Anorexia, nausea and vomiting constitute a spectrum of symptoms and signs whose net result is a reduction of food intake. This is an undesirable state of affairs, particularly in cancer patients who suffer both a decreased ability to withstand treatment and an impaired quality of life.

The nature of the largely subjective phenomena of anorexia and nausea is obscure; in cancer patients they usually reflect complications of the disease or of its treatment, but may well be a feature of advanced cancer per se. With advanced cancer, anorexia is probably multifactorial, with contributions from abnormalities of taste and smell, disorders of the central hunger-satiety mechanisms and, possibly, production by the tumor of intermediate metabolites that affect central and peripheral mediators of hunger and satiety (the so-called "anorexigenic metabolite hypothesis").

Nausea and vomiting, frequent and distressing side effects of cancer treatment, are an increasing problem as a result of more aggressive therapeutic modalities.

Recently, there was a plea for more effective antiemetics in this situation, although it is possible that present inadequacies of antiemetic treatment reflect less than optimal use of the agents available.

It is known from animal studies that there is considerable variation in pharmacokinetics among the antiemetic drugs and this has not been sufficiently studied in humans. Effective use of these drugs clearly depends on greater understanding of their dose response characteristics and pharmacokinetics.

This review covers current concepts of the mechanisms of nausea and vomiting as a result of cancer treatment and their management.

The Physiology of Vomiting

The mechanics of the act of vomiting have been well reviewed and will not be discussed further here. Vomiting is controlled by the vomiting center in the medullary reticular formation. It lies close to loci associated with vomiting-related afferents. Vomiting may result when input from three major sites reaches the vomiting center. These are the chemoreceptor trigger zone (CTZ), the loosely labelled "periphery" and higher central nervous system structures. There is a presumed threshold for each individual and, when the intensity of stimulation from these sites reaches a certain level, vomiting follows upon nausea.

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The CTZ has been localized to the floor of the fourth ventricle in the region of the area postrema. It was originally defined during studies of apomorphine induced emesis, and has subsequently been shown to be associated with vomiting due to a wide variety of substances including cytotoxic drugs and radiation. It is not clear how toxic substances interact with the CTZ to produce vomiting. The first requirement of such an interaction is that the agent or its metabolites should be capable of crossing the blood-brain-barrier (B-B-B). Such a property requires lipid solubility, which is found in a number of cytotoxic drugs, particularly the nitrosoureas. For other drugs (and metabolites) that do not cross the B-B-B, a peripheral emetic action is possible. An alternative is that they could result in the release or production in the periphery of substances that can cross the B-B-B to the CTZ. Such a possibility has not been investigated, but would be a plausible corollary of the “anorexigenic metabolite hypothesis.”

The second requirement for CTZ induced emesis is interaction of the drug (or its metabolite) with brain cells. This action could be direct, by analogy to the opiates, which are probably analogues of endogenous brain peptides and bind to specific common receptors. Similarly, it could simulate the action of various neurotransmitters, such as acetylcholine and dopamine. The relevance of observations such as apomorphine's action as both a dopamine agonist and a choline esterase inhibitor, and nitrogen mustard's cholinergic activity, to their emetic activity, is not known. Many antiemetic drugs have anticholinergic activity or interfere with dopaminergic transmission.

There appear to be both $H_1$ and $H_2$ histamine receptors in the CTZ and, while the area postrema is rich in histamine, the role of this substance in vomiting is not clear. The classical $H_1$ antagonists have a narrow clinical range of antiemetic activity largely limited to motion sickness and vestibular disorders. Neither $H_1$ nor $H_2$ antagonists protect against apomorphine induced vomiting.

Agents which produce vomiting after ablation of the CTZ are generally supposed to have a peripheral action, although such an assumption presupposes that there are no accessory receptor loci within the CNS. Undoubtedly some agents do indeed have a peripheral emetic action, which can be abolished by a vagotomy. Such agents also include ionizing radiation and nitrogen mustard. What happens between exposure to such agents and the initiation of vagal impulses is not known; neither is it known what local factors are active, nor whether gastrointestinal hormones are involved.

The association of emotion and nausea with vomiting are well recognized, as for example in the expression “sick with anxiety.” Negative emotional reactions to cancer treatment may become ingrained as conditioned reflexes in many patients. In fact, the author has had several patients receiving cytotoxic drugs who have clearly manifested this by vomiting even upon entering an oncology facility. The placebo effects of antiemetics have been well demonstrated.

