effective if given intravenously,³⁴ while dichloromethylene bisphosphonate^{34 35} and aminohydroxypropylidene bisphosphonate³⁶ are effective by mouth or intravenously. Unfortunately none of these preparations is generally available at present.

The crucial principle of management is that treatment of disequilibrium hypercalcaemia takes priority over investigation. The aim must be to reduce serum calcium to a safe but not necessarily normal concentration (say, below 3 mmol/l; 12 mg/100 ml) while investigations are completed and definitive treatment planned.

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Antiemetics and cytotoxic drugs

The chemotherapy of cancer has emerged from being a last ditch operation practised by enthusiasts to a well recognised form of treatment widely used and which is highly successful in some forms of neoplastic disease. The use of drugs for this purpose seems likely to increase. Unfortunately nearly all chemotherapeutic agents have serious and unpleasant side effects. For doctors myelosuppression is probably the most worrying, but most patients would say without hesitation that their main concern is the nausea and vomiting caused by some cytotoxic drugs. So severe and repellent may these symptoms be that patients with full knowledge of the implications may opt to stop treatment rather than continue to suffer.

Nausea and vomiting have never been very popular research topics, though they did receive some stimulus during the second world war when the authorities were looking for a drug which would minimise sea sickness in those taking part in beach landings. A vomiting centre was originally shown in the floor of the fourth ventricle in 1891,¹ but our present understanding of the central mechanism controlling vomiting is mostly based on a series of papers published in the 1950s.² Studies in cats identified an area on the dorsilateral aspect of the reticular formation, which when stimulated produced vomiting and which was thought to be the coordinating centre for the various activities concerned with vomiting. The same work confirmed that there was a further more superficial area in the area postrema which was stimulated by various circulating emetic agents including apomorphine, morphine, and copper sulphate, and which in turn activated the vomiting centre. This area has been termed the chemoreceptor trigger zone. Recently attention has been directed to the possibility that dopamine is a neurotransmitter in the stomach and may be concerned with vomiting.³ We still do not know how closely these findings in animals correspond to the mechanisms in man, but they appear very similar, so that emetic agents and antidotes may be tested in animals.

Not all cytotoxic drugs cause vomiting. Among those with an emetic action cisplatin is in a class of its own, but others

include mustine, high doses of cyclophosphamide, adriamycin, nitrosoureas, and dacarbazine. Why these particular agents should be so remarkably emetic is not known. They have no common mode of action or pharmacokinetic properties, nor do they differ in any obvious way from other cytotoxic drugs that do not cause vomiting.

The site of action of emetic cytotoxic drugs has been little studied. Mustine seems to stimulate the chemoreceptor trigger zone in dogs and to have a cortical and peripheral action in cats.⁴ The effects of cisplatin have been variously attributed to stimulation at peripheral sites⁵ and through the chemoreceptor trigger zone.⁶ Many emetic cytotoxics penetrate only poorly through the blood barrier, and there is often a delay of several hours before nausea and vomiting develop—puzzling features which argue that there may be some intermediate step or steps.

One recent proposal is that vomiting may be mediated through enkephalin pathways.⁷ Cytotoxic drugs may inhibit the synthesis in the chemoreceptor trigger zone of those enzymes which are responsible for the breakdown of enkephalin. The subsequent accumulation of enkephalin would then stimulate receptors in the chemoreceptor trigger zone with the release of dopamine, which acts as an intermediary. Decrease in production of enkephalin in an antiemetic medullary centre would then potentiate vomiting. This hypothesis would explain the delay between giving cytotoxic drugs and the development of symptoms. The failure of naloxone to inhibit vomiting could be due to stimulation by enkephalin of δ -receptors, which are not blocked by naloxone, rather than μ -receptors, which are. Much of this is, however, speculation and requires experimental confirmation.

Whatever may be the mode of action of these drugs the immediate problem is in trying to reduce vomiting. The widely used dopamine antagonists are believed to block receptors at the chemoreceptor trigger zone. The phenothiazines have been effective in several trials and the most useful are probably prochlorperazine and thiethylperazine.⁸ The butyrophenones haloperidol and droperidol are antiemetic and may be rather more effective than the phenothiazines.^{9,10} With the more powerful emetics, however, particularly cisplatin, these drugs do not afford complete protection.

Domperidone provides another approach. This dopamine antagonist has little if any central action but blocks dopamine receptors in the lower oesophagus and stomach and in one study was found to be a little more effective as an antiemetic than metoclopramide.¹¹

In conventional doses metoclopramide, another dopamine antagonist, has proved disappointing.^{12,13} In much larger doses (2 mg/kg) it appears to be more effective in preventing vomiting due to cisplatin than placebo or prochlorperazine.¹⁴ In that series side effects were reported as minor, though in a small series treated in that way P. L. Amlot (personal communication) noted that many patients had dystonic reactions.

Cannabis and its derivatives have also provoked interest. In addition to anecdotal reports of the antiemetic effect of cannabis, derivatives including delta-9-tetrahydrocannabinol and nabilone have been assessed in several trials.¹⁵ Delta-9-tetrahydrocannabinol is superior to a placebo¹⁶ and to prochlorperazine.¹⁷ Similar results have been obtained with nabilone and levonantradol.¹⁸

What limited experience there is suggests, however, that cannabinoids do not give complete protection against cisplatin¹⁹ and provoke a high incidence of side effects, including sedation, dysphoria, unsteadiness, and a dry mouth. Side effects occur more commonly in older patients. The results of the trial of BRL 4664, a cannabinoid related drug, reported at

p 350 is much in line with previous experience. In patients receiving the moderately emetic cyclophosphamide, adriamycin, vincristine, and prednisolone regimen and the more emetic mustine, vincristine, procarbazine, and prednisolone regimen control of vomiting was similar to that obtained with chlorpromazine. A higher dosage of BRL 4664 might have improved control, but combining the two antiemetics merely increased sedation to an unacceptable extent without improving antiemesis.

