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PHYSIOLOGY OF NAUSEA AND VOMITING

P. L. R. ANDREWS

INTRODUCTION: WHY IS THE MECHANISM NOT KNOWN?

Nausea and vomiting have been associated for many years with the use of general anaesthetics for surgical procedures, and descriptions of these side effects, induced by ether and chloroform, were included in the earliest textbooks of pharmacology and therapeutics. One of the first extensive descriptions of the phenomenon was by John Snow, published in 1848, within 18 months of the introduction of anaesthesia into Britain [93]. He observed that vomiting was more likely to occur if the patient had eaten recently. In most cases the vomiting lasted only a few minutes but in some it continued for hours or even days. He suspected that movement shortly after operation may have triggered the vomiting. Postoperative treatment included wine (which he considered more beneficial than smelling salts!) and Battley's solution of opium.

There has been a general trend towards a decrease in the incidence and intensity of the problem because of the use of less emetic anaesthetic agents, improved pre- and postoperative medication (e.g. analgesics), refinement of operative technique and identification of patient predictive factors [33]. However, in spite of these advances, nausea and vomiting still occur with unacceptable frequency in association with surgery and anaesthesia and the description of it as "the big little problem" [56] encapsulates much of the general perception. Although anaesthetics have been used to facilitate surgical procedures for almost 150 years, why is the mechanism of nausea and vomiting not known? This probably reflects at least four factors.

The complexity of the problem. Careful clinical studies of the phenomenon should give important clues to the mechanism but a consideration of the variables shows how difficult it may be to get other than some general indications. If we take a simple example using two patient variables (age, gender), three operative site variables (head and neck, abdomen, other), two premedication variables and three different anaesthetics, then the number of possible combinations is 36. It is clear, therefore, that to identify a mechanism or to assess the effects of an intervention on emesis requires a considerable number of patients in well controlled trials.

Inadequate quantification of the phenomenon. Although there have been a large number of clinical trials, in general the phenomenon has been poorly quantified; many studies fail to distinguish between nausea and vomiting, or retching and vomiting, although in most, but not all, of the more recent studies these variables have been fully quantified. In addition, until recently there was little detailed information on the time course of postoperative nausea and vomiting (PONV), a particularly useful source of clues about mechanisms.

Inadequate antiemetic regimens. Although emesis is a common symptom of disease, a side effect of many therapies (e.g. cytotoxic chemotherapy, radiotherapy, L-dopa) and a result of "natural" stimuli (e.g. motion, pregnancy), the physiology of emetic mechanisms has not been an area of particularly intense research since the classical studies of Wang and Borison in the late 1940s and 1950s [102–104]. Interest in basic mechanisms has been rekindled in recent years because attention has focused on the particularly distressing nausea and vomiting induced by anticancer chemotherapy. Additionally, the success of 5-hydroxytryptamine-3 (5-HT_3) receptor antagonists (e.g. ondansetron and granisetron) in treating this emesis has provided critical insights into the pathways involved in this form of emesis [8]. If 5-HT_3 receptor antagonists are found to be as effective against PONV as they are against anticancer therapies then it may at last be possible to identify the predominant mechanism involved.

Animal models. One major factor that has limited physiological and pharmacological studies of the mechanism of PONV is the apparent lack of a suitable animal model. Many of the common laboratory species such as rats and rabbits do not vomit irrespective of the stimulus, although they appear to exhibit "behavioural equivalents" of nausea. Carnivores (cat, dog and ferret) and laboratory primates (monkey, marmoset), as far as is known, respond to virtually the same range of emetic stimuli as man, including cytotoxic drugs and radiation, although there are considerable species differences in sensitivity. However, these species do not appear to

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P. L. R. ANDREWS, PH.D., Department of Physiology, St. George's Hospital Medical School, Cranmer Terrace, Tooting, London SW17 0RE.

suffer from pregnancy sickness, and postoperative and postanaesthetic emesis is not a commonly encountered problem. When PONV is encountered, it can often be ascribed readily to the premedication (e.g. morphine) or to the particular surgical procedure, although again there are species differences. For example, vomiting is not an uncommon sequelae to truncal vagotomy in the dog (and man) but is rare in the ferret [Bingham and Andrews, unpublished observation]. Perhaps it is not surprising that animals do not have PONV as experimental and even veterinary surgery do not mimic the entire clinical experience of a patient undergoing elective or emergency surgery.

Whatever the reason for the apparent differences between man and animals, the lack of an appropriate model has certainly hampered identification of mechanisms and hence the design of rational therapies based upon such an understanding. As a result, the tendency in PONV research has been to undertake clinical trials of agents whose antiemetic activity has been demonstrated against other stimuli such as motion (e.g. atropine) or gastrointestinal motility disorders (e.g. domperidone, metoclopramide). This approach continues with the trials of the 5-HT_3 receptor antagonists such as ondansetron (Zofran) which have been demonstrated to be effective to date against cytotoxic chemotherapy and radiotherapy-induced emesis [6, 37].

Taking these limitations into account, this review attempts to identify the specific mechanisms by which premedication, surgery and anaesthetics may activate the emetic reflex. Although the review is highly speculative in parts, the mechanisms proposed are, in general, testable. Before discussing the afferent, integrating and motor mechanisms of the reflex, it is perhaps worth reviewing nausea and vomiting in a more general biological than clinical context.

NAUSEA AND VOMITING IN BIOLOGICAL AND CLINICAL CONTEXTS

Definitions and functions

Nausia is an unpleasant, but not painful, sensation referred to the pharynx and upper abdomen, associated with a desire to vomit or the feeling that vomiting is imminent. It may be brief or prolonged, often occurring in "waves" and precedes vomiting or occurs in isolation. Vomiting may actually alleviate the sensation of nausea.

Vomiting is the forceful expulsion of upper gastrointestinal contents via the mouth and is usually, but not always, preceded by retching where no expulsion takes place but which involves activation of the same muscle groups (see below). Vomiting should not be confused with gastro-oesophageal reflux or regurgitation, neither of which is forceful nor involves the same pattern of muscle activation as retching and vomiting.

Nausea and vomiting are most often regarded clinically as undesirable side effects but in the natural world they have specific functions contributing to the survival of the animal. In the obligatory functions of eating and drinking, as with breathing, the body exposes itself to toxins [38]. The senses of vision, taste and smell are all used to provide information about food before swallowing, but many poisons are not bitter tasting, foul smelling or brightly coloured and so may not be identified by these senses that may be regarded as the first line of defence. After the contaminated food has passed the upper oesophageal sphincter, it can only be removed from the body rapidly by vomiting or possibly by diarrhoea. For the toxin to be ejected it must first be recognized as such, and this occurs by detectors in the lumen of the upper gut (pre-absorptive) and the circulation (post-absorptive). These detectors trigger a series of events which may be summarized and rationalized as follows: (i) nausea to stop further ingestion and to facilitate the development of a learned aversion so that the food is rejected before ingestion when encountered again; (ii) gastric relaxation to reduce gastric emptying of the contaminated food and intestinal retroperistalsis to return any contaminated food to the stomach; and (iii) retching and vomiting to purge the stomach.

Viewing nausea and vomiting from this perspective has implications for the way they are regarded in the clinic. First, as far as can be ascertained, the vomiting reflex evolved as a defensive reflex centred around the gastrointestinal tract. Mechanisms for the ejection of contaminated food are found throughout the animal kingdom, ranging from invertebrates, such as the starfish, to vertebrates including fish (e.g. trout, sharks and tuna), amphibia (e.g. frog) and birds (e.g. seagull, hawk), although the motor mechanism differs somewhat from that used by mammals. For vomiting to be evoked in any species, all that is needed is that the stimulus triggers one of the detection systems: there is no requirement for a specialized system for each type of stimulus. Second, the nausea and vomiting evoked by contaminated food is considered to be "appropriate" in that it leads to expulsion of the driving stimulus but in most clinical contexts the nausea and vomiting are "inappropriate" and have several additional adverse effects which are outlined below.

Consequences of PONV

If PONV was without detrimental effects to the patient, either real or potential, then there would be less pressing need to identify the mechanism and design therapies. However, this is clearly not the case and the effects of nausea and vomiting may be even more extensive than is at first appreciated. They may be classified into three types.

Physical. Retching and vomiting are fairly violent and intense physical acts and as such may place considerable stress upon certain structures, even in healthy subjects, particularly if protracted. These include oesophageal tears, possibly resulting in haemorrhage (Mallory–Weiss syndrome) and rupture of the oesophagus (Boerhaave syndrome), rib fracture, gastric herniation, muscular strain and fatigue, and rupture of cutaneous vessels in the upper body. The occurrence of these in association with PONV is unlikely because of its usually mild and brief nature, but this list serves to illustrate the

forces involved in vomiting and why vomiting may cause wound dehiscence, intraocular bleeding and bleeding of skin flaps in the upper body after plastic surgery [94, 100].

