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.¹³ 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.¹⁴ Most of the patients who became hypothyroid had pre-existing antithyroid antibodies.¹⁵ 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.¹⁶ Fear of the side effects of anticancer 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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- 1 Anonymous. Interleukin-2: sunrise for immunotherapy [Editorial]. *Lancet* 1989;i:308.
- 2 Moertel CG. On lymphokines, cytokines, and breakthroughs. *JAMA* 1986;256:3141.
- 3 Bloom M. Cancer MDs clash over interleukin therapy. *Science* 1987;235:154-5.
- 4 Rosenberg SA, Lotze MT, Muul LM, *et al.* Special report: observations on the systemic administration of autologous lymphokine activated killer cells and recombinant interleukin-2 to patients with metastatic cancer. *N Engl J Med* 1985;313:1485-92.
- 5 West WH, Taur KW, Yancelli JR, *et al.* Constant infusion of recombinant interleukin-2 in adoptive immunotherapy of advanced cancer. *N Engl J Med* 1987;316:898-905.
- 6 Kotasek D, Vercellotti GM, Ochoa AC, Bach FH, White JG, Jacob HS. Mechanism of cultured endothelial injury by lymphokine-activated killer cells. *Cancer Res* 1988;48:5528-32.
- 7 Cotran R, Pober JS, Gimbrone MA Jr, *et al.* Endothelial activation during interleukin-2 immunotherapy; a possible mechanism for the vascular leak syndrome. *J Immunol* 1987;139:1883-8.
- 8 Cotran RS, Gimbrone MA Jr, Bevilacqua MP, Mendrick DL, Pober JS. Induction and detection of a human endothelial activation antigen in vivo. *J Exp Med* 1986;164:661-6.
- 9 Denicoff KD, Rubinow DR, Papa MZ, *et al.* The neuropsychiatric effects of treatment with interleukin-2 and lymphokine-activated killer cells. *Ann Intern Med* 1987;107:293-300.
- 10 Christiansen NP, Skubitz KM, Nath K, Ochoa A, Kennedy BJ. Nephrotoxicity of continuous intravenous infusion of recombinant interleukin-2. *Am J Med* 1988;84:1072-5.
- 11 Dunn MJ. Non-steroidal anti-inflammatory drugs and renal function. *Annu Rev Med* 1984;35:411-28.
- 12 Sosman JA, Kohler PC, Hank JA, *et al.* Repetitive weekly cycles of interleukin-2. II. Clinical and immunological effects of dose schedule, and addition of indomethacin. *JNCI* 1988;80:1451-61.
- 13 Nora R, Abrams JS, Tait NS, Hiponia DJ, Silverman HJ. Myocardial toxic effects during recombinant interleukin-2 therapy. *JNCI* 1989;81:59-63.
- 14 Schwartzentruber D, Lotze MT, Rosenberg SA. Colonic perforation: an unusual complication of therapy with high dose interleukin-2. *Cancer* 1988;62:2350-3.
- 15 Atkins MB, Mier JW, Parkinson DR, Gould JA, Berkman EM, Kaplan MM. Hypothyroidism after treatment with interleukin and lymphokine activated killer cells. *N Engl J Med* 1988;318:1557-63.
- 16 Mitchell MS, Kempf RA, Harel W, *et al.* Effectiveness and tolerability of low dose cyclophosphamide and low dose intravenous interleukin-2 in disseminated melanoma. *J Clin Oncol* 1988;3:409-24.

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 so 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 transanal¹ or transphincteric route.² 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 1972³ and later modified and perfected.⁴ 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 local radiotherapy also requires wide stretching of the anus,⁵ and, though good results have been reported,⁶ it has not been widely adopted outside a few enthusiastic centres. Cryodestruction with liquid nitrogen is theoretically attractive, but despite initial enthusiasm few centres continue to use it. Furthermore, intercavity radiation and cryodestruction are suitable only for distal rectal 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 prostatic resection. In 1979 Zinken and colleagues described the use of a urological resectoscope in six patients with carcinoma of the lower rectum.⁷ The resectoscope was used to cut a hole and so to 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.⁸ It possibly may be the procedure 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.⁹ It is possibly easier to use than a urological resectoscope. The problem with the Nd-YAG laser is that in

Britain the equipment costs over £50 000, whereas urological resectoscopes cost less than a 10th of that figure and all urological departments are equipped with them. Only in hospitals where the Nd-YAG laser is employed in vascular and oesophageal surgery may it seem sensible for colorectal surgeons to perform palliative procedures with it.

