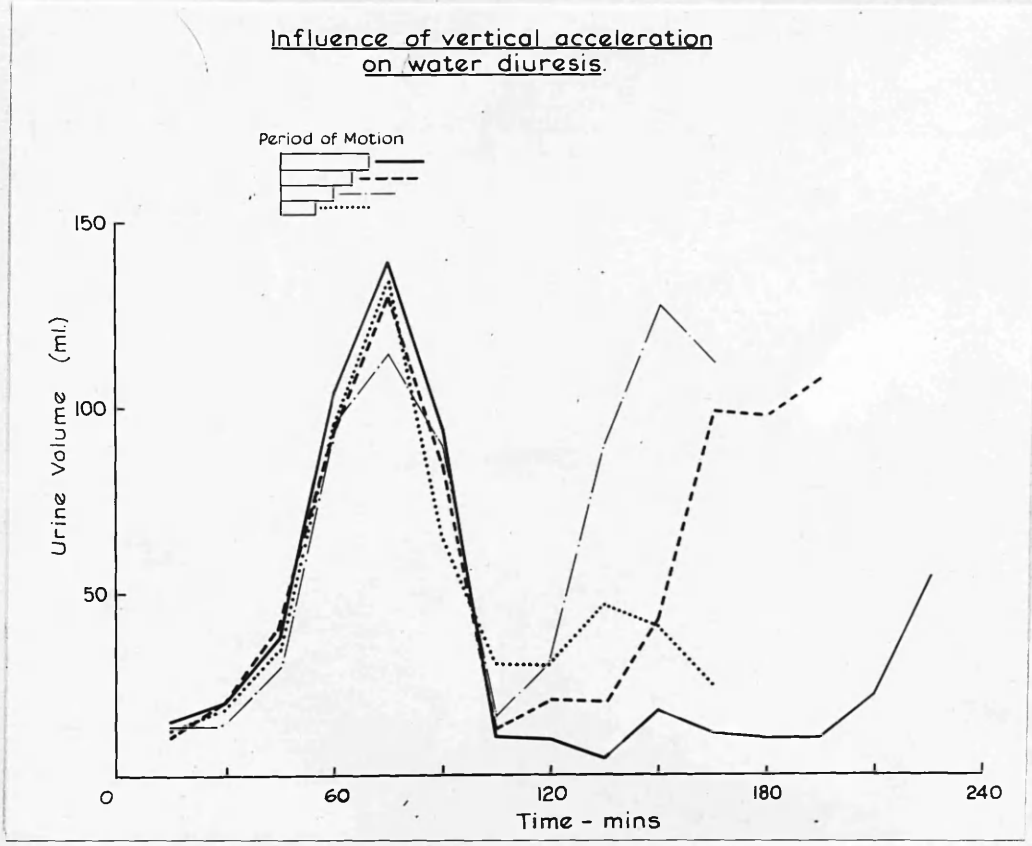

Fig. 7.2.

One man was exposed to motion of varying duration on different occasions.
The degree and duration of antidiuresis was proportional to the duration of motion.

Usually nausea accompanied inhibition of diuresis, and was absent when there was no inhibition. In one test nausea was absent but diuresis was inhibited for seventy-five minutes.

The effect of exposing one man to vertical motion for different periods of time is shown in Table 7.2 and in Fig. 7.2. As the period of motion increased, so did the duration of diuresis and the severity of symptoms.

Another group of experiments was conducted in two men on the effects of vertical motion on water diuresis induced by method B. In control experiments on ten normal men who drank water but were not exposed to motion, the "peak time" measured in this method varied from 75 to 105 minutes. In ten other tests normal men were given subcutaneous injections of saline or of pitressin after drinking the water load. After saline (two tests) the peak time was unchanged (mean ninety-five minutes), but it was prolonged to an average of 125 minutes after 25 mU. of pitressin (four tests) to 120 minutes after 50 mU. of pitressin (three tests) and to more than 180 minutes after 100 mU. of pitressin (one test). Exposure of two men to vertical motion (Table 7.3 and Fig. 7.3) caused prolongation of the peak time which was proportional to the duration of motion. The delay in excretion of the water load was usually, but not always, accompanied by nausea.

The /

Table 7.3

Influence of vertical motion on water diuresis in two subjects

Subject	Duration of motion (mins.)	Measurement of antidiuresis - "peak time" (mins.)	Symptoms
B.I.	10	95	None
	20	165	Mild nausea
	30	195	Moderate nausea
J.J.L.	10	130	Moderate nausea
	20	75	No symptoms
	20	105	Mild nausea
	30	120	No symptoms

The effect of motion on water diuresis was also tested by method C. In this method the antidiuretic effect was measured by the ratio of the volume of urine passed in the forty-five minutes which followed exposure to motion to the volume passed in the forty-five minutes preceding motion. In determining this ratio the urine passed during exposure to motion was not included. In the absence of an antidiuretic effect the value of this ratio was 1.0. In six control tests in which motion was not applied, the ratio lay between 0.82 and 1.14. The lower values were caused by a reduction in the volume of successive specimens. An antidiuretic effect was indicated by a value of this ratio of less than 0.80, the smallest volume of urine being in the first or sometimes the second specimen passed after motion.

In Table 7.4 the results of fifteen tests are presented of vertical motion for thirty minutes in the sitting subject. Pronounced inhibition of diuresis occurred in three men in whom the ratio of the urine passed after motion to urine passed before motion was 0.17, 0.17 and 0.11 respectively. One of these men experienced mild nausea, one complained of excessive salivation but not of nausea and the third noted no symptoms. In one other man the ratio was 0.74, indicating slight antidiuresis, and in the remaining eleven subjects it ranged from 0.86 to 1.36 (mean 1.00). None of these twelve men experienced unpleasant symptoms.

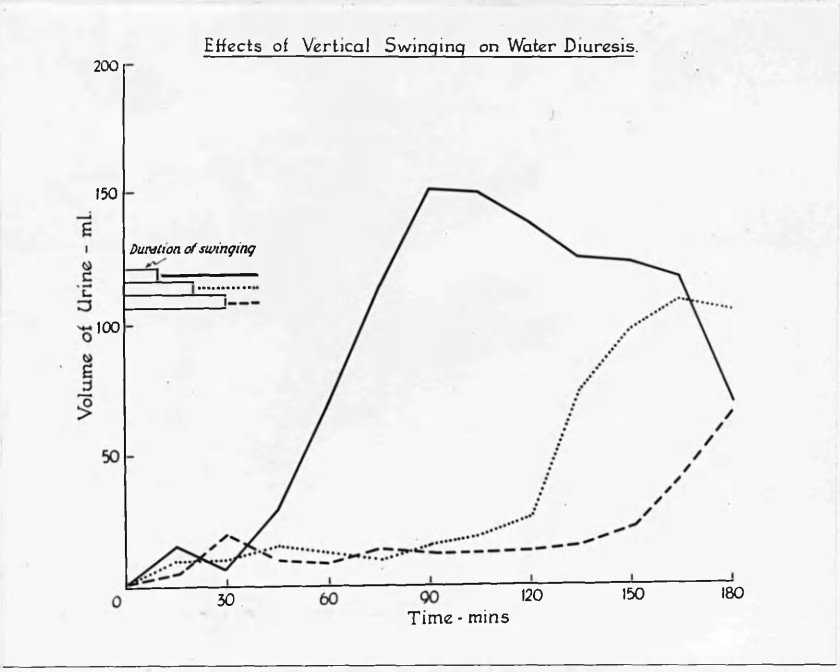

Fig. 7.3.