The major physical problem associated with vomiting in the postoperative period is aspiration of vomitus and the triggering of cardiorespiratory reflexes. A component of the motor programme of the vomiting reflex ensures that the airways are protected but, because of the effect of anaesthesia, reflex coordination may be impaired in some patients. Similar problems may occur after over-indulgence with alcohol or in patients with damage to the brain stem. The mechanism underlying the failure of this automatic protective reflex for the airways is unclear but suggests a differential effect of anaesthetics on brain stem neurones. Under even deep surgical anaesthesia, animals and man continue to breathe spontaneously but vomiting is rare. During vomiting the intrathoracic pressure exceeds atmospheric because of transmission of increased intra-abdominal pressure to the thorax, thus for aspiration of vomitus to occur there must be stimulation of inspiration and opening of the glottis during this expulsive phase. In addition to failure of the coordination mechanism, there may also be depression of the mechanism that usually increases the level of arousal before vomiting.

Metabolic. The metabolic consequences of vomiting have been described extensively and include anorexia, dehydration and alkalaemia. These metabolic effects tend to occur when there is prolonged vomiting and are unlikely to be a problem in PONV as it is usually of short duration.

Psychological. The psychological impact of nausea and vomiting associated with anticancer chemotherapy and radiotherapy has long been recognized but PONV may also have such effects. Nausea is a very aversive stimulus and if induced by a particular food may induce a life-long aversion to that food [80]. This aversion is appropriate and forms part of the body's defence mechanism against poisonous foods. In the context of surgery, the nausea (and vomiting) are associated with the operative experience and may induce an aversion to further surgery, although for most patients this is unlikely to be a problem as multiple experiences of surgery are not common in the life of an individual. In addition, if a patient experienced PONV on one occasion, there may be an expectation that it may occur with subsequent surgery. In one study, the incidence of PONV was three times greater in patients who had previous experience of PONV [81]. This suggests that the sensitivity of the emetic reflex may be altered by higher inputs, although the pathways involved are not defined. This observation has a broader implication as it may suggest that the sensitivity of an individual to a particular emetic stimulus is contributed to by their previous emetic history. This may account for the increased incidence of nausea and vomiting after surgery, anticancer therapy with cytotoxic drugs and pregnancy in patients who are sensitive to motion stimuli. If the emetic pathways become sensitized to other stimuli by motion, there is no reason why there should not be cross-sensitization between other stimuli.

WHY DO POSTOPERATIVE NAUSEA AND VOMITING OCCUR?

The section above has emphasized that nausea and vomiting are natural responses that may be regarded as components of the body's defence system against ingested toxins: why then should anaesthesia and surgery induce nausea and vomiting? The reason does not lie in the fact that there is anything particularly special about anaesthesia and surgery but that, as with so many clinical situations in which nausea and vomiting occur, some feature of this treatment is capable of activating the emetic detectors. Thus it is not necessary to propose specialized detectors for each type of stimulus but only to show how the stimulus under consideration activates one of the triggers for the system. The logic of this approach is apparent when we consider that the vomiting reflex is present in animals that evolved long before medicine originated: the detectors that trigger the reflex evolved to identify potentially hazardous features of the natural and not the clinical environment. A similar argument can be proposed for motion sickness which, although it can be induced by riding some animals (e.g. camel), is associated most usually with man-made forms of transport.

The vomiting induced by contaminated food present in the gut lumen is appropriate as it leads directly to the ejection of the stimulus and as such is self-limiting. In contrast, many clinically relevant emetic stimuli are located in the plasma and, although they may trigger vomiting, the stimulus remains, contributing to the protracted nature of the emetic response seen with some drugs.

Although in broad terms we can say "why" anaesthesia and surgery can induce nausea and vomiting, the question "how" is much harder and as yet we do not have a satisfactory answer, even though it is possible to identify several of the most likely possibilities. Before discussing these specific mechanisms, the basic mechanisms of emesis will be reviewed briefly to provide a framework for discussion.

GENERAL MECHANISMS OF EMESIS

Three major components comprising the vomiting reflex can be identified: emetic detectors, integrative mechanisms and motor outputs. These will be discussed separately.

Emetic detectors

The key question that must be addressed is how the various components that may contribute to PONV, such as opioid premedication, the anaesthetic and surgical manipulation, trigger detection systems that have evolved primarily to detect ingested toxins? The section below describes the main ways in which the emetic system is stimulated and the way in which the stimuli relevant to PONV may cause activation are discussed in the sections that follow.

Abdominal visceral afferents. As the major function of the vomiting reflex is to protect against the accidental ingestion of toxins in the food, it is not surprising that the gut should have detection systems capable of activating the reflex. Indeed the gut afferents may be viewed as the second line of defence against poisoning via food if it has circumvented detection by vision, taste and smell which represent the first line [38]. The vagus is the major nerve involved in the detection of emetic stimuli and in its abdominal course contains about 80–90% afferent fibres. Electrical stimulation of the abdominal vagal afferents is capable of inducing emesis within 20 s, thus illustrating the potential of the pathway for rapid ejection of gastric contents (6). Two types of vagal afferent fibre are involved in the emetic response: (i) mechanoreceptors, located in the muscular wall of the gut are activated by both contraction and distension of the gut [4, 49]. Distension of the gastric antrum (e.g. by over-eating) or proximal small intestine (e.g. by obstruction) may induce nausea and vomiting by stimulation of these afferents; (ii) chemoreceptors, located in the mucosa of the upper gut, monitor several features of the intraluminal environment. They respond to mucosal stroking, acid, alkali, hypertonic solutions, temperature and irritants (e.g. copper sulphate) [4, 48, 49]. As lesion studies have shown that the emesis induced by intragastric hypertonic sodium chloride and copper sulphate is reduced or abolished by vagotomy, it is likely that it is these mucosal afferents that are responsible [6, 104]. Emesis induced by intraluminal bacterial toxins, such as staphylococcal enterotoxin, can also be abolished by vagotomy [96] and it is probable that such agents can also activate the mucosal vagal afferents, although this has not been studied formally.

The substrate for the polymodal mucosal chemoreceptor is not known but the current hypothesis suggests an arrangement rather like that in the taste buds or carotid body with a "detector cell" responding to a range of stimuli and releasing a neurotransmitter to discharge an afferent terminating in close proximity. In the intestine, the enterochromaffin cell has been proposed as the detector cell, although this awaits experimental confirmation.

Area postrema. The studies of Wang and Borison [102–104] brought about a major change in understanding the way in which emetic agents were detected and subsequently triggered the vomiting reflex. It had long been known that emesis could be induced by application of chemicals to the dorsal surface of the brain stem and it was assumed that this was through direct stimulation of the vomiting centre, thought to be located in this region. However, Wang and Borison [102, 104] demonstrated that several stimuli were detected by cells of the area postrema, termed the chemoreceptor trigger zone for emesis, which in turn activated the vomiting centre. Whilst there is no doubt that the area postrema when appropriately activated can induce emesis, its description as the chemoreceptor trigger zone has lead to the assumption that *all* chemicals in the circulation must induce emesis by this route.

The area postrema in man is a U-shaped structure a few millimetres long located in the caudal part of the fourth ventricle in the region of the obex [66]. Significantly, the area postrema is present in animals with (e.g. ferret) and without (e.g. rat) an emetic reflex, which suggests that it has functions other than emesis [25]. The area postrema is one of the circumventricular organs of the brain and is outside the blood–brain barrier and the cerebrospinal fluid–brain barrier [66]. It is therefore relatively permeable to polar molecules in the blood or cerebrospinal fluid, a feature which makes it ideally suited for a general chemoreceptor function.

Vestibular system. The vestibular labyrinthine system is essential for induction of emesis by motion stimuli. However, the evolutionary significance of an emetic response to motion is puzzling, but Treisman [98] proposed that when an animal is poisoned it may become unsteady on its feet and hence the labyrinths may be stimulated by such swaying motion. Obviously such a mechanism cannot apply to patients, although sudden movements of the head should be avoided after treatment to minimize any labyrinthine input to the vomiting centre, particularly in patients who have been relatively immobile for some time in a recumbent posture. The labyrinthine input should also be borne in mind when moving patients laying down on trolleys after surgery, as this additional input may induce emesis. Experimental studies in man suggest that the position of the head (and therefore the degree of labyrinthine stimulation) can influence the emetic response to apomorphine [53] which acts via the area postrema, and hence there is no reason why other emetic stimuli should not be affected in a similar way.

There is limited evidence that the vestibular system may be involved directly in the emetic response to some drugs. Studies in the dog revealed that removal of the vestibular system reduced the emetic response to lobeline, L-dopa and nicotine but not pilocarpine or apomorphine [71]. The most likely explanation is that these drugs are able to discharge vestibular afferents and to facilitate the primary effects they have on the emetic mechanism.

Higher influences. Studies in decerebrate animals have revealed that the integrative circuitry for the motor components of the emetic reflex reside in the brain stem and that such animals are capable of responding to emetic stimuli acting via the area postrema, vagus or even vestibular labyrinths. The role of higher cerebral influences is at present unclear but there is little doubt that inputs from such areas (e.g. limbic system) can induce nausea and vomiting [90].

These higher inputs appear to have a mainly facilitatory role in modulating the sensitivity of the brain stem emetic mechanism rather than acting as primary detectors of the emetic stimuli.

