should be told which benzodiazepines to use and why, whether to take them short term or intermittently, and what effects (including adverse effects) to expect. The likely duration of use should be explained before the first dose is taken. If, on starting treatment, patients expect that it will be of short duration they find it easier to reduce the dose later and then to stop the treatment.¹⁰

Patients using benzodiazepines long term should be reviewed to see whether they continue to need them. When no justification exists patients should be introduced to the idea of stopping the drug. Do not threaten patients with abrupt cessation of a drug that they associate with keeping them well: explain that the original need for treatment may no longer apply; recommend slow reduction; and explain the possibility of a short term, self limiting, discontinuation syndrome. This avoids such symptoms being prematurely misinterpreted as indicating a return of prior insomnia or anxiety.

General practitioners should be aware of the negative effects of not prescribing benzodiazepines. Sedative tricyclic antidepressants, antihistamines, and neuroleptics are more toxic. Untreated, or inadequately treated, patients remain chronically disabled. Furthermore, they may try to relieve persisting distress with alcohol or other agents that have worse short and long term adverse effects.

Some people seek benzodiazepines for non-medical purposes—last week's letters pages provide several examples (p 1709).¹¹ Such behaviour should be recognised and strategies adopted for the safe use of prescribed drugs. Doctors should not prescribe benzodiazepines for patients they don't know unless genuine clinical indications exist—in which case only

small amounts should be prescribed. Alternatives to drugs should be offered.¹²

Doctors should avoid stigmatising people with mental illness by implying that everybody should be able to overcome mental distress without the need for drugs. The principles for reducing use of benzodiazepines in general practice apply to drugs for any condition; this is not exclusively an issue for people with psychiatric problems.

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- 1 Tyrer P, Murphy S. The place of benzodiazepines in psychiatric practice. *Br J Psychiatry* 1987;151:719-23.
- 2 Salzman C, Watsky E. Rational prescribing of benzodiazepines. In: Hallstrom C, ed. *Benzodiazepine dependence*. Oxford: Oxford University Press, 1993:13-27.
- 3 Cormack MA, Sweeny KG, Hughes-Jones H, Foot GA. Evaluation of an easy, cost-effective strategy for cutting benzodiazepine use in general practice. *Br J Gen Pract* 1994;44:5-8.
- 4 American Psychiatric Association. *Benzodiazepine dependency, toxicity, and abuse*. Washington, DC: APA, 1990.
- 5 National Health and Medical Research Council. *Guidelines for the prevention and management of benzodiazepine dependence*. Canberra: NHMRC, 1991. (Monograph series No 3.)
- 6 Wright N, Caplan R, Payne S. Community survey of long term daytime use of benzodiazepines. *BMJ* 1994;309:27-8.
- 7 Romach MK, Somer GR, Sobell LC, Sobell MB, Kaplan HL, Sellers EM. Characteristics of long-term alprazolam users in the community. *J Clin Psychopharmacol* 1992;12:316-21.
- 8 Gilbert A, Innes JM, Owen N, Sansom L. Trial of an intervention to reduce chronic benzodiazepine use among residents of aged-care accommodation. *Aust NZ J Med* 1993;23:343-7.
- 9 Shader RI, Greenblatt DJ. Use of benzodiazepines in anxiety disorders. *N Engl J Med* 1993;328:1398-405.
- 10 Clift A. Dependence on hypnotics. In: Hallstrom C, ed. *Benzodiazepine dependence*. Oxford: Oxford University Press, 1993:203-19.
- 11 Correspondence. Misuse of benzodiazepines. *BMJ* 1994;308:1709-10.
- 12 Victorian Medical Postgraduate Foundation. *Drug seeking for benzodiazepines: the recognition and management of patients seeking benzodiazepines for non-medical purposes*. Melbourne: VMPF, 1994.

Bone marrow transplants from peripheral blood

Set to transform medical oncology

Treating malignant disease with very high dose chemotherapy, often with total body irradiation, has become established during the past decade, particularly for lymphomas and leukaemias. Reinfusion of some of the patient's bone marrow (collected before high dose chemotherapy) has improved the outcome of these very intensive regimens. These autologous bone marrow transplants (autografts) entail about four weeks' pancytopenia,¹ and despite improvements in supportive care this procedure is associated with substantial morbidity and a 5-10% mortality, mainly due to myelosuppression.

Normal bone marrow contains enough undifferentiated stem cells to allow long term reconstitution (engraftment), but it seems to lack those more committed progenitors that would lead to engraftment within two or three weeks. In the past few years it has become possible to collect such committed progenitor and stem cells not from within the bone marrow cavity but from peripheral blood. The use of peripheral blood stem cells as autografts has changed much of haematological practice and will transform medical oncology within the next few years.

Until 1984, the stem cell content of either bone marrow or peripheral blood could be estimated only indirectly by in vitro colony forming assays. Since then a monoclonal antibody, now called CD34, which reacts with a haemopoietic progenitor cell surface antigen, has become available.² Cells positive for CD34 constitute only 0.1% of mononuclear cells in blood—one tenth the proportion found in bone marrow.³

Because of these low proportions, collecting sufficient cells for an autograft proved too difficult for routine use.^{4,5}

Nearly 20 years ago populations of stem and progenitor cells were found to increase in peripheral blood during the recovery phase from intensive chemotherapy,⁶ and the first attempts to explain this phenomenon (by collecting such "mobilised" blood progenitor cells) were made in 1984.⁷ More recently, the administration of haemopoietic growth factors, such as granulocyte colony stimulating factor and granulocyte macrophage colony stimulating factor, after chemotherapy was found to increase the number of circulating CD34 positive cells up to 100-fold to a number far exceeding the yield from bone marrow harvesting.⁸ Enough progenitor cells to ensure rapid and stable engraftment can be collected from one to three sessions of aphereses on consecutive days.⁹ Such autografts of peripheral blood stem cells have been used for many hundreds of transplants with the unexpected and dramatic benefit of a reduction in the duration of neutropenia and, especially, thrombocytopenia to less than two weeks, leading to shorter hospital stays and lower procedural costs.^{4,10} This accelerated recovery is thought to be due to reinfusion of larger numbers of progenitors more mature than their marrow counterparts; these therefore develop into functional blood cells more quickly.