Dexamethasone or methylprednisolone in high dosage has also been reported to reduce vomiting with highly emetic cytotoxics.^{20,21} Why steroids should prevent vomiting is not known, but one possibility is inhibition of release of prostaglandin, though there is no supportive evidence for this. Combinations of antiemetics have received less attention in terms of trials than single drugs, though the combination of prochlorperazine and diphenhydramine has been reported to be more effective than either drug alone,²² and the addition of a sedative tranquilliser lorazepam has been reported to enhance the efficacy of perphenazine.²³ Possibly combinations of drugs should be tried more widely (on grounds of the binding of antiemetics to receptors which are putatively concerned with vomiting) in order to block the vomiting mechanism at several stages.²⁴

Various psychotherapeutic techniques have been tried not only to relieve vomiting induced by drugs but also to prevent the build up of conditioning which may result in vomiting even before treatment is given. In general, however, the control of vomiting due to cytotoxic drugs is unsatisfactory. Vomiting may often be prevented with the less emetic drugs, and here the phenothiazines appear safe and fairly effective. With powerful emetics, particularly cisplatin, the most effective drugs or perhaps combination of drugs has not been worked out. Possibly the vomiting reflex may need to be blocked at more than one stage if effective control is to be attained. In addition other areas of the brain may be stimulated by circulating emetics, and delineation of their position and the neurotransmitters concerned in their activities might suggest other types of blocking agent.

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Sunbeds

Ultraviolet radiation has been claimed,¹ though not universally,² to improve health, energy, and work rate. Many would agree, arguing that they certainly feel better on a sunny day. Possibly by extrapolation, a sun induced tan is now equated with wellbeing, although there is no objective evidence to support the association. The misconception has, however, opened up very lucrative possibilities for manufacturers of emitters of ultraviolet radiation. Equipment of all shapes and sizes has recently appeared in premises of all types in every part of the land. Sunbeds in particular are very popular and widely claimed to be able to tan without burning while avoiding the hazards of natural sunlight. But are they?

Terrestrial sunlight contains both ultraviolet B (280-315 nm) and ultraviolet A (315-400 nm) radiation. Ultraviolet B usually induces a tan readily but burns first,³ while long term exposure is known to induce premature aging and cancers of the skin. Ultraviolet A usually induces a tan before it burns³ and has been considered not to have serious long term effects. Sunbeds were therefore designed to emit solely ultraviolet A, generally giving skin dose rates⁴ some two to three times those of sunlight.⁵ But, importantly, some ultraviolet B contamination may also occur,⁴ with dose rates at times not too much less than those of sunlight on a bright day.⁵ Moreover, ultraviolet A alone may be associated with degenerative changes in human dermal connective tissue after repeated heavy exposure.⁶ Mutagenesis and cell death have been noted in microorganisms.⁷ Skin cancers may possibly develop in mice after continuous exposure to high doses of ultraviolet A.⁸ Cataracts seem likely to occur as a consequence of chronic intermittent irradiation of the eye with ultraviolet A.⁹ Yet despite these possible hazards customers flock to obtain a tan. Some may be disappointed. In one study after a two week course of moderate sunbed exposure, only 10 out of 33 people obtained a good tan, whatever their stated tanning capacity in sunlight.⁴ Even those who did tan usually obtained only moderate protection against later sunburning. People may also go red after using a sunbed and exposure to natural sunlight later that day may exacerbate the redness. Many will

itch, and some may develop photodermatoses, particularly polymorphic light eruption,⁴ or may suffer aggravation of already existing conditions, most seriously lupus erythematosus.¹⁰ Some sunbed users taking or applying potentially photosensitising substances (for example, some antibiotics, diuretics, perfumes, and aftershave lotions) will develop discomfiting irritation, erythema, or eczema, often followed by unsightly pigmentation. No long term effects of sunbeds have yet been recorded, but intuition strongly suggests that degenerative changes should be expected both of the skin and, unless they are suitably protected, of the eyes. And since the only objective advantage of sunbed irradiation is the production of vitamin D,⁴ also available in the normal diet, in medical terms lying on a sunbed, either in the short term or in the long term, is not a pastime to be encouraged.

So what is being done to protect sunbed users? The Health and Safety Executive is issuing a guidance note on the hazards and optimal methods of sunbed operation for manufacturers and operators, who themselves have recently formed the Association of Sun Tanning Operators. Many operators will probably still have little understanding of the principles of operation of their units or of ultraviolet dosimetry. In practice, what information there is from official sources concerned with public health and safety suggests that sunbeds are actually causing only relatively few and usually minor short term mishaps in Britain, albeit with no objective good effects to balance these. In the long term the poor cost to benefit ratio in both money and time for customers may well reduce the popularity of sunbeds within the next few years. Indeed, the effects of long term exposure to sunbeds seem likely to remain much less important than those of long term exposure to sunlight. In the mean time, customers will no doubt continue to indulge themselves in the occasional visit to a sunbed parlour, even if they are really enjoying not the ultraviolet radiation but rather the music from the stereo headphones, the warmth from the infrared lamps, the breeze from the electric fan, and the spray from the water bottle.

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