Miscellaneous inputs. Nausea and vomiting can be activated from several other regions of the body. Unpleasant tastes can induce nausea and retching, although it is not clear if this is a primary response or

secondary to association with illness experienced as a result of prior exposure (a learned aversion). Nausea, and gagging in particular, can be evoked readily by mechanical stimulation of pharyngeal afferents projecting to the brain stem in the glossopharyngeal nerve. There may be a heightened awareness of this region associated with nausea.

After gastronomic over-indulgence, it was common practice for the Romans to retire to the Vomitorium and stimulate their tympanum with a feather to induce prompt emesis. This procedure stimulates the auricular branch of the vagus nerve, also known as Arnold's nerve or the Alderman's nerve.

Ventricular cardiac afferents may induce nausea and vomiting in man and experimental animals, and their activation probably accounts for these symptoms (particular nausea) before, or in association with, myocardial infarction [1, 92].

Organization of the vomiting reflex

The motor components of the reflex are mediated by both autonomic and somatic nerves. All these motor pathways have non-emetic functions. For example, the vagal non-adrenergic, non-cholinergic innervation of the stomach mediates gastric relaxation for the storage of food and the phrenic nerve contracts the diaphragm for inspiration. In the vomiting reflex, these and many other motor pathways are activated in a unique pattern. Vomiting can be considered to be a stereotyped motor programme involving co-ordination between many physiological systems and between the autonomic and somatic components of the nervous system. An impression of the degree of co-ordination may be gained from the observation that the retrograde giant contraction in the small intestine is not initiated until the proximal stomach has relaxed and retching does not start until the retrograde giant contraction has reached the stomach [61].

The term vomiting centre has been used widely to describe the central emetic co-ordinating mechanism. As in other areas of physiology, such terminology is now only used as a convenient shorthand for the co-ordinating system and as a substitute for an adequate description of the neuroanatomical substrates subserving such a function.

The co-ordination of the motor components of the vomiting reflex occurs in the brain stem. It is here that the vagal motor neurones supplying the gut and heart originate in the dorsal motor vagal nucleus and nucleus ambiguus. In addition, the dorsal and ventral respiratory groups regulating the phrenic nerve output from the cervical spinal cord are located in the brain stem as are the presympathetic neurones which maintain sympathetic tone to the heart and blood vessels. The output of these nuclei must be co-ordinated to produce the characteristic vomiting pattern described above. A promising candidate for this task is the nucleus tractus solitarius. This is probably the major integrative nucleus for visceral afferent information and, in addition, the ventral portion forms the dorsal respiratory neuronal group involved in the regulation of respiration [70]. Another candidate for the co-ordinating area is the parvicellular reticular formation and this has been reported to have many of the neuroanatomical connections consistent with such a role [69].

Motor components of the vomiting reflex

Whilst the often spectacular ejection of upper gastrointestinal contents is the most obvious component of the vomiting reflex, it represents only the culmination of a series of motor events involving both the autonomic and somatic divisions of the nervous system. For convenience we shall divide the reflex into two separate, but usually consecutive phases: pre-ejection and ejection.

Pre-ejection. The pre-ejection or prodromal phase is characterized by the sensation of nausea, the physiological basis of which is poorly understood. There are several visible signs such as cold sweating, cutaneous vasoconstriction and pupil dilatation mediated by sympathetic nerves and salivation mediated by parasympathetic nerves. In addition, changes occur in visceral function such as tachycardia and a reduction in gastric secretion, both mediated probably by sympathetic activation. Immediately before the onset of the ejection phase there is profound relaxation of the proximal stomach mediated by vagal efferent nerves activating postganglionic neurones in the stomach wall [48]. These neurones probably use vasoactive intestinal polypeptide (VIP) or nitric oxide as neurotransmitter. In conjunction with this, a retrograde giant contraction originates in the mid-small intestine and travels towards the stomach. The retrograde giant contraction is under vagal control and the transmitter involved is acetylcholine. These two gut motor events are of particular interest as they can be argued to have a clear function in the reflex—the gastric relaxation serving to confine orally ingested toxin to the stomach and the retrograde giant contraction returning any contaminated gastric contents to the stomach ready for ejection [39, 61]. The pre-ejection phase is usually, but not invariably, followed by the ejection phase.

Ejection phase. This phase comprises retching and vomiting with oral expulsion of gut contents only occurring during vomiting. The function of retching is unclear but it may be involved in overcoming the multicomponent antireflux barrier present in the region of the gastro–oesophageal junction (see [5] for discussion). Both retching and vomiting involve principally contractions of the somatic muscles of the abdomen and diaphragm. During retching the abdominal muscles and the entire diaphragm contract synchronously whereas during vomiting the peri-oesophageal diaphragm relaxes, presumably to facilitate passage of gastric contents into the oesophagus and hence to the outside world [7, 70]. Thus the actual expulsion of gastric contents is caused by compression of the stomach by the descending diaphragm and the contracting abdominal muscles under the influence of somatic motor neurones [7, 70]. During retching and vomiting, all animals adopt a characteristic posture, presumably to optimize

compression of the stomach by the somatic muscles and to minimize strain on muscle groups and structures not involved in vomiting [7].

HOW ARE POSTOPERATIVE NAUSEA AND VOMITING TRIGGERED?

It is most likely that there is not one single feature of the surgical environment that is the single cause of PONV but the cause is probably multifactorial with a differing contribution from each factor depending upon the precise clinical situation. From the studies undertaken it is possible to identify the most likely triggers that induce PONV and to propose how they activate the reflex. For convenience each is reviewed separately. The factors are placed in the approximate temporal sequence in which the patient is exposed.

Preoperative Factors

Food

The induction of anaesthesia shortly after a meal is well known to be associated with emesis during both the induction and the postoperative period [22, 87]. In the case of elective surgery it is possible to be sure of the time the last meal was eaten but in the case of accident victims this may not be possible. In addition, although reasonable time may be allowed by the anaesthetist for gastric emptying to occur (4–6 h), this may still not ensure that the stomach is empty as there is large individual variation in normal gastric emptying rates with the liquid phase of a meal emptying exponentially and the solid phase linearly after a lag phase. Also, emptying rate is dependent upon the volume and chemical composition of the meal, with fatty meals being emptied relatively slowly. In addition, any trauma associated with the accident is likely to induce a slowing of emptying via sympathetic activation.

Although it may seem self-evident that the presence of food promotes retching and vomiting, the mechanism requires some consideration. Food, unless consumed in very large quantities, is not an emetic stimulus so why should it be so under these conditions? As mentioned above, postoperative emesis does not appear to be common in laboratory animals, however, emesis sometimes occurs on induction. In the ferret (a carnivore), urethane (ethyl carbamate) given i.p., produces a reliable, stable and long-lasting anaesthesia particularly suitable for neurophysiological studies. The time to surgical anaesthesia is about 10 min. In the vast majority of animals, when urethane is administered the animal rapidly becomes immobile, although there may be profuse salivation. However, if the animal has not been deprived of food for at least 12 h, retching and vomiting occur in almost all animals within a few minutes of administration [Bingham and Andrews, unpublished observations]. This emesis occurs after the animal has lost postural control but before surgical anaesthesia and hence may be considered to take place in stage II of anaesthesia (the excitement phase). Because of the nature of the anaesthetic and route of administration these observations do not have a direct parallel to the human experience, however they do illustrate an important point: two stimuli, neither of which alone induce emesis, can combine to induce the response. The food induces abdominal vagal afferent activation both by its volume and chemical composition and this in combination with a central effect of the anaesthetic may provide a sufficient emetic drive. In addition, in this phase where postural reflexes are lost, the animal may have nystagmus which provides an additional "pro-emetic" stimulus via a vestibulo–visual mismatch as occurs in motion sickness.

Following a meal, the gut also releases several hormones (e.g. gastrin, motilin, peptide YY), some of which have been shown to activate neurones in the area postrema when applied from micropipettes and to induce emesis when given systemically in high doses or into the cerebral ventricular system [29, 30, 31, 60]. Thus some circulating gut hormones could sensitize the area postrema and hence the emetic reflex to the effects of other stimuli. There is also an increase in hepatic portal vein 5-HT after a meal [86] or administration of the gastrin analog pentagastrin [46] and this may also have a sensitizing effect on the gastrointestinal afferents as has been suggested to occur after cytotoxic drugs and radiation and to contribute to the emetic side effects of these anticancer therapies [8].

In man, the problem of vomiting during the induction phase of anaesthesia can be minimized by using a rapid induction technique combined with cricoid pressure (Sellick's manoeuvre) as consciousness is lost [76].

The above discussion raises an important general issue that will be a recurrent theme in this review, of interactions between stimuli or sensitization to one stimulus by another. It also illustrates the difficulty of elucidating the mechanism of PONV as even the simple problem of the interaction between food and anaesthesia in the induction phase has several possible mechanisms.

The presence of food in the stomach is also reported to increase the incidence of nausea and vomiting in the postoperative period [22]. The mechanisms involved are probably similar to those outlined above but are augmented by the perioperative and postoperative factors outlined below.