**The Treatment of Nausea and Vomiting**

**General**

In any patient it is important to rule out a potentially treatable lesion such as CNS metastasis, bowel obstruction, uremia, water intoxication or adrenal failure. Patients should be treated in a calm, reassuring environment, ideally alone and away from the sight or smell of food. Since early satiety is a feature of advanced cancer, frequent small feedings are more desirable than large meals that in themselves may be anorexigenic or nauseating.
"Patients should be treated in a calm, reassuring environment, ideally alone and away from the sight or smell of food."

for such patients. Gastritis frequently accompanies the anorexia and nausea between chemotherapy treatments, and an antacid may be beneficial.

**Antiemetic Drugs**

The use of atropine as an antiemetic was first suggested in 1869, based on observations that some manifestations of nausea and vomiting resembled cholinergic activity. The first report of its use as such appeared in 1880. During World War II, extensive air and seaborne movements of troops led to great interest in antiemetics, and the efficacy of the belladonna alkaloids, particularly scopolamine hydrobromide, was firmly established. The development of antihistamines and phenothiazines during and after the war has led to the current confusing range of antiemetics of varying activity and side effects now available to the clinician.

Potential antiemetics are generally screened for activity in animals using various emetic challenges. The most commonly used challenges are intravenous apomorphine and oral copper sulfate. The former represents stimulation of the CTZ and the latter indirect stimulation of the vomiting center from the periphery.

**Sedatives**

Sedative drugs have a largely ancillary role in the management of nausea and vomiting, as large doses are required to produce even a minor antiemetic effect. They may have a place in the patient whose anxiety is contributing to such symptoms.

**Centrally Acting Cholinergics**

The centrally acting cholinergics such as atropine and scopolamine are satisfactory in preventing emesis following oral copper sulfate, but are relatively ineffective in combating the effects of apomorphine. They have a shorter duration of action than new classes of antiemetics and their use is now largely restricted to anesthetic practice. Recently the use of scopolamine by continuous transdermal administration with chemotherapy has been reported. The results of this study are awaited with interest.

**Antihistamines**

In 1947, it was discovered accidentally that the antihistamine dimenhydrinate could prevent motion sickness. Since then, a number of substances have been evaluated and found to be effective, including diphenhydramine, cyclizine and meclizine. They differ little in their effectiveness, the main difference being in their duration of action.

The mode of action of antihistamines is not known. They have little effect on either apomorphine or copper sulfate induced emesis. There is little correlation between their antihistaminic or anticholinergic potency and their antiemetic effects. They are felt to have a narrower spectrum of antiemetic activity than the phenothiazine group, being useful largely for motion sickness and vestibular disturbances. There have been reports of some effectiveness for radiation sickness.

**Phenothiazines**

The antiemetic effectiveness of chlorpromazine was first reported in 1953 and since then a variety of congeners of varying activity have been synthesized. They are all good inhibitors of the apomorphine response and some, such as promazine, perphenazine and thiethylperazine, raise the oral copper sulfate threshold.

There do appear to be significant structure activity relationships. In particular, halogenation of the R₁ side chain seems to confer increased antiemetic activity, while reducing the possibility of dose related sedation and hypotension. Unfortunately the same structure-activity is correlated with their propensity to produce extrapyramidal side effects, due to
their interference with dopaminergic transmission. Their activity does not appear to be correlated with either their anticholinergic or antihistaminic actions.

**Butyrophenones**

Butyrophenones are a group of non-phenothiazine antipsychotic tranquilizers which cause little sedation and have few autonomic side effects. They do cause a high incidence of extrapyramidal side effects in therapeutic doses. Haloperidol is the one most commonly used and is effective in protecting against an apomorphine challenge. In doses of two to four mg. daily it has been effective in prophylaxis and treatment of nausea and vomiting of diverse etiology including that following chemotherapy and radiotherapy. 15, 16

**Trimethobenzamid**

Trimethobenzamide has some structural similarities to reserpine and the antihistamines. It is only one-tenth to one-twentieth as effective as chlorpromazine in suppressing apomorphine induced vomiting and is ineffective against copper sulfate. It has little antihistaminic action, few autonomic side effects and causes little respiratory depression. Extrapyramidal side effects have been reported infrequently. It does not appear to be as effective as other antiemetic agents, even when given parenterally. 17, 18

**Benzquinamide**

Benzquinamide is a benzquinoline derivative structurally unrelated to any other antihistamine. It is effective against apomorphine induced vomiting. It has mild antihistaminic, anticholinergic and sedative properties in man and animals. It has been reported to be superior to trimethobenzamide and prochlorperazine when given orally, 18 but at the dose used was no more effective than a placebo in a study using 5-fluorouracil as the emetic agent. 19