With the increased availability of computed tomography in district general hospitals and the advent of prospective Medical Research Council trials in the management of colorectal cancer, tomography is becoming accepted as a routine preoperative investigation in patients with cancer once the diagnosis has been established historically. Often patients with a short history who seem to be in good general health will be found on scanning to have extensive liver metastases or advanced spread to the local lymph. Such patients may commonly become symptom free after local removal of the tumour by transanal diathermy loop excision performed under fluid distension of the rectum or by Nd-YAG laser ablation through an endoscope.

Surgeons who have to care for patients with colorectal cancer should select those patients for whom radical excision will not be curative and treat them with procedures that are cost effective and have a low morbidity. This approach will spare the humiliation and misery of spending the last few

months of their lives adjusting to a colostomy or recovering incompletely from major operations. One of the reasons why the idea of a colostomy strikes fear into the hearts of patients is that there have been too many anecdotal accounts of patients who have had a colostomy for rectal cancer, have never recovered completely, and have gone relentlessly downhill. Our aim should make these stories a thing of the past.

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- 1 Parks AG, Stuart AE. The management of villous tumours of the large bowel. *Br J Surg* 1973;60: 688-95.
- 2 Mason AY. Trans-sphincteric exposure of the rectum. *Ann R Coll Surg Engl* 1972;51:320-31.
- 3 Crile G, Turnbull RB. The role of electrocoagulation in the treatment of carcinoma of the rectum. *Surg Gynecol Obstet* 1972;135:391.
- 4 Eisenberg HW. Sequential electrocoagulation and resection for carcinoma of the rectum. *Surg Gynecol Obstet* 1984;159:471-4.
- 5 Papillon J. *Rectal and anal cancers. Conservative treatment by irradiation: an alternative to radical surgery.* Berlin: Springer-Verlag, 1982.
- 6 Gunderson LL, Martin JK, Beart RW, *et al.* Intraoperative and external beam irradiation for locally advanced colorectal carcinoma. *Ann Surg* 1988;207:52-60.
- 7 Zinken LD, Katz LD, Rosin JD. A method of palliation for obstructive carcinoma of the rectum. *Surg Gynecol Obstet* 1979;148:427-8.
- 8 Berry AR, Souter RG, Campbell WB, Mortensen MJMcC, Kettlewell MGW. Endoscopic transanal resection of rectal tumours—a preliminary report of its use. *Br J Surg* (in press).
- 9 Mellow MH. Endoscopic laser therapy as an alternative to palliative surgery for adenocarcinoma of the rectum—comparison of costs and complications. *Gastrointest Endosc* 1989;35:283.

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),² and this has reached clinical fruition in the licensing of vigabatrin in Britain in 1989.

Vigabatrin (γ -vinyl- γ -aminobutyric acid; 4-aminohept-5-enoic acid) is a synthetic derivative of GABA and a specific, irreversible inhibitor of GABA transaminase—the enzyme responsible for the catabolism of GABA.^{3,4} 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 mice⁵ and rats⁶ and in the cerebrospinal fluid of patients with epilepsy.⁷ In models of epilepsy in animals vigabatrin shows variable but generally broad spectrum anticonvulsant activity.^{3,4} The time course of seizure protection relates more closely to the increase in synaptosomal GABA concentrations than to concentrations in the whole brain.⁸

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.⁹

Since 1984 seven European double blind placebo controlled trials (six crossover¹⁰⁻¹⁵ and one parallel¹⁶) 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.¹⁷ 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 (K A 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.¹⁸

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.⁹ 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.¹⁹

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 well²⁰; excitement and agitation are prominent side effects in children.