Although we have concentrated on the pro-emetic effects of food, the nauseating effects of food deprivation should not be neglected as it is more common for patients to undergo surgery after a period of food deprivation. Palazzo and Strunin [75] reported a small study of healthy volunteers which showed that 56% of females reported nausea after fasting in the waking state for about 7 h whereas for men only 38% experienced nausea, beginning approximately 8.5 h after fasting. Whilst these studies may not be directly applicable to patients who are usually deprived of solids overnight before surgery in the morning, they may be relevant to patients whose surgery is delayed until later in the day.

Psychological stress

Patients are likely to be concerned about the forthcoming surgery and have some degree of stress

response. The precise involvement of stress in the induction of emesis is poorly defined, although both animal and human studies have demonstrated that electrical stimulation of the cerebral cortex can induce emesis [90]. In addition, there are several endocrine responses to stress including the secretion of ACTH, growth hormone and prolactin. The possible involvement of these in PONV is discussed in more detail below as part of a consideration of the endocrine response to surgery.

Some studies have suggested that anxious patients may involuntarily swallow large amounts of air before operation and this may contribute to distension of the upper gastrointestinal tract that is thought to contribute to the genesis of PONV (see below). It has been suggested that aerophagy occurs in about 10% of cases [75].

The reason for surgery

The impact on PONV of the underlying problem requiring surgical intervention is often overlooked but may be a significant factor in some cases. In a patient in which nausea and vomiting are a component of the disorder for which they are requiring surgery (e.g. raised intracranial pressure, upper gastrointestinal tract obstruction) it is likely that the emetic system is already in a sensitized state. This argument may also apply to abortion performed during the early part of the first trimester of pregnancy when pregnancy sickness is present in the vast majority of women: one survey of 1000 women reported an 85% incidence of nausea and a 50% incidence of vomiting [9]. The mechanism responsible for pregnancy sickness is unknown but it is proposed that it represents a state in which the central emetic mechanism is sensitized. The influence of sex hormones on the emetic reflex is illustrated by the greater sensitivity of women to virtually all emetic stimuli (e.g. motion, cytotoxic chemotherapy) and the fourfold increase in risk of PONV after tubal ligation in the first eight menstrual days [16].

Perioperative Factors

Premedication

Differences in patient premedication is considered to be one of the main factors contributing to the large variation in the incidence of PONV between studies. Two major classes of premedicant agents are used: analgesics and antiemetics. The impact of current antiemetics upon the incidence of PONV is discussed elsewhere in this issue but it is worth mentioning that atropine in a commonly used dose of 0.6 mg i.m. can delay gastric emptying. This may contribute to postsurgical gastric stasis and hence PONV.

The main analgesics that have been studied in the context of PONV are morphine and pethidine. In considering the contribution of these and other drugs to PONV their intrinsic emetic and antiemetic effects which may be dose-related need to be considered together with the duration of action. The complexity of the problem can be illustrated by reference to animal studies of the emetic effects of morphine. In the ferret, the threshold dose of morphine-inducing emesis (retching or vomiting) is 0.1 mg kg^{-1} s.c. with all animals in the group responding at 0.2 mg kg^{-1} s.c. As the dose is increased, both the incidence and amount of emesis decrease until at 5 mg kg^{-1} there is no response to morphine, even though the animals do not show marked sedation [97]. Similar observations in the cat lead to the proposal of an opioid-activated antiemetic centre [34]. It is envisaged that the emetic effect of morphine and related opioids (e.g. loperamide) is via an action on opioid receptors (probably μ) known to be present in the area postrema (area postrema ablation abolishes the emetic response). As the dose of morphine is increased, it is envisaged that the antiemetic centre proposed to be located in the reticular formation is accessed and activated leading to a reduction in the emetic drive. This hypothesis is supported not only by the bell shaped dose–response curve seen with morphine, pethidine and loperamide, but also by studies demonstrating an antiemetic effect of high dose morphine and fentanyl against a range of other emetic stimuli including cytotoxic drugs [14]. The type of opioid receptor involved in the antiemetic component of the curve has not been identified with certainty and, although the μ receptor is strongly implicated from animal studies with fentanyl [14] and human studies with alfentanil [83], other studies using loperamide implicate the δ receptor [20]. Identification of the receptor type may lead to the identification of novel broad spectrum antiemetic drugs.

In contrast with the antiemetic effects of 5-HT_3 receptor antagonists against radiation and cytotoxic drug-induced emesis, these agents do not block morphine, morphine-6-glucuronide or loperamide-induced emesis in the ferret [20, 97]. In view of the differences in the metabolism of morphine between the ferret and man, caution should be exerted in extrapolating these results to man, although to date the ferret has been predictive of the clinical efficacy of this class of antagonist. The emetic effects of both morphine and morphine-6-glucuronide were blocked by naloxone.

The question of the relative contributions of morphine itself and its metabolites to the therapeutic and toxic effects has often been discussed. In man the major metabolites of morphine are morphine-3-glucuronide and morphine-6-glucuronide, the latter contributing about 10% of the metabolic product of morphine. Morphine-3-glucuronide does not appear to have any analgesic action or any significant binding to opioid receptors. Clinical trials of morphine-6-glucuronide show that it has potent analgesic activity (0.15–0.6 mg kg^{-1}) but in contrast with morphine does not appear to induce nausea, dysphoria or clinically significant cardiorespiratory effects (see [97]). In general, it appears that the emetic and other side effects in man are caused by the actions of the parent molecule and not by one of the metabolites.

Three other actions of the opioids may contribute to PONV. First, morphine and pethidine in analgesic doses decrease gastric emptying. This leads to accumulation of gastric secretion and swallowed saliva, possibly contributing to distension of the stomach. As the effects of morphine on gastric

emptying may be prolonged, this delay in emptying is likely to extend into the postoperative period when the patient may attempt to take liquids or even food. The decrease in gastric emptying is reported to be associated with an increase in antral and duodenal tone [74]. Thus, when the stomach is distended in this state, the tension in the muscular wall is higher than usual for a similar distension in the absence of morphine, leading to an increased discharge in the mechanoreceptive afferents which are known to be capable of triggering emesis when adequately stimulated.

Second, both morphine and pethidine appear to increase the sensitivity of the emetic reflex to activation by labyrinthine stimulation as indicated by the increase in the incidence of nausea and vomiting in ambulatory, as opposed to recumbent, patients given opioids [89]. The mechanism of this effect is not known but the opioids may have an action in the vestibular nucleus where leu-enkephalin-containing fibres and neurones are found (see [68]). This possibility appears unlikely because if the opioids directly activated the vestibular system, the incidence of emesis might be expected to be higher in recumbent subjects. An alternative possibility is that the activation of the area postrema and hence the vomiting centre by the opioids reduces the threshold for triggering emesis by other stimuli such as motion. This mechanism is supported by studies showing that the emetic threshold for apomorphine (acting on the area postrema) is dependent upon head position, presumably because of differing degress of labyrinthine stimulation [53].

Third, morphine and other opioids enhance the release of 5-HT from the small intestine, probably by disinhibition of tonically inhibitory neural pathways to the enterochromaffin cells [82]. The release of 5-HT has been implicated in the mechanism of emesis induced by anticancer therapies (see above). It appears that this mechanism does not play a major role in PONV, as 5-HT_3 receptor antagonists do not block emesis induced in animals by morphine, morphine-6-glucuronide or loperamide [20, 97].

An additional way in which opioids may influence emesis is via the release of vasopressin (ADH) from the posterior pituitary. Vasopressin is associated not only with nausea and vomiting but animal studies have shown that it may also reduce gut motility.

Intubation

At some point during the insertion of an airway via the mouth it is inevitable that there is stimulation of the pharyngeal mechanoreceptive afferents that project to the brain stem, predominantly in the glossopharyngeal nerve. Stimulation of these afferents can evoke the gagging reflex and, if stimulation continues, retching and even vomiting. The gag reflex may be triggered in anaesthetized animals (e.g. urethane anaesthetized ferret), although when the airway is in place, the gagging subsides. This is likely to be a result of combination of adaptation of the afferents and increasing depth of anaesthesia. The stimulation of irritant receptors in the larynx and upper airway is unlikely to contribute to the nausea and vomiting because, although these afferents can evoke the cough reflex, there is no evidence that they can trigger emesis.

Intraoperative Factors

The two main potential intraoperative contributors to PONV are the anaesthetic and the surgical procedure. The influence of these and their various components on PONV are discussed below.

Anaesthesia

As PONV is reported to occur with a wide variety of structurally diverse anaesthetic agents, we should consider whether the state of anaesthesia itself may contribute to the emesis in addition to any direct pharmacological effects of the anaesthetic agents.