The water load was given at zero time, immediately before exposure to motion. One man was swung for different periods of time on different occasions. The time which elapsed before diuresis reached its peak was proportional to the duration of motion.

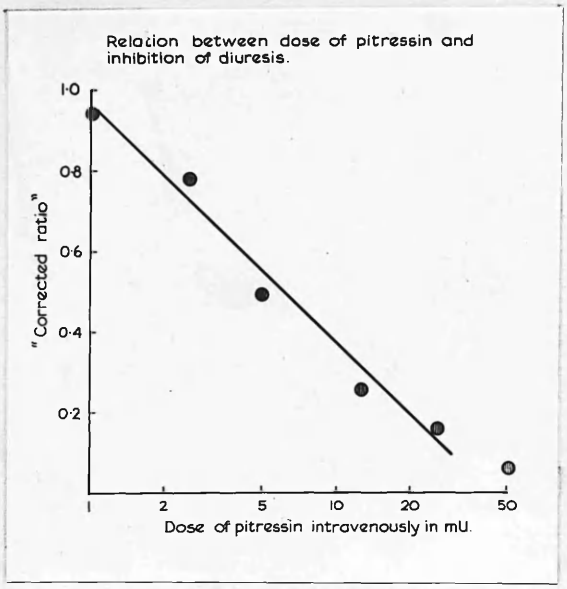

Fig. 7.4.

The "corrected ratio" was proportional to the log-dose of pitressin.

Table 7.4

Influence of vertical motion on water diuresis - subject seated upright. (Method C.)

Subject	Urine output (ml.) in 45 minutes		Ratio- vol.before/ vol.after	Symptoms
	Before motion	After motion		
D.McF.	800	134	0.17	Salivation, shivering; no nausea.
S.K.	595	593	1.00	None.
N.B.	1090	935	0.86	None.
J.B.	885	785	0.87	None.
B.J.B.	470	536	1.14	None.
A.W.M.	534	725	1.36	None.
K.C.W.	808	931	1.15	None.
B.I.	505	87	0.17	Very mild nausea.
J.K.	366	40	0.11	Dizziness; no nausea.
N.G.W.	644	551	0.86	None.
R.M.Q.	683	704	1.03	None.
H.F.	646	576	0.89	None.
T.B.	641	556	0.87	None.
C.S.	704	676	0.96	None.
W.D.	992	735	0.74	None.

Duration of motion was 30 minutes in all cases.

Table 7.5 Influence of rotation with sagittal head movement on water diuresis.

Subject	Volume of urine(ml.) passed:		Ratio	Symptoms
	In 45 mins. before motion	In 45 mins. after motion		
J.M.	766	794	1.04	None
R.G.K.	860	712	0.83	None
P.B.	953	857	0.90	None
A.H.	806	63	0.08	Mild nausea
E.L.	686	597	0.87	None
C.C.	632	691	1.09	None
B.I.	632	492	0.78	Moderate nausea
R.H.	1000	1085	1.09	None
J.S.A.	811	380	0.46	None
H.M.C.ø	512	0	-	Vomited
J.C.	510	452	0.89	None
H.A.K.	798	33	0.04	Moderate nausea

ø Rotated for 2 minutes 20 seconds only.
Unable to pass any urine at all for one hour after motion.

Rotation with sagittal head movement.

This form of motion readily causes motion sickness (1, 2, 3) and in the present tests it usually provoked at least a sensation of disorientation. Twelve men were subjected to this form of motion during a water diuresis induced by method C. The chair was rotated at 10 revolutions per minute for five minutes or until the subject complained of nausea, whichever was shorter. Water diuresis was markedly inhibited in four men, and there was slight antidiuresis (ratio 0.78) in a fifth (See Table 7.5). One man complained of nausea after two minutes and twenty seconds of motion. The chair was immediately stopped and a few minutes later the man vomited. During the succeeding hour nausea gradually disappeared, but the man was unable to pass any urine. While this was without doubt due to bladder inhibition, it is likely that the quantity of urine formed in the hour after motion was very small. This was classed as an instance of marked antidiuresis. Of two other men who experienced moderately severe nausea one had marked inhibition of diuresis (ratio 0.04) and one only slight inhibition (ratio 0.78). One man had mild nausea accompanied by marked antidiuresis (0.08); another had no symptoms but some inhibition of diuresis (0.46). The other men experienced neither antidiuresis nor untoward symptoms.

Four /

Four men in whom diuresis was unaffected by rotation for five minutes were rotated, in a second test, for ten minutes. None experienced symptoms and water diuresis was not inhibited (ratios 0.92, 1.04, 0.89, 0.95). A fifth man who had no inhibition after five minutes' motion was rotated for ten minutes in a second test at a rate of 11 revolutions per minute. He experienced mild nausea and diuresis was profoundly inhibited (ratio 0.07). A sixth man who had had no inhibition after five minutes' motion was rotated a second time at 12 revolutions per minute. The motion was stopped after four minutes because the subject was feeling nauseated. Diuresis was markedly inhibited (ratio 0.07).

Complex movement.

In two men exposed to complex motion for fifteen minutes diuresis, induced by method A, was inhibited for 75 and 105 minutes respectively. In a third man swung for twenty-five minutes diuresis was not inhibited. In three other men tested by method C diuresis was not inhibited after fifteen minutes' motion, although one of the three experienced mild nausea.

Blood pressure.

In ten tests the blood pressure was recorded before and after motion. Usually no change was detected, but in a few men, including those who did or did not experience antidiuresis, a fall of 10-15 mm.Hg. was noted after motion.

Renal /

Renal function studies.

Renal function studies were performed in ten men who experienced inhibition of diuresis after exposure to vertical or rotating motion, and in thirteen men in wheom diuresis was not inhibited by similar motion. The urinary constituents which were determined were the total osmotically active solutes, the creatinine and the sodium concentration. The methods are described in Appendix 2. The findings in a typical test are presented in Table 7.6 · and the results of all ten tests are summarized in Table 7.7. The following information emerged:-

1. After motion the urine flow decreased by a large amount in all tests - by more than 90% in four.
2. This fall was accompanied by an increase in the concentration of solutes, of creatinine and of sodium, which in several cases was tenfold.
3. The excretion of total solutes was little changed in four cases and fell by up to 50% in six cases.
4. The excretion of creatinine was virtually unchanged in all tests, although in some tests the excretion during extreme antidiuresis (urine flow less than 1 ml./min.) was a little below the control value.
5. In eight of nine tests the excretion of sodium fell by about 50%.

