The management of the hypovolaemia and hypotension is based on giving colloid and the judicious use of pressor agents. Low dose dopamine infusions (2-3 µg/kg/min) may be effective in maintaining the blood pressure but should be used with caution. Higher doses further decrease renal perfusion and have been associated with cardiotoxicity, including supraventricular tachycardias, ventricular ectopic beats, myocardial infarction, and cardiac arrest. One of the advantages of the treatment protocol of continuous infusion is that it gives scope for the infusion to be interrupted if the patient becomes hypotensive—which may be preferable to the use of pressor agents.

Two other unusual side effects have been noted: bowel perforation and hypothyroidism. In at least some patients the perforation was at the site of an unresected tumour, and histological examination has shown tumour necrosis. Most of the patients who became hypothyroid had pre-existing antithyroid antibodies. It may be that the activation of natural killer cells provides effector cells for antibody dependent cellular cytotoxicity or that coexisting autoreactive T cells have also been activated.

Despite this wide array of side effects in most patients they are predictable and may therefore be handled effectively. It is almost always possible for the patient to be treated in an ordinary hospital ward, and already reports have appeared of the successful use of interleukin 2 in outpatient departments. Fear of the side effects of anticaner drugs inhibits their use and drives patients who could benefit from them into the arms of alternative practitioners. Oncologists should learn how to use new drugs—even if the side effects are strange—so that their patients are not deprived of effective treatment.

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Advanced rectal cancer

New techniques are now available for conservative and palliative management

The prognosis of advanced cancer of the rectum is poor; patients with liver metastases usually live no more than six to nine months. Despite this grim outlook many surgeons believe that abdominoperineal resection is good palliation for advanced rectal cancer—a belief often held because resection is the only method of palliation they know. Yet it cannot make sense to attempt resection in a patient with liver metastases and to condemn the patient to spending potentially the best three of his or her remaining six months convalescing after a major operation—and that is if all goes well. Furthermore, in elderly patients the risk to life of major resections is high. Surgeons should, therefore, look carefully at the audited results of their achievements with resection in palliating advanced rectal cancer. Those who have carried out such a close analysis have found the results disappointing and have sought alternative, less aggressive and dangerous methods of palliation.

In patients who are poor risks small potentially curable lesions can be managed successfully with local resection by the transanal or transphincteric route. This approach is not usually feasible for advanced, large, or fixed tumours, and for these surgeons have used other non-radical approaches. Electrofulguration with electric cautery was reported in 1972 and later modified and perfected. Usually fulguration is performed through a large rigid endoscope, and this requires prolonged anal dilatation. The elderly patient may not tolerate this dilatation, which may have disastrous results on an already tenuous continence. Chemotherapy has been tried, and (as with so many advanced gastrointestinal cancers) the results have been cruelly disappointing with the drugs available. Intracavity radiotherapy also requires wide stretching of the anus, and, though good results have been reported, it has not been widely adopted outside a few enthusiastic centres. Cryoextraction with liquid nitrogen is theoretically attractive, but despite initial enthusiasm few centres continue to use it. Furthermore, intercavity radiation and cryoextraction are suitable only for distalrectal tumours.

Two newer methods for local tissue destruction are now available. One is diathermy resection in a fluid medium—borrowing the techniques used by urologists for bladder and prostate resection. In 1983 and colleagues described the use of a urological resectoscope in six patients with carcinoma of the lower rectum. The resectoscope was used to cut a hole and so increase the size of the lumen and prevent obstruction during the limited life expectancy of patients with terminal disease. Since then many small series have been reported. Recent favourable reports place this technique in the forefront of non-operative debulking palliative manoeuvres. It possibly may be the method of choice in palliation of rectal tumours in patients with a limited prognosis because of liver metastases or advanced local node disease.

In other parts of the world the Nd-YAG laser is being employed to achieve similar ends and with similar results. The neodymium-yttrium aluminium garnet (Nd-YAG) laser can be used through a probe introduced through a flexible endoscope. It is possibly easier to use than a urological resectoscope. The problem with the Nd-YAG laser is that in
Vigabatrin

Rational treatment for chronic epilepsy

The neurochemical mechanisms underlying seizure disorders are largely unknown, but a logical pharmacological approach to treatment is to develop antiepileptic drugs which either enhance synaptic inhibition or reduce excitatory neurotransmission.1 Most experimental work has focused on synaptic inhibition mediated by γ-aminobutyric acid (GABA), and this has reached clinical fruition in the licensing of vigabatrin in Britain in 1989.

Vigabatrin (γ-vinyl-γ-aminobutyric acid; 4-aminohex-5-enolic acid) is a synthetic derivative of GABA and a specific, irreversible inhibitor of GABA transaminase—the enzyme responsible for the catabolism of GABA.2 The drug seems to exert its antiepileptic action by inhibiting the breakdown of GABA and so increasing the concentrations at the synapse of this inhibitory neurotransmitter. It increases, in a dose dependent manner, concentrations of GABA in the brains of mice and rats and in the cerebrospinal fluid of patients with epilepsy.3 In models of epilepsy in animals vigabatrin shows variable but generally broad spectrum anticonvulsant activity.4 The time course of seizure protection relates more closely to the increase in synapticosomal GABA concentrations than to concentrations in the whole brain.5

In man vigabatrin is rapidly absorbed—peak plasma concentrations occur within one to two hours, the bioavailability is 60-80%, and the half life is five to seven hours. Most (80%) of the drug is detected unmetabolised in the urine, and its renal excretion correlates with the creatinine clearance. A preliminary single blind clinical trial suggested a dose related antiepileptic effect in patients whose epilepsy was resistant to treatment.6

Since 1984 seven European double blind placebo controlled trials (six crossover7-10 and one parallel11) lasting up to 12 weeks have confirmed the antiepileptic efficacy of the drug in adults with chronic epilepsy. About 50% of patients showed a reduction in the frequency of seizures of more than a half, including roughly 15% with a reduction of more than three quarters, but complete control of seizures was uncommon. In a few patients the frequency of seizures may have increased, as may occur with any multiple treatment.12 Patients with partial seizures with or without secondary generalisation (the commonest form of chronic epilepsy) showed the best response. Acute and reversible side effects were remarkably similar to those with the standard antiepileptic drugs, the most common being drowsiness, fatigue, dizziness, and behavioural changes. Slight weight gain was also noted in a few patients. There may be a slightly increased risk of depression, but most patients show an improved mood associated with better control of seizures (KA Birkbeck et al., 18th epilepsy international congress, New Delhi, 1989). The total daily dose of vigabatrin in these studies varied from 1.5 g to 3 g, usually given twice daily, though a once daily regimen was also reported to be effective.13

No clear relation between the concentration in the blood and the clinical effect of the drug has been shown, presumably because the antiepileptic action of the drug is related to the pharmacokinetics of GABA transaminase inhibition.14 As the drug is not bound by protein, is excreted unchanged in the urine, and is not influenced by enzyme inducing drugs, interactions with other antiepileptic drugs are not expected and have not been reported, apart from a slight unexplained fall in serum phenytoin concentrations.15

As with all antiepileptic drugs the acute exacerbation of seizures may occur after the sudden withdrawal of vigabatrin.16 Experience of its use has been limited in the various epileptic syndromes in childhood that are resistant to treatment, but again partial seizures seem to respond best and myoclonic syndromes do less well;17 excitement and agitation are prominent side effects in children.