How could the state of anaesthesia contribute to postoperative emesis? Although anaesthesia has been used to block emesis induced by radiation [106], and halothane itself has been reported to have some antiemetic effects at low concentrations [108], the state of anaesthesia may still contribute to PONV. During anaesthesia the patient may be in a recumbent posture and immobile for an extended period, particularly if muscle relaxants are used. In particular the head will be immobile leading to a reduction in the tonic discharge from the vestibular labyrinths for the duration of the surgery. Even during sleep the body never approaches such a state of immobility. When the patient begins to awaken from anaesthesia, the head is often one of the first parts to move, particularly if the patient tries to sit up, leading to a sudden vestibular discharge further enhanced if the patient is being returned to the ward in this drowsy state. In addition, there may be some nystagmus and the pupil diameter may not have returned to normal after anticholinergic premedication leading to vestibulo–visual mismatch or conflict as can be produced by some types of motion (e.g. swings, sea travel) [36].

Anaesthetics

General effects. If the state of anaesthesia itself was the main cause of PONV then the incidence of PONV may not be expected to be so variable and, in particular, there would be little difference between inhalation and i.v. anaesthetics. Therefore, it appears that it is the pharmacological and related properties of the anaesthetics themselves that make the main contribution. Although at first sight this appears self-evident because if anaesthetic agents are emetics then why does emesis occur primarily on induction and recovery and only rarely during anaesthesia when they are at their highest concentration? The answer presumably lies in the multiple effects of anaesthetics: emesis being induced by the anaesthetic agent but being blocked by the state of surgical anaesthesia. Thus, although the anaesthetic (emetic) is activating emetic pathways for the whole time it is present, the effects are only expressed outside the periods of surgical anaesthesia. Whilst this hypothesis provides a conceptual framework, it has not been formally tested and in fact some studies argue against such effects. For example, in man and the ferret, sub-anaesthetic concentrations of halothane

can reduce emesis induced by either vagal afferent stimulation or other anaesthetics (trichloroethylene and nitrous oxide [108]). This antiemetic effect of halothane together with its rapid induction and recovery times may contribute to the low incidence of emesis with this agent. The potential antiemetic properties of other inhalation anaesthetics has not been studied, although such effects appear unlikely as cyclopropane, nitrous oxide and ether are associated with a higher incidence of emesis than halothane [33, 45]. In the urethane anaesthetized ferret, whilst emesis induced by apomorphine and cisplatinum is blocked, animals can still respond to abdominal vagal afferent stimulation, intragastric hypertonic solutions (e.g. NaCl) and occasionally radiation [6, 10, unpublished observations]. The apparent lack of relationship between the anaesthetic potency of the various agents and the emetic potency suggests that the mechanism of emesis resides in the pharmacological properties of the agents themselves.

Very few dose–response studies have been undertaken relating the incidence of vomiting and nausea to the dose of anaesthetic in the absence of surgery. One study [78] showed a general relationship between the percentage of nitrous oxide (20–40 %) and the incidence and intensity of nausea. With 40 % nitrous oxide the nausea persisted for several hours.

Pharmacological effects of the anaesthetics. The pharmacological action of the anaesthetics that has received most attention is their interaction with adrenergic receptors or their adrenomimetic effects. Jenkins and Lehay [54] proposed that agents such as cyclopropane and diethyl ether that are associated with a high incidence of PONV increase circulating concentrations of catecholamines whereas halothane and methoxyflurane that induce a lesser degree of PONV do not increase catecholamine concentrations and in fact have adrenergic receptor blocking properties. This hypothesis is supported by studies showing that emesis can be induced in the cat by intracerebroventricular injection of adrenergic receptor antagonists acting on the alpha-adrenergic receptor. Emesis was not induced by beta-adrenoreceptor activation. More recent studies have implicated both the alpha-1 and alpha-2 receptors in the area postrema in emesis [17]. As it is the circulating concentrations of catecholamines that are increased, the most likely source is the adrenal medulla reflecting an increase in sympathetic drive [91]. Emesis would then result from the effect of the catecholamines on the area postrema and neuronal recording studies in the dog have shown that both adrenaline and noradrenaline cause firing [29]. If this hypothesis is correct then alpha-adrenergic antagonists should block PONV but curiously this possibility appears never to have been tested directly, although the beta-adrenergic receptor antagonist propranolol has been of some benefit in cyclic vomiting in children [105]. The release of adrenaline by intense sympathetic activation of the adrenal medulla has also been implicated in the mechanism of emesis induced by hypotension and pain [75, 85].

The involvement of the area postrema in PONV has been tested in only one experimental study as far as the author is aware. Vomiting is seen in dogs and monkeys after cyclopropane [12]. In the dog, the incidence of emesis during recovery from cyclopropane anaesthesia (33.3 % in oxygen), administered 10–30 min after feeding, was related to the duration of anaesthesia: 5 min—35 %; 10 min—66.6 %; 15 min—80 %; 20 min—100 %. Ablation of the area postrema rendered the dogs refractory to the emetic effects of cyclopropane even when given at 3–6 times the emetic threshold. This study certainly implicates the area postrema in emesis induced by cyclopropane but does not allow a distinction to be made between a primary effect of the anaesthetic on the area postrema and a secondary effect via the release of an endogenous emetic such as adrenaline which then acts on the area postrema.

As noted above, recordings have been made from the area postrema and of necessity these studies have been performed on anaesthetized animals [2, 26, 29, 31] or isolated tissue [28]. In dogs anaesthetized with thiamyl sodium 25 mg kg^{-1} i.v. and pentobarbitone 25 mg kg^{-1} i.v., spontaneous neuronal activity was never recorded from the area postrema [29, 31]. In contrast, in rats anaesthetized with urethane and chloralose and cats anaesthetized with pentobarbitone, the area postrema was spontaneously active [2]. Area postrema neurones were also spontaneously active in explants maintained *in vitro* with a frequency range of 0.4–22 Hz [28]. From these limited studies it is not possible to draw any useful conclusions about the effects of anaesthetics on the area postrema, particularly as recordings have not been made in animals anaesthetized with the more emetic inhalation anaesthetics.

Although attention has focused on the effect of anaesthetics on the area postrema as the cause of emesis, an additional possibility could involve the antiemetic centre [34]. It is envisaged that this area of the brain stem when active inhibits the vomiting centre and thus prevents emesis. Anaesthetics have differential effects on neurones in different parts of the brain [11] and hence it is possible that PONV occurs because this centre is very sensitive to the depressant effect of the anaesthetic and is slow to recover its tonic activity in the postanaesthetic period. Thus PONV may result from both direct emetic effects of the anaesthetic and surgery and be facilitated by the indirect effect of prolonged inhibition of the antiemetic centre.

Recording studies of abdominal vagal afferents that are known to be capable of triggering emesis do not suggest that they are activated by anaesthetics such as urethane or barbiturates. If these afferents are involved in PONV, it is most likely by signalling the abnormal patterns of gastrointestinal motility associated with surgery and anaesthesia.

The above section has focused on the specific pharmacological effects of anaesthetics on the main inputs of the brain stem emetic co-ordinating mechanisms. However, anaesthetics have much more general pharmacological effects on the brain and PONV may be an expression of such effects rather than an indication of specific effects on the emetic reflex pathways. For example, there is considerable evidence from studies in rats that many anaesthetics

(e.g. pentobarbitone, diethyl ether, halothane and nitrous oxide) influence 5-HT metabolism in the brain [3, 27, 41]. After halothane and nitrous oxide anaesthesia, there was a reduction in 5-HT synthesis and utilization, the former probably caused by reduction in tryptophan hydroxylase. These effects were apparent in both brain stem and forebrain tissue within 15 min of anaesthesia. Studies with diethyl ether in mice showed that it increased the synthesis of 5-HT whereas pentobarbitone reduced 5-HT turnover [3]. These studies illustrate that anaesthetics could trigger emesis by modulation of neurotransmitter release at forebrain sites known to be capable of activating emesis or at brain stem sites such as the nucleus tractus solitarius which receives inputs from the area postrema and the vagal afferents.

Physical effects of volatile anaesthetics. The incidence of PONV is greater with volatile than with i.v. anaesthetics and hence PONV could be contributed to by the physical effects of the anaesthetics. Although an increase in middle ear pressure has been implicated [39], the main effects are suggested to be on the gut [75, 76]. First, during manual ventilation with a mask (particularly by less experienced anaesthetists [51]) gas may pass into the stomach and upper intestines leading to distension and activation of abdominal, vagal and splanchnic afferents which in turn may trigger emesis. Palazzo and Strunin [76] considered that distension was a major factor and commented that emesis was less frequent if such ventilation was avoided by a period of preoxygenation [57]. Second, the gut may be distended by gas, particularly nitrous oxide. In the presence of an alveolar nitrous oxide concentration of 75% it has been estimated that the gut volume would increase by 500 ml h^{-1} of anaesthesia [see 56, 57]. In the stomach, such distending volumes are not likely to be of significance as the stomach has a considerable storage capacity but in the small intestine the impact is greater. It is worth bearing in mind that the belching reflex is likely to be suppressed under anaesthesia and in the postoperative period and hence this may lead to the prolonged accumulation of gas in the stomach that would normally be voided. In addition, as small and large intestinal motility are reduced the elimination of gastrointestinal gas as flatus is also reduced, leading to accumulation that may become painful.