Table 7.6 Renal function during antidiuresis induced by vertical motion.

Specimen No.	Urine		Total osmotically active solutes		Creatinine		Sodium	
	Volume ml.	Flow ml./min.	Concentration mM/l.	Excretion rate mM/min.	Concentration mg./ml.	Excretion rate mg./min.	Concentration mEq/l.	Excretion rate μEq/min.
1	237	15.8	38	0.56	0.08	1.26	15.2	240
2	229	15.3	38	0.58	0.08	1.22	10.6	162
3	221	14.7	40	0.59	0.09	1.32	11.4	168
4	39	2.6	232	0.60	0.39	1.01	18.9	49
5	20	1.3	576	0.77	1.12	1.46	66.4	86
6	39	2.6	352	1.02	0.53	1.38	20.9	54

All collection periods were of 15 minutes.
After specimen 3 had been passed the subject was exposed to vertical motion for 20 minutes.
Thereafter the bladder was emptied, the specimen rejected, and the fourth collection period commenced.

Table 7.7 Biochemical changes in urine during inhibition of water diuresis induced by motion.

Subject	Motion		Water excretion ml./min.		Osmolar excretion mM/min.		Creatinine excretion mg./min.		Sodium excretion μEq./min.	
	Type	Duration mins.	Before	After	Before	After	Before	After	Before	After
B.I.	Vertical	20	15.3	2.8	0.61	0.76	1.27	1.28	165	63
D.M.F.	Vertical	30	17.8	3.0	1.02	0.96	1.37	1.23	112	99
J.K.	Vertical	30	8.1	0.9	0.94	0.83	2.17	1.94	-	-
R.McM.	Rotation; head flexion	4	17.2	1.2	1.53	0.84	1.17	1.45	227	138
H.A.K.	do.	5	22.2	0.7	1.19	0.53	0.92	0.75	401	160
J.S.A.	do.	5	18.0	8.4	2.04	1.30	1.40	1.29	83	40
A.H.	do.	5	17.9	1.4	1.56	0.98	1.56	1.41	458	245
J.C.	do.	10	12.1	0.8	0.89	0.52	1.24	1.34	168	72
T.P.	Chaotic	2	20.4	3.5	1.89	1.06	1.40	1.41	617	383
B.A.	Chaotic	3½	14.0	2.4	1.46	1.42	1.17	1.18	519	722

These figures are the mean values for 45 minutes before and 45 minutes after exposure to motion.

Biological assay.

In three experiments in which antidiuresis occurred in response to motion, the urine passed before and after motion was assayed biologically for antidiuretic activity by my colleague Miss Fay Johnston. In the method used, which is described in Appendix 4, the depression of diuresis in water-loaded rats which followed intravenous injection of a sample of urine was compared with that produced by a known amount of pitressin. The antidiuretic activity of the urine sample was then expressed in terms of the concentration of pitressin which exerted the same antidiuretic effect in the same rat. The method was sensitive to 10 microunits per ml. of pitressin. In all three cases the urine passed before exposure to motion contained no detectable antidiuretic activity, but after motion urine samples contained activity equivalent to from 50 to 880 microunits of pitressin per ml. (Table 7.8). The antidiuretic activity of the urine was destroyed when the urine was left in contact with sodium thioglycollate solution for fifteen minutes before being injected into the rat.

Mechanism of the antidiuresis.

A fall in urine flow in the presence of a sustained water load is most often due to the release of the antidiuretic hormone of the posterior pituitary (ADH) (4 - 6). Antidiuresis from /

Table 7.8 Antidiuretic activity of urine before and after motion.

Subject	Before motion		After motion		
			Specimen		
	Volume of specimen ml.	Antidiuretic activity ø	No.	Vol. ml.	Antidiuretic activity ø
J.C.	166	0	4	9	50
A.M.	273	0	4	13	880
R. McM.	298	0	4	14	200
			5	14	100
			6	24	50

ø The antidiuretic activity was expressed as the concentration of pitressin in μu. per ml. which produced the same antidiuretic effect as did the specimen.

from this cause is characterized by a fall in urine output to 1 ml. per min. or less, which begins five to ten minutes after the hormone is released. The low rate of urine flow continues as long as the concentration of circulating ADH exceeds a critical level. The circulating hormone is destroyed and partly excreted, so that the amount of hormone released determines the duration of antidiuresis. When the concentration of hormone falls below its critical level the rate of urine flow returns exponentially to its control level. During the antidiuresis the glomerular filtration rate is unchanged and the concentration of solutes rises, although their rate of excretion falls slightly because of delayed passage along the tubules. The level of urine flow depends on the solute load (7). ADH is excreted in the urine where it can be detected by injecting the urine into a test animal. The antidiuretic activity of the urine is destroyed by treatment with sodium thioglycollate solution (8). A fall in urine output can also be brought about by changes in the renal circulation (9, 10), notably a fall in pressure in the renal artery, rise in pressure in the renal vein or constriction of the efferent arterioles. Total anuria may result from a profound fall of renal artery pressure. Constriction of efferent arterioles may be mediated by nervous mechanisms or by mechanical /

mechanical origin and is accompanied by albuminuria. Antidiuresis due to renal haemodynamic changes, as usually encountered, is characterized by a reduction in urine flow of about 50% which lasts as long as the exciting stimulus. Removal of the stimulus results in an immediate return to control rates of urine flow. During the antidiuresis the excretion of solutes falls while their concentration in the urine is little changed. ADH cannot be detected in the urine passed during antidiuresis.

The antidiuresis of motion was thought to be due partly or wholly to the liberation of ADH for the following reasons:-

1. When the motion was applied during water diuresis the inhibition of diuresis began a few minutes after cessation of the stimulus and continued for up to two hours, suggesting chemical rather than venous mediation of the response.

2. The fall in urine flow was frequently very great - from 10-20 ml./min. to about 1 ml./min. - in the absence of any significant change in blood pressure or other marked systemic reaction.

3. /

3. When motion was applied while the rate of urine flow was low because of maximum ADH action due to dehydration (method B), the rate of urine flow did not fall; instead the diuresis which should have accompanied absorption of the water load was delayed. This delay was probably due to release of a chemical substance with antidiuretic properties. It could not be attributed to delayed water absorption, because antidiuresis followed motion applied during water diuresis (method A).

4. During antidiuresis glomerular filtration, measured by endogenous creatinine excretion, was unchanged, and excretion of sodium and of total solutes fell slightly. Similar changes were demonstrated after intravenous injection of pitressin, and the findings from a typical experiment are shown in Table 7.9.

5. The urine passed during antidiuresis contained antidiuretic activity as demonstrated in water-loaded rats. The antidiuresis was similar in pattern to that caused by pitressin, and the activity was destroyed by sodium thioglycollate.