**Metoclopramide**

Metoclopramide is another non-phenothiazine agent with interesting actions on the gut as well as its central antiemetic effects. Unlike the parasympatholytic action of the other antiemetics, it tightens the distal esophageal sphincter and enhances gastric emptying. These effects may enhance its central antiemetic action. It has been shown to be effective against both apomorphine and copper sulfate induced vomiting and clinically to have an effectiveness comparable to prochlorperazine and perphenazine when given parenterally. Given orally, it is no more effective than a placebo in patients receiving 5-fluorouracil. 20 It has negligible cardiovascular, sedative or antihistaminic side effects. It is not yet available in the United States.

**Cannabinoids**

Following anecdotal reports that smoking marijuana could protect against the emetic effects of cytotoxic chemotherapy, it has been shown that a marijuana extract, delta-9-tetra-hydrocannabinol (THC) is more effective as an antiemetic than a placebo. 21 Comparative studies against established antiemetics are underway in several centers. In normal subjects, it does increase appetite, and has been used as an anodyne in patients with advanced bronchogenic carcinoma. 22 THC's mode of action is not known.

**Pyridoxine**

Pyridoxine, as pyridoxal-5-phosphate, acts as a coenzyme in many biological reactions including decarboxylation, transamination and deamination. In its absence, tryptophan is converted to xanthenuric acid. As xanthenuric acid excre-

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tion is increased in patients following irradiation, it has been suggested that pyridoxine might act as an antiemetic in that situation by repleting body stores of the vitamin. It has yet to be shown that pyridoxine is much more effective than a placebo as an antiemetic, although it appears to reduce anorexia and nausea in radiotherapy patients. Its effectiveness does seem to depend on the enthusiasm of the radiotherapist prescribing it.

Clinical Trials of Drugs to Prevent Chemotherapy Related Vomiting

In 1963, Moertel reported that thiopropazate and prochlorperazine were more effective than a placebo after 5-fluorouracil. In 1969, they showed again that thiopropazate and also thiethylperazine were effective. The results with each agent were comparable. Oral metoclopramide was not effective. A study reported in 1975 confirmed the efficacy of prochlorperazine, but found that benzquinamide was ineffective. In all of these studies, 10 mg. of the antiemetic was given orally 20 minutes before meals while the patients were undergoing daily 5-fluorouracil injections for five days.

In 1973, Plotkin and others showed that haloperidol (one to two mg. given after the onset of nausea and/or vomiting) was effective in about 70 percent of patients after administration of a variety of cytotoxic drugs.

Phenothiazines and related drugs cause release of prolactin by suppression of prolactin inhibitory factor. The role of prolactin in the progression of human breast cancer is highly controversial, and on humanitarian grounds alone, it seems reasonable to give these patients phenothiazine antiemetics in short courses to cover chemotherapy.

Clinical Trials of Antiemetics in Radiotherapy

With 60 to 70 percent of placebo reactors among evaluated patients, the assessment of the effectiveness of antiemetics used to treat radiation sickness can be difficult. The most comprehensive study to date has been that of Stoll who found that the most potent agents were haloperidol and trifluoperazine, with agents such as chlorpromazine and prochlorperazine being somewhat less effective. Pyridoxine was little more effective than a placebo. The effectiveness of haloperidol has been confirmed in additional studies, although conflicting reports have appeared regarding the effectiveness of other antiemetics from the phenothiazine class. Antihistamines such as cyclizine are probably also effective.

Practical Aspects

Much has yet to be learned of the causes of anorexia, nausea and vomiting after chemotherapy or radiotherapy. Until the mechanisms involved have been more fully elucidated, rational prophylaxis and treatment of these symptoms will not be possible. Research efforts directed toward evaluating the role of CNS neuro-transmitters, prostaglandins and gastrointestinal hormones may be fruitful. In the meantime, we should pay careful attention to the patients' general surroundings, nutritional and metabolic status, and seek the best antiemetic drugs and dose schedules from what are currently available. Until more controlled studies are done, it is suggested that agents working on both the CTZ and vomiting center be used. Suitable drugs include prochlorperazine (Compazine), perphenazine (Trilafon),