Endocrine effects of anaesthetics. The endocrine effects of anaesthesia and surgery are extremely complex and their relative contributions to the observed changes have not been identified. A discussion of this extensive literature is beyond the scope of this review; however, a large number of peptide hormones (angiotensin II, AVP, bombesin, gastrin, insulin, neuropeptide Y, neurotensin, somatostatin, TRH and VIP) [29, 30] have been shown to induce emesis when given either i.v. or into the cerebral ventricles of animals, or both, usually at doses in excess of those required for the usual physiological actions. The mechanism for the induction of emesis is proposed to be via the area postrema and many (but not all) of these peptides can activate area postrema neurones when applied by pressure microinjection or iontophoresis.

Cardiovascular effects of anaesthetics. Arterial pressure frequently decreases during anaesthesia and this may be compounded further by haemorrhage and surgical manipulation. Hypotension may induce nausea and possibly vomiting, although the mechanism is unclear. One possibility is that hypotension may induce a large sympathetic discharge resulting in the release of adrenaline from the adrenal medulla which may then trigger emesis by an action on the area postrema. Another possible mechanism involves activation of vagal afferent mechanoreceptors with unmyelinated axons located in the ventricles of the heart. The precise physiological function of these afferents is unclear, but they can trigger emesis and may be responsible for the nausea and vomiting associated with vaso–vagal fainting, and infero–posterior myocardial infarct [92]. These receptors can be activated under several conditions, including myocardial ischaemia and tachycardia with hypovolaemia [92]. The latter could occur both during anaesthesia or in the postoperative period as the patient attempts to sit upright when there may be venous pooling in the lower body. These cardiac afferents also evoke reflex gastric relaxation predominantly via activation of vagal efferent non-adrenergic, non-cholinergic inhibitory neurones and this may contribute to the delay in gastric emptying associated with anaesthesia and surgery [1, 55].

Hypotension is generally considered to be more likely to be involved in the nausea and vomiting occurring during spinal anaesthesia. In a study of patients with spinal anaesthesia undergoing gynaecological surgery, the incidence of emesis was greater when systolic blood pressure was < 80 mm Hg. Maintenance of blood pressure using ephedrine reduced the incidence of emesis from 66% to 10% [85].

Gastrointestinal effects of anaesthetics. Anaesthetics may induce nausea and vomiting by causing disruption of gastrointestinal motility which may be compounded by the effects of surgery itself on gut function. Although anaesthetics modify motility throughout the gut, of particular relevance to emesis are the effects of anaesthetics on the lower oesophageal sphincter and gastric motility.

The effects of anaesthetics on the lower oesophageal sphincter (LOS) are important not because such effects may induce emesis but primarily because of the contribution that the LOS makes to preventing reflux of gastric contents into the oesophagus and hence regurgitation into the mouth with the associated risk of aspiration, particularly in recumbent subjects. In general, inhalation anaesthetics produce reduction in lower oesophageal sphincter pressure. This is seen with nitrous oxide in oxygen and is enhanced by the presence of halothane and enflurane [35]. A recent study showed a reduction in the number of spontaneous LOS contractions and the amplitude of provoked (balloon distension) LOS contractions with increasing concentrations of halothane (0.5–2.0 MAC). The authors argued that

the mechanism of the reduction was not due to a peripheral effect of the anaesthetic but reflected a central action on the brain stem pathways regulating the vagal outflow to the LOS [42].

The general pattern of gastric motility that emerges from animal studies is one of a suppression of gastric and upper small intestinal motility by anaesthetic agents such as pentobarbitone, urethane, cyclopropane and halothane, although stimulation has been reported with ether that persisted beyond the period of anaesthesia [74] and a recent study of enflurane anaesthesia in the rat failed to demonstrate an effect on gastric emptying [15].

The mechanism of this suppression has been ascribed usually to a peripheral effect, for example, on the release of acetylcholine from the myenteric plexus or an increase in sympathetic discharge having either a direct effect or via the release of adrenaline. However, a recent study in the ferret suggests that a vagal mechanism may be involved. Gastric antral motility was monitored using implanted miniature strain gauges and the influence of pentobarbitone anaesthesia on the migrating motor complex (MMC) monitored [47]. The MMC occurs in the interdigestive phase (i.e. MMC activity is present in patients deprived of food before surgery) and is a periodic burst of motor activity that originates in the stomach and migrates along the small intestine to the terminal ileum. In man the periodicity of the MMC is about 90 min. In the ferret study, pentobarbitone abolished MMC cycling but activity began to return at the stage when the limb withdrawal reflex returned, although the animals were not capable of spontaneous movement. The effect of pentobarbitone on the MMC was not affected by naloxone or guanethidine but was modified by chronic abdominal vagotomy. This procedure prevented the abolition of the MMC by pentobarbitone but there was a reduction in amplitude. These studies indicate that the reduction in gastric motility under anaesthesia may be contributed to by vagal mechanisms, either a reduction in vagal cholinergic drive or an increase in the vagal non-adrenergic, non-cholinergic inhibitory pathways or a combination of both.

How can anaesthetics modify these vagal drives? One possible mechanism may be via the area postrema. Vagally mediated gastric relaxation may be induced by the action of emetic agents such as morphine and apomorphine on the area postrema [65] and a similar effect could account for both the emetic and motility suppressing effects of anaesthetics. It should be borne in mind that reduction in gastric motility almost invariably accompanies nausea and vomiting and thus the motility effects seen with anaesthetics may be a more general reflection of activation of emetic mechanisms rather than a specific effect of the anaesthetic on the autonomic nervous system. The same argument may apply to the sympathetic activation that accompanies anaesthesia as this occurs also in association with nausea and vomiting. The second possibility is a more selective effect of the anaesthetics on the vagal outflow from the brain stem by modulation of neurotransmission in the brain stem reflex pathways.

Although animal studies indicate that anaesthetics and anaesthesia alone can reduce gastric motility, for obvious reasons comparable information is not available for man, although it is likely that similar effects occur, particularly when combined with the effects of surgery (see below).

During anaesthesia and surgery, the reduction in gastric antral motility associated with relaxation of the pyloric sphincter may promote the reflux of bile into the stomach. Bile is known to be an irritant to the gastric mucosa and this may provide an additional stimulus to emesis by stimulation of gastric mucosal vagal afferents.

The general cardiovascular effects of anaesthesia were discussed briefly above but some anaesthetics may have more profound effects on the mesenteric circulation and reduce perfusion. The significance of this lies in the observation that relatively brief periods of ischaemia may sensitize the gut afferents to their natural stimuli. The mechanism probably involves the local release of agents such as 5-HT, substance P, bradykinin and prostaglandins. This means that in the postoperative period, as normal gut function returns, the central nervous system may be bombarded by an abnormal level of afferent activity from the gut adding further to the emetic drive from other factors.

An additional factor that should be considered is the effect of the anaesthetics on the release of 5-HT from the enterochromaffin cells in the mucosa of the upper intestine. The release of 5-HT from these cells has been implicated in the mechanism by which radiation and cytotoxic anticancer drugs induce emesis. The possible involvement of 5-HT is discussed elsewhere in this issue but 5-HT release can be induced by opioids, adrenaline, ischaemia and mechanical stimulation of the gut, factors that may be present during anaesthesia and surgery [82].

Effect of anaesthetics on intracranial pressure. Raised intracranial pressure may cause headache, nausea, vomiting and inhibition of gastric motility [44, 52]. Because of vasodilatory effects on cerebral blood vessels, halothane, enflurane, isoflurane and ketamine cause an increase in intracranial pressure that could contribute an additional trigger to emesis. Barbiturates (thiopentone, pentobarbitone) lower intracranial pressure and when used in combination with the above anaesthetics offset any tendency to increase in pressure [40].

General effects of the surgical procedure

The contribution of surgery itself to PONV can be resolved into two components; the general effects of virtually any type of surgical procedure and the effects of specific types of surgical procedures that are reported to be associated with a high incidence of PONV. The general systemic, endocrine and metabolic effects of surgery are familiar to anaesthetists and surgeons but which of the multitude of factors are most likely to be involved in PONV? These factors are examined briefly to illustrate this aspect.

Gastrointestinal motility. Although anaesthetics reduce motility, the effect of surgery is more

profound and outlasts the duration of surgery. For abdominal surgery, the rank order of influence on motility appears to be skin incision < muscle division < laparotomy < gut manipulation [67]. Even in animals under full surgical anaesthesia, noxious levels of distension of the intestine sufficient to evoke reflex cardiovascular changes also produce a reflex, sympathetically mediated inhibition of gastric motility [73]. The inhibition of motility has non-sympathetic (vagal inhibitory or endocrine) components, as in experimental animals sympathectomy only reduces the duration of postoperative ileus but does not prevent it [67].