The /

Table 7.9 The effects of motion on renal function compared with the effects of pitressin

Procedure	Spec. No.	Urine flow ml./min.	Osmolar excretion mM./min.	Creatinine excretion mg./min.	Sodium excretion Eq./min.
Vertical motion for 20 minutes.	1	15.8	0.56	1.26	240
	2	15.3	0.58	1.22	162
	3	14.7	0.59	1.32	168
	4	2.6	0.60	1.01	49
	5	1.3	0.77	1.46	86
	6	2.6	1.02	1.38	54
100 mCl. pitressin injected intravenously.	1	14.9	1.37	1.34	121
	2	13.1	1.44	1.18	89
	3	13.5	1.40	1.28	76
	4	1.2	0.62	0.86	37
	5	1.3	0.76	1.21	51
	6	1.2	0.85	1.24	43

The evidence is consistent with the view that inhibition of diuresis by motion was due to release of ADH. The evidence, though strong, is circumstantial. Proof would require the demonstration that patients with diabetes insipidus did not show inhibition of diuresis after adequate exposure to motion. No suitable patient has been available for this test.

While it is likely that ADH release is largely or wholly responsible for the antidiuresis of motion, the participation of other mechanisms cannot be excluded.

Quantitative aspects.

If it is assumed that antidiuresis was due solely to liberation of ADH, the amount released can be estimated.

Method A.

The "peak-to-peak" time can be used to estimate the amount of ADH liberated from the formula of Burn and Grewal (11) already quoted in chapter 5. From Table 7.2 it can be estimated that in one subject vertical motion for fifteen, twenty and twenty-five minutes liberated about 10, 100 and 1,000 mU of ADH respectively.

Method B. /

Method B.

This method depends on the assumption that at the start of the experiment a large amount of ADH is circulating in the dehydrated subject. After the drinking, and rapid absorption from the empty gut, of a water load, maximum diuresis is delayed until the circulating hormone is destroyed. The time required for its destruction is a of the amount. In control tests subcutaneous injections of 25 and 50 mU of pitressin delayed the time to maximum diuresis by about thirty minutes, and 100 mU by more than 100 minutes. From Table 7.3 motion for twenty and thirty minutes in subject B.I. had about the same effect as 50-100 mU of pitressin subcutaneously, and in J.J.L. the effect of thirty minutes' motion was equivalent to 25-50 mU of pitressin subcutaneously.

Method C.

Improved accuracy was possible with this method. In the conditions of this test normal subjects were given intravenous injections of different doses of pitressin, after the third control urine specimen had been collected. Five minutes after the injection the bladder was emptied, the specimen was rejected, and three more fifteen-minute urine specimens were obtained. The ratio of urine passed in forty-five minutes after the injection to urine passed in forty-five /

forty-five minutes before the injection was determined. This ratio was then "corrected" by subtracting thirty from both numerator and denominator, representing the urine which continues to be excreted during maximum ADH activity (7). This corrected ratio was now plotted against the logarithm of the dose of pitressin, when a straight line graph was obtained over the range 2.5 to 50 mU. The graph for one man is shown in Fig. 7.4 and parallel but not identical graphs were obtained in five other men. The sensitivity of the method could be extended by lengthening or shortening the period of urine collection. The amount of ADH liberated by motion was estimated from the graph after calculating the appropriate value for the "corrected ratio".

The urine passed after injection of pitressin was also assayed for antidiuretic activity in the rat. In seven such tests, in which the dose of pitressin ranged from 12.5 to 50 mU, the amount recovered in the urine was from 3.5% to 8.6% of the injected dose (mean 6%), agreeing with other published figures (12). No activity was detected in the urine after injection into the subject of 5 mU of pitressin or less.

The urine passed during the antidiuresis of motion was assayed in rats, and the quantity of ADH released was estimated /

Table 7.10 Estimate of amount of antidiuretic hormone secreted in response to motion.

Subject	Volume of urine (ml.)		Ratio of urine output after to before motion		Estimated quantity of ADH released mU.	ADH detected in urine mU.	Estimated quantity of ADH released mU.
	In 45 minutes before motion	In 45 minutes after motion	Uncorrected	Corrected			
J.G.A.	811	380	0.46	0.45	7.5	Nil	-
B.I.	689	126	0.18	0.15	24		
D.McF.	800	134	0.17	0.14	24		
T.P.	918	157	0.17	0.14	24		
B.A.	631	107	0.17	0.13	25		
A.H.	806	63	0.08	0.04	> 50	11.4	190
J.K.	365	41	0.11	0.03	> 50		
R.McM.	776	52	0.07	0.03	> 50	5.4	90
J.C.	546	37	0.07	0.01	> 50	0.45	7.5
H.A.K.	798	33	0.04	0.004	> 50		

estimated approximately on the assumption that the urinary excretion of ADH represented 6% of this amount. In Table 7.10 are recorded the results of these estimates, together with the estimate of the amount of ADH released derived from the value of the "corrected ratio". The amount of ADH liberated by motion varied in ten subjects from 5 mU to more than 50 mU (probably up to 1,000 mU). Fair agreement was obtained between these two methods of estimation. The results of all methods were of roughly the same order of magnitude, though method C was probably the most accurate.

Relation between nausea and inhibition of diuresis.

When nausea (and in one case vomiting) were caused by motion, water diuresis was usually inhibited, and the duration of antidiuresis was roughly proportional to the severity of the symptoms. When water diuresis was not inhibited, symptoms were almost always absent. Three explanations of this association may be considered:-

1. The inhibition of diuresis was caused by nausea.
2. The symptoms were caused by release of ADH.
3. Antidiuresis and nausea were caused concurrently but independently by motion.

1. It is known that emotional stimuli can cause release of antidiuretic hormone (6, 12-16) and nausea might have had such /

such an effect. However, Tables 7.1, 7.3 and 7.4 show that on several occasions water diuresis was inhibited, usually only briefly, in the absence of nausea. Although the duration of antidiuresis was usually proportional to the severity of the symptoms, prolonged antidiuresis sometimes occurred in the presence of only mild symptoms. These arguments are not conclusive, but they make it unlikely that nausea caused antidiuresis.

2. Even when severe nausea occurred the amount of ADH released probably did not exceed one unit, and was sometimes only about 100 mU. Although large doses of pitressin cause nausea and other symptoms similar to those found in motion sickness (17, 18), the amounts released by motion do not cause symptoms.

3. It remains most likely that nausea and antidiuresis were independent responses to the stimulus of motion, and that they occurred at about the same threshold level. A similar explanation was offered in chapter 5 of the relation between antidiuresis and nausea in response to apomorphine.

Neither nausea nor antidiuresis as observed in these tests is a sensitive measure of a physiological change. It is necessary for the physiologically large amount of 2.5 mU of /

of pitressin to be released before antidiuresis is apparent by the methods used here. It is also probable that physiological changes take place before the symptom of nausea is recognised (19).