Tetrahydrocannabinol (15 mg. two hours before chemotherapy and for two doses afterwards) has been shown to be more effective than a placebo, and may be so in patients refractory to standard antiemetics.
| Generic Name   | Trade Name | Dose Units | Recommended Dose qid |
|---------------|------------|------------|---------------------|
| Cyclizine     | Marezine   | 50 mg tabs | 50 mg tid or qid, up to 200 mg daily |
|               |            | 50 mg amps | 50 mg tid or qid, IM only, up to 200 mg daily |
|               |            | 100 mg supp| 100 mg tid or qid, up to 400 mg daily |
| Benzquinamide | Emete-Con  | 50 mg vial | 0.5–1.0 mg/kg IM. First dose may be repeated in one hour, then every 3–4 hours. First dose only may be given IV (0.2–0.4 mg/kg) |
| Perphenazine  | Trilafon   | 2, 4, 8, 16 mg tabs | Up to 30 mg daily in divided doses |
|               |            | 5 mg amps  | 5–10 mg IM up to 30 mg daily |
|               |            |            | 5 mg IV single dose only |
| Prochlorperazine | Compazine | 5, 10 mg tabs | 10 mg tid or qid |
|               |            | 10, 15 mg "spansules" | 15–20 mg daily |
|               |            | 10 mg amps | 5–10 mg IM every 3–4 hours, up to 40 mg daily |
|               |            | 25 mg supp | 25 mg bid |
| Thiethylperazine | Torecan   | 10 mg tabs | 10–30 mg daily |
|               |            | 10 mg amps | 10–30 mg daily. IM only. |
|               |            | 10 mg supp | 10–30 mg daily |
| Trimethobenzamide | Tigan    | 250 mg caps | 250 mg tid or qid |
|               |            | 200 mg amps | 200 mg tid or qid. IM only. |
|               |            | 200 mg supp | 200 mg tid or qid |
thiethylperazine (Torecan). These may be given orally, and if so should be taken in full dosage about two hours before the anticipated onset of nausea and vomiting. The parenteral administration of antiemetics, particularly intravenous injection, is better reserved for hospitalized patients. For treatment of patients at home, the suppository is often a satisfactory vehicle for administration. We have found benzquinamide (Emet-con) to be a useful agent; however, a major drawback is that it is available only for injection.

"It is not wise to leave unsupervised patients on high doses for several days to treat the prolonged nausea and anorexia which frequently persist after chemotherapy."

The frequency of side-effects associated with antiemetic drug use is high, and in every patient a decision to use such a drug should be weighed against possible side-effects and frequent lack of efficacy. 27

The elderly and young are particularly susceptible to extra-pyramidal side-effects. To minimize this possibility, it is better to use the drugs in short courses to cover the few hours following chemotherapy. It is not wise to leave unsupervised patients on high doses for several days to treat the prolonged nausea and anorexia which frequently persist after chemotherapy. If an extra-pyramidal reaction occurs, it can be abolished quickly if necessary by the intravenous injection of diphenhydramine hydrochloride (Benadryl) 10 to 50 mg. There is no role for prophylactic anti-Parkinsonian agents, which could in theory reduce the antiemetic's effectiveness. If an extrapyramidal reaction should occur, and vomiting is severe enough to require an antiemetic, one may use more cautious doses of a different drug under close supervision.

There are a variety of other side-effects seen with antiemetics. Before using, the prescriber should be familiar with the package insert.

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**TABLE 2**

**IMPORTANT SIDE-EFFECTS OF ANTIEMETIC DRUGS**

| Category               | Side-Effects                                                                 |
|------------------------|-------------------------------------------------------------------------------|
| Parasympatholytic:     | dry mouth, constipation, urinary retention, blurred vision, angle-closure glaucoma |
| Adrenergolytic:        | orthostatic hypotension, vasomotor collapse                                   |
| Central Nervous System:| drowsiness, extrapyramidal symptoms and signs, potentiation of other psychoactive agents (e.g., alcohol, sedatives, narcotics) |

methobenzamide (Tigan) has the advantage of being available in oral, rectal and parenteral preparations, and is relatively free of side-effects.
The role of timing of chemotherapy to minimize nausea and vomiting has not been explored. Frequently patients are able to sleep off their symptoms if treatment is given late in the day. Others find that treatment early in the day, with an empty stomach, is better tolerated.

In conclusion, it should be stressed that nausea and vomiting often severely affect the quality of life of cancer patients.

Their treatment is often approached without enthusiasm by the physician whose first priority is treatment of the cancer, rather than the patient, and who is often discouraged by previous lack of success with antiemetics. With attention to the patient's general surroundings, and trial and error with antiemetics, many people will be able to better tolerate their treatment.

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