The significance of delayed gastric emptying and reduced intestinal motility induced by the anaesthetic and surgery is twofold. First, during surgery the delay or stasis leads to accumulation of fluid secretions, it may facilitate the reflux of bile into the stomach and may lead to the accumulation of gas (anaesthetic, air swallowed before surgery or endogenously produced). All of these could induce activation of gastrointestinal visceral afferents including nociceptors if the stimulus is intense. Because the patient is anaesthetized and possibly paralysed, activation of these afferents does not induce emesis, but they induce several reflex endocrine changes, the effects of which may outlast the duration of surgery. As the patient gradually regains consciousness with these distensive stimuli still present, this afferent barrage may give rise to sensations of upper abdominal discomfort and nausea and even trigger vomiting. In addition, the prolonged stimulation of the afferents that occurs during surgery may serve to induce a long-lasting sensitization of the central nervous pathways involved in nociception and emesis. Second, the effects of the surgical trauma may persist long beyond the surgical period so that when the patient is conscious and apparently recovered from anaesthesia, gastric emptying and intestinal motility may still be reduced and hence the gut may be unable to cope with a normal meal even if the patient wishes to eat. This situation is analogous to patients with severely delayed gastric emptying who become nauseated or even vomit after a normal sized meal as occurs with non-ulcer dyspepsia.

Endocrine effects. The endocrine effects of anaesthesia and surgery are complex and the way in which they may relate to PONV have only recently begun to be investigated. Apart from adrenaline, one of the hormones with a relatively well described involvement in the response to surgery and emesis is vasopressin (AVP, ADH). This increases during surgery partly because of the effect of analgesia, but mainly because of the effects of surgery itself. Anaesthesia (halothane, isoflurane) appears to reduce the basal plasma concentration of vasopressin but it is increased markedly by the surgical procedure itself [57]. One study considered gastric manipulation to be the most potent procedure for the release of vasopressin and undertook an experimental study in the dog to identify the pathway [99]. They concluded that the main pathway was splanchnic nociceptive afferents with the vagal afferents not having any role. This contrasts with a study in the anaesthetized ferret in which electrical stimulation of the central end of the abdominal vagus was shown to be a potent stimulus for vasopressin release [50]. Whatever the pathway, there is no doubt that vasopressin is released during surgery in quantities that are many times those required for maximal antidiuretic activity. The reason why vasopressin is of such interest is that similar increases in plasma concentrations have been seen in man with other emetic stimuli such as motion, apomorphine and cytotoxic chemotherapy (see [7]). The increase in vasopressin bears a closer relationship with nausea than vomiting but it is as yet unclear if it is a cause or a consequence of the nausea, although some studies suggest that it increases before the onset of the reporting of nausea.

Specific effects of surgery

Certain types of surgical procedures are reported to be associated with a relatively high incidence of PONV and this section reviews the mechanisms that may be involved.

Ophthalmic surgery. Ocular surgery is associated particualrly with a high incidence of PONV in adults and children. A large study (607 patients) of patients aged 1 to > 60 yr provided a detailed characterization of the phenomenon [18]. Two types of emesis were identified: early, that occurring on the operating table at the end of surgery or soon after in the recovery ward and delayed emesis, occurring outside this immediate recovery period. The incidence of early emesis was higher with squint surgery (10%) than with non-squint ocular (1.8%) and orbital (2.7%) surgery. For delayed emesis the incidences were 57% for squint surgery, 18% for non-squint ocular surgery and 23% for orbital surgery. In contrast with a common perception that children are more sensitive to the emetic effects of ocular surgery, this study failed to identify an effect of age, although female gender was a predisposing factor for both squint and non-squint procedures. The time course of PONV was studied in children (mean age 7.2 yr) after strabismus surgery without any antiemetic administration [63]. Within 2 h of surgery 25% were vomiting, by 4–6 h this had increased to 60% and by 24 h had only increased slightly to 65%. This pattern supports the conclusions from the above study that there are two components to the emetic response after this type of surgery.

It has been proposed that at least part of the PONV is caused by an oculo–emetic reflex triggered by manipulation of, and trauma to, the squint corrected eye [18]. The authors support this suggestion by pointing out that surgical procedures involving considerable intraoperative manipulation of the eye (retinal detachment surgery) and giving rise to residual eye discomfort are associated with increased incidence of early and delayed emesis whereas when there is little manipulation or residual discomfort low incidences of emesis occur. The afferent pathway of the reflex has not been investigated, however, the better known oculo–cardiac reflex provides some insight [43].

Pressure on the eyeball or traction of the extrinsic muscles of the eye evokes reflex bradycardia because of activation of vagal efferents and suppression of sympathetic efferents. The afferent pathway is in the trigeminal nerve that projects to the brain stem where the autonomic outflow to the heart can be influenced. It is likely that it is activation of these trigeminal afferents that triggers emesis, although this has not been demonstrated directly. Other mechanisms may be involved as emesis is uncommon in patients with trigeminal neuralgia when presumably there is intense activation of this pathway [52]. An additional mechanism that probably contributes to emesis when the operated eye is unbandaged, is the temporary interocular mismatch between the normal and corrected eye and the vestibulo–visual mismatch that this engenders. Both of these inputs may induce a motion-sickness-like state (see [36] for a review of the neurophysiology of motion sickness).

Ear, nose and throat surgery. The high incidence of emesis associated with surgery of the middle ear is perhaps not surprising and is likely to be caused by activation of the vestibular afferent pathways involved in motion sickness, particularly if the system has been sensitized by opioid premedication (see p. 9S). In addition to vestibular afferents, the auricular branch of the vagus (Arnold's nerve) supplying the tympanum may also be involved as stimulation readily induces emesis.

Nausea, gagging and emesis may be induced readily by mechanical stimulation of the pharynx resulting in activation of glossopharyngeal afferents projecting to the brain stem. The incidence of vomiting after paediatric tonsillectomy may approach 81% [101]. Surgical trauma may lead to some inflammation and sensitization of these afferents as occurs in patients with a "sore throat". Similar processes may be induced by the presence of an orotracheal tube and contribute to the emesis in the postoperative period even though the tube is removed. It has been reported that the incidence of PONV is greater in patients maintained with an orotracheal tube than with a nasotracheal tube [100]. This difference was ascribed to the angle at which the tubes impact the pharynx and presumably relates to different regional sensitivities for evoking the gag reflex from the pharynx.

The reason why nasal surgery should induce emesis is unclear as although stimulation of nasal afferents can evoke sneezing (involving some of the same somatic motor pathways as vomiting) and painful sensations, there are no reports of the direct induction of emesis. The emesis may be secondary to the pain but may also be caused by stimulation of pharyngeal and gastric afferents by swallowed blood and this may also be involved in ear and throat surgery.

Abdominal surgery. Intra-abdominal operations are more emetic than extra-abdominal operations irrespective of patient gender [75, 76]. During abdominal surgery it is inevitable that there is some displacement, manipulation and traction placed upon the gut and associated mesentery even if the gut itself is not the subject of the surgical procedure. The gut is invested with both vagal and splanchnic afferents that discharge in response to these types of mechanical stimuli [4, 49]: thus each surgical manoeuvre is signalled to the central nervous system. In addition to the gastrointestinal tract, other intra-abdominal and pelvic structures such as the kidney, bladder and uterus are invested with afferents that are activated by mechanical stimulation. It is the vagal afferents supplying the upper gut that have the main role in triggering emesis and, although a direct role for splanchnic afferents in activating emesis has not been possible to demonstrate, they clearly have a permissive role, which is discussed in more detail below [6].

In addition to direct activation of afferents, surgical manipulation of the intestine also induces release of 5-HT from the enterochromaffin cells. This 5-HT can cause both direct activation of the afferents and also produce long-lasting sensitization to other stimuli (see [7, 8]). Handling may also induce synthesis and release of a wide range of substances from the gut wall that may modulate visceral afferent activity (e.g. CCK, prostaglandin, interleukin) or enter the circulation to act on the area postrema (e.g. neuropeptide Y).

Gynaecological surgery. In response to virtually all emetic stimuli, women are more sensitive than men so it is perhaps not surprising that gynaecological surgery should be associated with a high incidence of PONV. Understanding the mechanism of PONV after gynaecological surgery is complicated by the prevailing hormonal status of the woman (e.g. four times higher incidence during menses and lower postmenopausally [16]). These observations are consistent with the view that the changing endocrine environment sensitizes the brain stem emetic mechanisms to the action of other emetic stimuli as has been proposed for pregnancy sickness [9]. One interesting observation is that the incidence of PONV was higher when dilatation was accompanied by curettage than with curettage alone [72]. This observation is also consistent with reports that vomiting is more common in gynaecological operations when the vagina is packed [77]. Studies in the rat have shown afferents supplying the uterus, the broad ligament and vaginal cervix that project to the spinal cord predominantly in the hypogastric nerve with a minor contribution from the pelvic nerve. These afferents are sensitive to gentle probing and rubbing in the region of the receptive field, ischaemic stimuli, bradykinin and 5-HT [19]. Limited evidence was presented that the afferents are more sensitive in oestrous and when the tissue was subjected to surgical manipulation. From these observations it is clear that the types of surgical procedures occurring during gynaecological surgery stimulate these afferents and, although there is no evidence that such afferents can directly induce emesis, they are likely to contribute to the general afferent load on the central nervous system which sensitizes the emetic pathways (see below).

In laparoscopic procedures, the insufflation of the

abdominal cavity leads to abdominal discomfort if the abdomen is not adequately decompressed after the procedure, further adding to the general level of unpleasant sensations arising from the abdomen.