Individual susceptibility.

There is a wide range of individual susceptibility to the antidiuretic effect of motion, reminiscent of the individual susceptibility to motion sickness (20). It is likely that these two are related, and it might be possible to determine the susceptibility of say aircrew recruits to motion sickness by studying the effects of motion in the laboratory on water diuresis.

Pathogenesis of motion sickness.

If antidiuresis is indeed part of the syndrome of motion sickness, an end-point is available for studying quantitatively the relative effects of different types of motion in causing motion sickness. Previous investigators have had to use as their end-point the proportion of a population who vomited (21 - 23) or who showed other less well-defined effects. The literature thus contains much inconclusive and contradictory material. It was not the object of the present study to explore this point extensively, but a few observations will be mentioned.

Inhibition of water diuresis was produced most readily by a combination of rotation and sagittal head movement, a form of motion which is known to be very liable to cause motion sickness (1 - 3). Antidiuresis was not produced by angular acceleration alone, and this is in keeping with the observation that stimulation of the semicircular canals alone rarely, if ever, causes motion sickness. Linear acceleration alone did cause inhibition of diuresis. This motion was most effective when it was applied in the fronto-occipital plane with the subject sitting. Motion in the same plane of the head was not effective when the subject was lying. This may have been a protective effect of recumbency, or it may have been because in the sitting subject the stimulus applied to the otolith by this motion was the resultant of the horizontal acceleration and the downward pull of gravity (26). Linear acceleration in the vertical plane of the head caused diuresis to be inhibited both in the seated and the supine subject. Horizontal movement in the supine subject did not cause inhibition of diuresis. In this position linear acceleration was also applied in the vertical axis of the head, but the stimulus to the otolith was the resultant of this force and the downward pull of gravity.

These experiments, the results of which are summarized in Table 7.11, are too few to allow conclusions about the pathogenesis /

Table 7.11 Influence of head position on antidiuretic response to vertical motion (Method B.).

Subject	Position of trunk	Position of head	Duration of motion mins.	Antidiuresis "peak time" mins.	Symptoms
B.I.	Supine	Horizontal	20	90	None
B .I.	Supine	Vertical	20	135	None
J.J.L.	Supine	Horizontal	30	60	None
J.J.L.	Supine	Vertical	30	90	None

Table 7.12 Effect of chlorpromazine on antidiuresis of motion.

Subject	Dose of chlorpromazine mg.	Motion		Index of antidiuresis					Symptoms
		Type	Duration mins.	Method A peak-to-peak time mins.	Method B peak time mins.	Method C			
						Vol. urine before motion ml.	Urine after motion	Ratio	
J.B.	0	Horizontal	5	105					Mild nausea
J.B.	25	Horizontal	5	0					Mild nausea
J.B.	25	Horizontal	5	60					Mild nausea
B.I.	0	Vertical	20	75					Moderate nausea
B.I.	50	Vertical	20	0					No symptoms
B.I.	0	Vertical	20		165				No symptoms
B.I.	50	Vertical	20		90				No symptoms
A.H.	0	Rotation and sagittal head movement	5			806	63	0.08	Mild nausea
A.H.	25	Rotation and sagittal head movement	5			706	175	0.25	No symptoms
H.A.K.	0	Rotation and sagittal head movement	5			798	33	0.04	Moderate nausea
H.A.K.	50	Rotation and sagittal head movement	5			826	65	0.08	No symptoms

Chlorpromazine was given by mouth two hours before exposure to motion.

pathogenesis of motion sickness, but are included here to indicate the potential value of the method.

Influence of chlorpromazine.

In the experiments summarized in Table 7.12 chlorpromazine was given by mouth in doses of 25 or 50 mg. two hours before exposure to motion. It has already been shown (chapter 5) that chlorpromazine itself did not significantly influence the course of a water diuresis, nor prevent the action of exogenous pitressin on the kidney. It is seen from the Table that chlorpromazine always diminished the antidiuretic effect of motion, and in three experiments the effect was abolished. The symptoms caused by motion were often absent when chlorpromazine was taken. This is in contrast with the observation of Chinn (23, 27) that chlorpromazine was not of value in preventing motion sickness; but these investigators used both a different form of stimulation (a sea voyage) and a different end-point (vomiting), which may partially explain the discrepancy.

The reduction or prevention of antidiuresis by chlorpromazine may have been because the drug diminished conduction of impulses between the vestibular nuclei and the supra-optic nucleus. The site and mechanism of this action will be further discussed later (chapter 8).

Discussion. /

Discussion.

It is likely that stimulation of the vestibular apparatus is predominantly responsible for the antidiuresis which follows exposure to motion. That excessive vestibular stimulation should lead to this teleologically irrelevant response of the posterior pituitary need not occasion surprise, both because excessive vestibular stimulation leads to a battery of non-purposive responses (motion sickness), and because the posterior pituitary is reflexly activated by many stimuli unrelated to the control of body water (pain (14, 15), faradism (13), exercise (28), noise (28), syncope (12, 16) and electric convulsion therapy (12)).

What is the relation between vestibular stimulation and antidiuresis? Does each group of vestibular impulses relay to the supra-optic nucleus and release a small quantity of ADH, until sufficient has accumulated to allow its detection? Or is it only after many vestibular impulses have occurred that a sudden discharge of ADH ensues? More data are needed to answer these questions. The first explanation seems more likely, although the data of Table 7.2 and the calculations made therefrom are not in keeping with a linear release of ADH with time.

Although /

Although the biological value of antidiuresis after vestibular stimulation is not apparent, the phenomenon may be useful in analysing the pathogenesis of motion sickness and as a simple test of susceptibility to motion. However, the original purpose of this section of the investigation was to throw light on the mechanism of the antidiuretic effect of apomorphine and its prevention by chlorpromazine. It was shown in chapter 5 that apomorphine inhibited water diuresis in seated but not in recumbent subjects. It was suggested in chapter 4 that an action of apomorphine might be the facilitation of the resting discharge of the vestibules. With the demonstration in this chapter that vestibular impulses can cause the release of antidiuretic hormone, an explanation of the antidiuretic effect of apomorphine in terms of facilitation of vestibular impulses may be offered. Both the effect of apomorphine and that of motion are prevented by chlorpromazine. The reduction of the antidiuretic effect when the subject lies down might be due to the reduction in vestibular activity in the recumbent position.

Summary. /

Summary.

Motion causes inhibition of water diuresis in man. This effect was seen most readily in response to complex motion, notably when angular rotation and sagittal head movement were combined. It also occurred, though less readily, after linear acceleration. It was not demonstrated after pure angular acceleration. The inhibition of diuresis was due to release of antidiuretic hormone, the amount released varying from less than 5 mU to about one unit. Those forms of motion most liable to cause motion sickness were also most liable to cause antidiuresis. Inhibition of water diuresis was nearly always accompanied by nausea. The latter may have been the cause of the antidiuresis, but more probably the two effects occurred independently in response to the same stimulus. Chlorpromazine diminished or abolished the antidiuretic effect of motion, and also reduced the symptoms due to motion. The antidiuretic effect of motion may prove useful in analyzing the pathogenesis of motion sickness. It allows an explanation of the phenomenon that the antidiuretic effect of apomorphine is abolished by recumbency.

References. /

References.

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CHAPTER 8

MODE OF ACTION OF APOMORPHINE AND CHLORPROMAZINE

In this section the main experimental findings of the study will be recapitulated. An attempt will be made to integrate these with other knowledge of the action of anti-emetic drugs summarized in Part 1 of the thesis. The chapter will conclude with a discussion of the mechanism of action of apomorphine and of chlorpromazine.

Clinical value of chlorpromazine.

The clinical evaluation of chlorpromazine, reported in chapter 1, was inconclusive, but suggested the effectiveness of the drug in preventing vomiting due to vestibular disease, cerebral tumour, renal disease and certain drugs.

From the literature the following additional information can be gleaned.

Pregnancy sickness. /

Pregnancy sickness.

In one well-controlled study (1) and in several partially controlled or uncontrolled ones (2 - 7) chlorpromazine was found to prevent and relieve pregnancy sickness:- both "physiological" vomiting of early pregnancy and hyperemesis gravidarum.

Motion sickness.

Two well-controlled experiments showed that chlorpromazine was of no value in preventing seasickness (8, 9).

Radiation sickness.

A number of claims were made that chlorpromazine was of value in the prevention of radiation sickness (3, 4, 10). All these studies were uncontrolled, and critical reading provides no real support for the belief that chlorpromazine was of value in this condition.

Uraemia.

A number of favourable but uncritical reports have been published (3, 4, 6, 11). The variable course of sickness /

sickness in this illness makes critical assessment of the results especially desirable. In the absence of such studies it must be considered that the value of chlorpromazine has not been established.

Meniere's syndrome.

Benefit in treating this condition has been repeatedly claimed (3, 4,11) but the data are insufficient to allow conclusions about the value of chlorpromazine to be drawn.

Cerebral tumour.

In one series vomiting was eliminated in ten of fourteen patients with cerebral tumour, and the condition of the remaining four was improved by chlorpromazine (6).

Post-anaesthetic sickness.

In a large well-controlled series chlorpromazine reduced the incidence of post-operative sickness from 80% to 60% (12). In other large and partially controlled studies the incidence of post-operative vomiting fell from 41% in a control group to 8% in a group treated with chlorpromazine (13) and from 28% in a control group to 13% in the chlorpromazine group (14).

Drugs. /

Drugs.

Digitalis.

Excellent results were claimed in all of six patients treated in one series (3).

Nitrogen mustard.

Excellent results were claimed in patients given chlorpromazine with barbiturates (15). Twenty-four of thirty-eight patients given chlorpromazine alone before an infusion of nitrogen mustard responded excellently (3).

Veratrum.

Chlorpromazine was of no value in preventing sickness due to veratrum alkaloids (16).

The alcohol-antabuse reaction.

Chlorpromazine prevented vomiting in sixty patients caused by alcohol in the presence of disulphuram ("antabuse") (4, 17).

Other drugs.

Chlorpromazine relieved sickness in six patients due to narcotic drugs (3), in two patients due to pethidine (6), and in four of six patients who were sick after aminophylline (3). There are fragmentary reports of the value of chlorpromazine in relieving sickness due to other drugs.

In summary, convincing evidence of the value of chlorpromazine as an anti-emetic drug is available in cases of cerebral tumour, pregnancy sickness, therapy with narcotic drugs and digitalis and the alcohol-antabuse reaction. There is also suggestive evidence of its value in sickness due to Meniere's syndrome, uraemia and therapy with nitrogen mustard and aminophylline. Its value in radiation sickness is unproved. There is convincing evidence that chlorpromazine is not of value in motion sickness and in vomiting due to veratrum alkaloids

Mode of action of apomorphine.

There is no direct evidence of the mode of action of apomorphine in man comparable with the experimental work in animals which demonstrated the significance of the CT zone in the production of vomiting by apomorphine.

The main relevant findings of the present study were these:-

1. The emetic of apomorphine was abolished or greatly reduced by the recumbent position.

2. Subemetic doses of apomorphine caused release of antidiuretic hormone. This effect was also reduced by the recumbent position.

3. /

3. Release of ADH occurred after subemetic stimulation of the vestibules.

4. Nystagmus caused by vestibular stimulation was enhanced by small doses of apomorphine.

The action of apomorphine in facilitating the effects of vestibular stimulation provides a clue to the understanding of the general mode of action of this drug. It is likely that apomorphine acted by facilitating interneuronal conduction in the reticular formation of the medulla, pons and midbrain between the nuclei of the 8th. and 3rd. nerves. Could a similar action also explain the emetic and antidiuretic effects of apomorphine? This question is partly answered by noting the similarity between the effects of apomorphine and those of excessive vestibular stimulation. The findings recorded in chapter 4 make it unlikely that the effects of apomorphine were solely due to facilitation of vestibular reflexes, but suggest a more general facilitation of reflexes initiated by other afferent stimuli. The influence of apomorphine on respiration, salivation, sweating and vasomotor control - referred to in chapter 2 - is in keeping with a widespread facilitating action of the drug on brainstem autonomic reflexes. Moreover, the fact that

both /

both vestibular stimulation and apomorphine caused release of ADH indicates that the facilitating action of apomorphine may extend to higher levels of the nervous system. This hypothesis cannot be directly proved in man, but is in keeping with the experimental facts and with current concepts of the mode of action of drugs on the nervous system.

To what extent can this view of the action of apomorphine be related to experimental evidence of its action in the dog and cat? At present no connection can be seen between the two sets of data. This is mainly because of the large gaps in our knowledge. We do not know if the CT zone exists in man, and if its presence is necessary for the emetic action of apomorphine. We do not know the influence of posture on the emetic effect of apomorphine in dogs and cats. Nor is it known whether apomorphine releases ADH in dogs and cats, and if it does, whether the CT zone is necessary for this action. It would seem unwise to attempt to reconcile the conflicting views on the mode of action of apomorphine in animals and in man until these gaps in our knowledge have been filled.

Anti-emetic /

Anti-emetic action of chlorpromazine.

A clue to the mode of action of chlorpromazine was found also in the experiments on nystagmus reported in chapter 6. A small dose of chlorpromazine did not itself influence vestibular nystagmus but it prevented the facilitating action of apomorphine. It is now suggested that chlorpromazine similarly antagonized the emetic and antidiuretic effects of apomorphine by preventing the facilitating actions of the latter on central autonomic reflexes.

Another clue to the site of action of chlorpromazine was provided by its influence on the antidiuretic effect of nicotine and of apomorphine. The antidiuretic action of nicotine was uninfluenced by posture, and was probably exerted directly on the supraoptic nucleus. The antidiuretic action of apomorphine was influenced by posture, and was probably due to facilitation of afferent impulses, especially those of vestibular origin. Chlorpromazine prevented the antidiuretic effect of apomorphine, but not that of nicotine. This suggested that here too chlorpromazine acted by blocking the facilitating action of apomorphine on central nervous reflexes.