Time Course of PONV and the Role of Postoperative Factors

The factors described above may be involved in the postoperative period provided they have a sufficiently long time course or they have initiated secondary processes (e.g. sensitization of afferents) with prolonged effects. It is probable that both mechanisms are involved.

Typically, PONV lasts < 24 h with nausea and vomiting being most intense during the first 2 h, although the precise pattern depends upon many factors. In general retching and vomiting subside before the sensation of nausea.

Drugs and anaesthetics

Of the drugs given before operation, morphine and related opioids are the ones that are most likely to contribute to PONV by still being present in the postoperative period, having a direct emetic effect, sensitizing the vestibular system and by inhibiting gastric motility.

If anaesthetics have a direct pharmacological effect on the vomiting mechanism it might be expected that the agents most associated with PONV are eliminated more slowly, but the rate of elimination expressed as a percentage of initial alveolar concentration does not support this: nitrous oxide > cyclopropane > halothane > ether [84]. The lower incidence of emesis with halothane may be because it is present for several hours at sub-anaesthetic concentrations which are probably antiemetic [108].

The rate of recovery from anaesthesia also affects the incidence of PONV as sedation itself supresses the emetic reflex. Hence, if recovery is rapid, the patient may reach a state of arousal where emesis can be triggered before the emetic stimuli have subsided. In addition, when the patient becomes conscious he will be aware of his condition and able to perceive (and report!) nausea and pain. There may also be mismatched visual and vestibular inputs. In addition, the feeling of being "out of control" of the body, lightheaded and dizzy may make some patients anxious. The importance of giving reassurance to the patient in this period should not be underestimated. Removal of such inputs may go some way to explaining why long periods of postoperative sleep may reduce the incidence of PONV.

The use of neostigmine to facilitate the reversal of neuromuscular block has been associated with an increased incidence of PONV [59]. This could be a result of marked stimulation of gastric motility which would activate vagal afferents and trigger central emetic mechanisms sensitized by other factors. Direct activation of central cholinergic pathways may also be involved as pilocarpine and nicotine can induce emesis via the area postrema [24].

Prolonged disruption of gut function

After surgery, and especially general and abdominal surgery, there is a reduction in gut motility. Although gastric motor function usually returns before intestinal and colonic function, it is the disruption of gastric motility that leads usually to postoperative symptoms such as nausea and vomiting, particularly when the patient begins to eat. The delay in gastric emptying is caused by activation of inhibitory reflexes during surgery and their continued activation, probably as a result of activation of nociceptors resulting from tissue damage and trauma. The manipulation of the gut during surgery may have induced the release of local mediators (e.g. 5-HT) that induce sensitization of the gastrointestinal afferents. Under these conditions when the patient attempts to eat, food remains in the stomach adding its distensive effect to any fluid (saliva, gastric secretion, bile) that may have accumulated. One study in patients with severe PONV aspirated a volume of 698 ± 141 ml/24 h from the stomach [32]. In this sensitized state the afferent discharge induced may be capable of inducing emesis.

Although the activation of upper gastrointestinal tract afferents initially appears the most likely pathway for the induction of emesis in the immediate postoperative period, their significance is questionable. For the afferents to trigger emesis they must be active at least in the first postoperative hours when emesis is most frequent. As most patients do not attempt to take food or even appreciable volumes of fluid in this period, this cannot be the stimulus, nor can excessive motility, as motility is reported to be suppressed. If the visceral afferents are active then the most likely drive is from local mediators released by surgical manipulation but this occurs only during abdominal and pelvic surgery. Therefore, in non-abdominal surgery the role of the abdominal afferents in early PONV is probably minimal but may make a greater contribution when the patient begins to eat and drink before normal gastric function has returned.

Pain

The role of pain in the genesis of PONV is difficult to assess from a mechanistic viewpoint, although studies in man have claimed an association between the two. The problem with pain is that in animal studies the evidence for an involvement of splanchnic nociceptive afferents in emesis is limited. The major pathway for emesis is via vagal afferents with the splanchnic afferents having a permissive but not critical role. In addition, PONV is associated with surgical procedures in many areas that have never been implicated in direct activation of the emetic mechanism (e.g. uterus). How can these apparently discordant observations be reconciled?

In man there is evidence that pain is often associated with the sensation of nausea rather than with frank vomiting, with one study reporting that in the postoperative period only 10% of patients had pain without associated episodes of nausea in contrast to 58% in which the two were associated [75, 76]. It is well known that when subjects are nauseated they will be more likely to vomit, thus pain and vomiting may be linked via nausea. The pathway involved in nociceptor-induced nausea is

not known, but activation of visceral nociceptors influences activity in the brain stem both in the nucleus tractus solitarius [13] and reticular formation [21, 79, 88]. From these areas the information may readily access regions of the cerebral cortex involved in conscious perception.

Pain itself induces general arousal or alerting of the central nervous system. It may be that by increasing the level of consciousness the patient is alert enough to experience the nausea generated by other inputs. Thus pain need not cause nausea but merely facilitate its expression.

Activation of nociceptors may also produce longer-lasting changes in the central nervous system that alter the threshold for emesis. In pathological pain (i.e. that following tissue damage) there is sensitization of the afferents at both peripheral and central sites [107]. The peripheral sensitization is caused by the release of a variety of agents (e.g. 5-HT, histamine, cytokines) from damaged and inflamed tissue. Central sensitization is caused by release of afferent neurotransmitters with a long duration of action and the release of excitatory amino acids that prolong synaptic potentials. More intriguingly, even brief periods of afferent activation may alter gene expression in central nervous system neurones resulting possibly in modification of many aspects of neuronal function [107]. If nociceptor activation produces similar changes in, for example, the nucleus tractus solitarius, this could provide a mechanism for pain reducing the threshold for induction of emesis from the conventional inputs (e.g. area postrema, gut afferents).

Activation of visceral nociceptor pathways inducing nausea appears to be an attractive mechanism to account for postoperative nausea associated with a variety of types of surgery. In addition, animal studies have demonstrated that visceral pain reflexes may be reduced by antagonism of 5-HT_3 receptors with some but not all antagonists [73]. Could such an effect be involved in the antiemetic effect of ondansetron in PONV? Unfortunately, this appears unlikely as when postoperative pain and anxiety were measured as part of a study of the effects of ondansetron in PONV after laparoscopic procedures, there was no effect on these variables even though PONV was reduced [23].

CONCLUSION

It is apparent from the above discussion that many factors associated with anaesthesia and surgery may contribute to induction of PONV. Although for almost all of these factors it is possible to provide a plausible, if not experimentally proven, mechanism by which they could influence the emetic reflex, for several our level of understanding is inadequate. In particular, little is known about the mechanism underlying the genesis of the sensation of nausea and the ways in which pain and nausea are linked. Another area of particular ignorance in understanding the overall mechanism of PONV is identification of the role of the anaesthetic. We have seen how some drugs such as alfentanil appear to have antiemetic properties ascribed to an agonist action at μ opioid receptors [83] depressing activation of the central emetic pathways but does a similar mechanism account for the effects of low concentrations of halothane or is it caused by an adrenergic receptor antagonist action as has been suggested? [108]. It has been proposed that the emetic potential of the anaesthetics relates to their ability to release catecholamines [54] but this has not been actively studied in recent times. Whilst considerable progress has been made in understanding the effects of anaesthetics on somatosensory systems [11], a comparable degree of knowledge is lacking for the brain stem regions involved in emesis such as the nucleus tractus solitarius and the area postrema. It is unclear if the emetic effects of various anaesthetics relate to anaesthetic action or to a side effect (e.g. opioid receptor activation), although a superficial comparison of the relative hydrophobicity—anaesthetic potency ranking and the emetic potency ranking—reveals little similarity indicating that the emesis is most likely a side effect or indirect effect of these agents and does not relate to their anaesthetic action.

The problem of PONV has some parallels in emesis induced by cytotoxic chemotherapeutic agents where drug structure, cytotoxic action and emetic effect are poorly related. However, as 5-HT_3 receptor antagonists are effective against emesis induced by a wide variety of cytotoxic drugs, but not other stimuli [6], it is argued that the emetic potential may be an index of their ability to release 5-HT from the gut mucosa [8]. Preliminary clinical data indicate that ondansetron, at doses comparable to those effective against radiation and cytotoxic drug-induced emesis, has some effect in PONV [58, 62, 64]. The vast majority of data has been gathered from female patients undergoing gynaecological procedures and, although the results are encouraging, they cannot be generalized to all forms of PONV. The main reason for this is that 5-HT_3 receptor antagonists are not general antiemetics: ondansetron does not affect motion-induced emesis in man [95] or emesis induced by intragastric irritants or morphine in animals [6, 20, 97]. Thus it is conceivable that, although 5-HT_3 receptor antagonists may be of benefit in abdominal procedures because they may release 5-HT and activate visceral afferent pathways or the area postrema in a similar way to that proposed for anticancer therapies, they may be ineffective in ENT or ocular surgery. However, if 5-HT_3 receptor antagonists are effective against nausea and vomiting after a variety of anaesthetic and surgical procedures then at last we may have the key to the mechanism of PONV.

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