It /

It is unlikely that this provides the whole explanation of the action of chlorpromazine. Experimental studies have demonstrated many different actions of this drug on the central nervous system. Chlorpromazine probably also blocks the effects of direct afferent stimulation, but this effect is exerted rather less readily than its antagonism of facilitated impulses. Thus chlorpromazine had no effect on vestibular nystagmus, in a dose which was able to prevent the facilitating action of apomorphine. Chlorpromazine prevented the release of ADH by excessive vestibular stimulation, but was apparently unable to prevent the occurrence of motion sickness. A clinical observation supported the conception that chlorpromazine prevented the reflex autonomic effects of vestibular stimulation without interfering with the direct effects of such stimulation. In a patient with vestibular neuronitis, described in chapter 1, chlorpromazine prevented vomiting but did not affect dizziness.

Experimental evidence supporting this view of the mode of action of chlorpromazine is to be found in the electroencephalographic studies of Longo and his colleagues (18).

How /

How can this concept of the mode of action of chlorpromazine be applied to interpreting the evidence of its clinical effectiveness? It might be expected that chlorpromazine would prove most effective in preventing sickness caused by chemical substances which faciltate nerve conduction in the brainstem. Its next field of effectiveness would be in conditions caused by excessive afferent stimulation, involving central autonomic reflexes. It would be expected to be of little value in conditions due to non-nervous irritation of the vomiting mechanism. Too little is known of the pathogenesis of vomiting to allow classification of its causes in these categories. However, it might tentatively be suggested that apomorphine is an example of the first of these mechanisms, Meniere's syndrome of the second, and radiation sickness of the third; and the order of clinical effectiveness of chlorpromazine in these conditions is in keeping with the views expressed.

Throughout this study the methods of clinical pharmacology have been employed. These allow the establishing of facts and the testing of hypotheses, but are not suited to the conclusive demonstration of physiological mechanisms. It /

It is however suggested that the evidence presented here is in keeping with the belief that chlorpromazine owes its effectiveness as an anti-emetic drug in clinical practice mainly to its capacity to block the effects of excessive afferent nervous stimulation.

It is hoped that this conception may lead to the rational employment of anti-emetic drugs in clinical practice.

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APPENDIX 1.

DRUGS USED IN THIS STUDY

Apomorphine - Apomorphine hydrochloride, 1 mg./ml.
Ampoules of 1 ml. specially prepared by T. & H. Smith, Ltd., Edinburgh.

Atropine - Atropine sulphate, 0.75 mg.
White sugar-coated tablets specially prepared by May and Baker, Ltd., Dagenham.

Chlorpromazine - Chlorpromazine hydrochloride, 25 mg.
White sugar-coated tablets supplied by May and Baker, Ltd., Dagenham.
Ampoules of 2.5% sterile solution.

Hyoscine - Hyoscine hydrobromide, 0.75 mg.
White sugar-coated tablets specially prepared by May and Baker, Ltd., Dagenham.

Nicotine - Players cigarettes.

Posterior Pituitary Extract - Pitressin solution, 100 mU./ml.
Vials of 10 ml.
Specially prepared and re- assayed by Parke Davis & Co., Hounslow.

Promethazine /

Promethazine - Promethazine hydrochloride, 25 mg.

Blue sugar-coated tablets, supplied by May and Baker, Ltd., Dagenham.

Control Tablets - White sugar-coated tablets, indistinguishable in taste and appearance from the tablets of atropine, chlorpromazine and hyoscine.

Blue sugar-coated tablets, indistinguishable in taste and appearance from the tablets of promethazine.

Supplied by May and Baker, Ltd., Dagenham.

APPENDIX 2.

BIOCHEMICAL METHODS

Determination of osmolarity of urine.

A tube containing 3 ml. of urine was placed in a freezing mixture. The fluid was constantly stirred while the temperature was read with a micro-Beckmann thermometer. The temperature of the fluid fell steadily, then rose sharply, and remained constant for a time. This constant temperature was the freezing point of the urine. This was compared with the freezing point of distilled water determined in the same way, and the osmolarity of the urine calculated from the depression of the freezing point.

Creatinine concentration in the urine.

To 20 ml. of 1% picric acid and 1.5 ml. of 10% caustic soda in a volumetric flask a suitable volume of urine was added. The mixture was left for fifteen minutes, then made up to 100 ml. with distilled water. The colour of the solution was then read immediately in the Spekker absorptiometer, using an Ilford 604 spectrum green filter, or in the Unicam SP500 spectrophotometer at a wavelength of 480 m . A reagent blank and standard creatinine solutions /

solutions were similarly prepared. Calibration was linear in the absorptiometer in the range 0 - 1 mg.% and in the spectrophotometer in the range 0 - 0.2 mg.%. Urine dilutions were adjusted to give readings in the middle of this range. In the spectrophotometer maximum absorption occurred at 480 mμ., not at 520 mμ. as often stated. Triplicate determinations were carried out at 480, 500 and 520 mμ. with results which did not vary.

Sodium concentration in the urine.

After appropriate dilution with sodium-free distilled water, the sodium concentration of the urine was determined in the EEL flame photometer. Standard solutions of sodium chloride of 0.1 to 0.5 mEq./litre were used as comparison.

APPENDIX 3.

CONSTRUCTION OF SWINGS

Horizontal swing. (Fig. A.1)

A stretcher was suspended from the ceiling by four stout wires each 3 metres long. The period of this swing was 3.3 seconds (18 cycles per minute). It was swung by hand through an amplitude of 1 metre. This movement was mainly in the horizontal plane, the maximum vertical displacement being only 17 cms. A back rest could be added to the swing to allow the subject to be swung in an upright position.

Vertical swing. (Fig. A.2)

The apparatus consisted essentially of a stretcher suspended between four uprights, which could be moved up and down in grooves cut in the uprights. The movement of the stretcher was limited by two sets of springs, one at the bottom of the grooves, and one a distance of 1 metre above. A counterbalance arrangement facilitated manual operation of the swing. The operator applied a regular rate of swinging following a simple harmonic pattern.

Rotating chair. /

Rotating chair. (Fig. A.3)

This consisted of a simple wooden chair rotating evenly on ball bearings. The output from a $\frac{1}{2}$ h.p. electric motor was transmitted to the chair through an infinitely variable hydraulic gear box, reduction gear and right-angle bevelled drive. The drive was engaged and disengaged by a combined dog-clutch and brake. The speed of rotation of the chair was regulated by a sensitive hydraulic control. The speed was measured and recorded by a bush of 12 contacts at intervals of 30° which rotated with the chair and made contact with a fixed bush. This completed a circuit which activated a pen writing on moving paper.

Fig. A.1.

The horizontal swing.

Fig. A.2.

The vertical swing.

Fig. A.3.

The rotating chair.

APPENDIX 4.

IDENTIFICATION AND ASSAY OF ANTIDIURETIC HORMONE

I am indebted for the following notes to Miss Fay Johnston who carried out these assays.

Antidiuretic hormone was determined by observing the influence of the material on the rate of urine flow in water-loaded rats.

Male rats weighing 200 - 300 G. were deprived of food for eighteen hours but allowed free access to water. An oral dose of 5 ml. per 100 G body weight of tepid water was given, followed forty-five minutes later by 5 ml. per 100 G. body weight of 12% ethanol solution. When diuresis started the animals were anaesthetized with ether, and the bladder and one external jugular vein cannulated. Anaesthesia was maintained by intravenous injections of 20% ethanol solution.

The antidiuretic activity of the urine was compared with that of a standard solution of posterior pituitary extract. Each intravenous injection was washed in with a constant volume of 0.9% saline. A time lag of two minutes was allowed to give the injection time to act.

The /

The antidiuretic potency (α) of a sample of urine was calculated from the formula,

$$\alpha = \frac{b}{a} \times 100$$

where a = volume of urine excreted by the rat in a period of ten minutes lasting from eight minutes before the injection to two minutes after the injection;

b = volume of urine excreted in the period three to thirteen minutes after the injection.

The potency so determined was matched with the potency of a known solution of pitressin. The method was sensitive to a concentration of 10 microunits of pitressin per ml.

APPENDIX 5.

ELECTRONYSTAGMOGRAPHY
(Figs. A.4 and A.5)

The method depended on the fact that normally a difference of electric potential exists between the cornea and the retina of the eyes. This potential difference can be recorded by placing electrodes at the angles of the eyes and on the forehead. Movement of the eyes in the horizontal plane causes changes in the potential which are proportional to the degree of movement.

Small triangular or V-shaped electrodes of silver-chloride were attached to the skin at the outer canthus of each eye. An indifferent electrode was attached to the skin of the forehead in the midline. During recordings the subject wore a felt hat. The leads from the electrode were carried through the brim of the hat and attached to flexible cable which could twist without tension. The cable was carried through an overhead ring and connected to the input of a DC-coupled amplifier. The output of the amplifier led to one channel of an Ediswan pen oscillograph. The other channels of the oscillograph were used for marking chair speed and time.

The /

The amplifier was used with high gain, long time constant (one second) and high-frequency filter. Each record was calibrated by asking the subject to look back and forward between two black spots on the wall a distance of 5^{o} apart. Amplification was arranged so that a swing of 5^{o}, equivalent to a voltage change of about 50 microvolts, gave a pen deflection of 10 - 20 mm.

The speed of the eye in the slow phase of nystagmus was measured by continuing the slope of the tracing to cut the baseline, and measuring the perpendicular distance corresponding to the distance travelled by the paper in one second. This was converted to degrees per second from the calibration record.

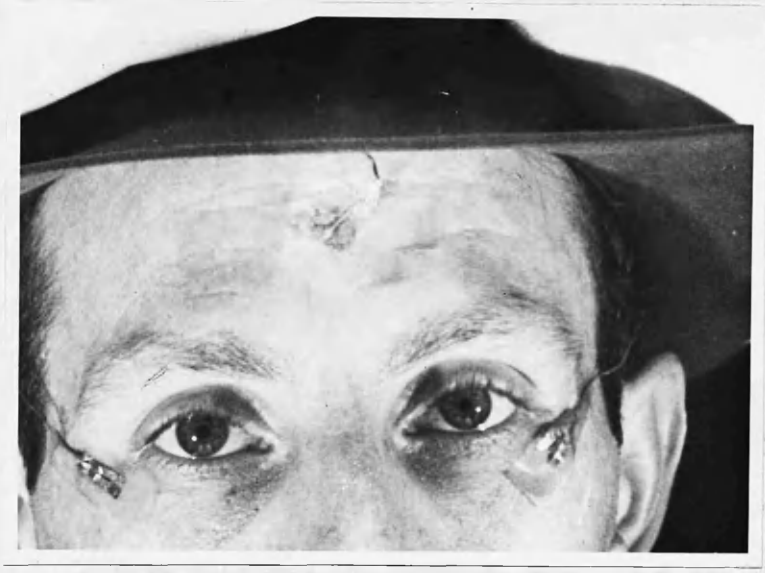

Fig. A.4.

Electronystagmography: method of attaching electrodes.

Fig. A.5.

Electronystagmography: recording post-rotatory nystagmus.

SUMMARY

1. A review of the literature of anti-emetic drugs showed that this title had been conferred on many substances by virtue only of their ability to prevent apomorphine-induced vomiting in dogs.
The evidence that such drugs prevent vomiting in human disease was less acceptable.
The new drug chlorpromazine was probably of value in cerebral tumour, pregnancy sickness, some forms of drug sickness and uraemia, but there was little support of its value in other forms of vomiting.

2. Personal experience with chlorpromazine in the treatment of thirty-six cases of vomiting from various causes was in conformity with these findings.

3. An experimental study in sixty normal human subjects showed that chlorpromazine was highly effective in preventing nausea and vomiting caused by apomorphine.
Hyoscine also prevented vomiting due to apomorphine but did not prevent nausea.
Atropine and promethazine were less effective in preventing vomiting than the other two drugs.

4. /

4. The emetic effect of apomorphine was prevented when the subject remained supine after the injection. An analysis of this effect showed that it was associated with reduction of afferent impulses in the recumbent position.

5. Subemetic doses of apomorphine caused inhibition of diuresis, due to release of antidiuretic hormone from the posterior pituitary. This effect was prevented by the supine position and by chlorpromazine.

6. Prolonged vestibular stimulation, insufficient to cause motion sickness, caused inhibition of diuresis due to release of antidiuretic hormone. This effect was prevented by chlorpromazine.

7. Nystagmus following vestibular stimulation was enhanced by apomorphine. Chlorpromazine prevented this effect of apomorphine, although it did not itself affect vestibular nystagmus.

8. It was suggested that apomorphine caused vomiting and antidiuresis in man by facilitating the effects of afferent stimulation in the autonomic centres of the hypothalamus, midbrain and bulb.
Chlorpromazine blocked these facilitating actions of apomorphine.

9. /

9. The action of chlorpromazine is to block preferentially facilitating impulses in the reticular formation. Larger doses may also block normal afferent impulses.

10. Clinically chlorpromazine is of value as an anti-emetic when sickness is caused by facilitation of afferent impulses. This is probably the case in many forms of drug-induced sickness. Chlorpromazine is of less value when vomiting is due to excessive afferent stimulation, as in motion sickness. Chlorpromazine is of no value when vomiting is caused by other mechanisms, as in radiation sickness.

11. Fuller knowledge of the action of anti-emetic drugs must await further studies of the pathogenesis of sickness in various clinical states.