Initial concern that collection of peripheral blood stem cells might not be sufficient for long term reconstitution of the function of bone marrow has not been confirmed.¹⁰ The more

rapid haematological recovery with peripheral blood stem cells has reduced the mortality associated with autografting to 2%. This allows the use of high dose chemotherapy and total body irradiation in conditions in which the risk of a bone marrow autograft was considered to be too high and extension of the age limit for autografting to beyond 70.

The impact of autografts of peripheral blood stem cells has so far been seen in haematological malignancies such as non-Hodgkin's lymphoma, Hodgkin's disease, acute and chronic leukaemia, and multiple myeloma.¹⁰ Their use will increase dramatically, however, in the treatment of solid tumours, and they have already been used in neuroblastoma and cancers of the breast, ovary, testis, and lung. Peters *et al* have shown a greater than 30% improvement in survival for selected high risk patients with breast cancer compared with survival after conventional chemotherapy.¹¹ These findings require confirmation in large multicentre studies, two of which are planned for Britain.

Use of repeated infusions of smaller doses of peripheral blood stem cells to support minor escalation of chemotherapy in outpatients may have an even greater impact on reducing the morbidity of chemotherapy for cancer.¹² In this context, unprocessed whole blood collected after administration of haemopoietic growth factors alone or with chemotherapy may contain sufficient peripheral blood stem cells to provide an alternative to relatively costly apheresis. Finally, allogeneic bone marrow transplantation may also benefit from this approach, with the donor being spared a general anaesthetic and the recipient's blood count possibly recovering more quickly.^{13 14}

This new found ability to collect haemopoietic stem cells will have other benefits. The CD34 marker enables their specific selection into a very small volume by one of several commercially available devices. CD34 positive progenitors are ideal targets for gene therapy techniques and the perfect starting point for the effective removal of contaminating tumour cells. For both applications the small volume facilitates handling and reduces costs.¹⁵⁻¹⁷ In addition, the development of reliable in vitro methods to amplify CD34 positive cells before transplantation will soon be possible and may eliminate pancytopenia after chemotherapy.

The cost effectiveness of haemopoietic stem cell transplants, whatever their source, is an important concern. Who will pay for these advances? The cost of an autograft for Hodgkin's disease has almost halved in two years because peripheral blood stem cells rather than bone marrow are used, and the total number of procedures has risen. Worldwide, the use of autografts continues to rise steeply.¹ Transplant centres will

need to reassure purchasers that patients are included in formal clinical trials whenever possible and that transplants of peripheral bone stem cells will not be used to intensify palliative chemotherapy for incurable patients. Despite these concerns such autografts may transform the prognosis for women with poor risk breast cancer and a significant number of patients with lymphoma and myeloma. In the next decade CD34 expansion techniques will eliminate neutropenia and thrombocytopenia, enabling all but a handful of the most intensive anti-cancer regimens to move to the outpatient clinic.

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- 1 Armitage JO. Bone marrow transplantation. *N Engl J Med* 1994;330:827-35.
- 2 Civin JC, Strauss LC, Brovall C, Fackler MJ, Schwartz H, Shaper JH. Antigenic analysis of hematopoiesis. III. A hematopoietic progenitor cell surface antigen defined by a monoclonal antibody raised against KG-1a cells. *J Immunol* 1984;133:157-65.
- 3 Bender JG, Unverzagt KL, Walker DE, Lee W, Van Epps DE, Smith DH, *et al*. Identification and comparison of CD34 positive cells and their subpopulations from normal peripheral blood and bone marrow using multicolor flow cytometry. *Blood* 1991;77:2591-6.
- 4 Kessinger A, Armitage JO. The evolving role of autologous peripheral stem cell transplantation following high-dose therapy for malignancies. *Blood* 1991;77:211-3.
- 5 Lobo F, Kessinger A, Landmark JD, Smith DM, Weisenburger DD, Wigton RS, *et al*. Addition of peripheral blood stem cells collected without mobilization techniques to transplanted autologous bone marrow did not hasten marrow recovery following myeloablative therapy. *Bone Marrow Transplant* 1991;8:389-92.
- 6 Richman CM, Weiner RS, Yankee RA. Increase in circulating stem cells following chemotherapy in man. *Blood* 1976;47:1031-9.
- 7 To LB, Haylock DN, Kimber RJ, Juttner CA. High levels of circulating haemopoietic stem cells in very early remission from acute non-lymphoblastic leukaemia and their collection and cryopreservation. *Br J Haematol* 1984;58:399-410.
- 8 Siena S, Bregni M, Brando B, Ravagnani F, Bonadonna G, Gianni AM. Circulation of CD34+ hematopoietic stem cells in the peripheral blood of high-dose cyclophosphamide treated patients: enhancement by intravenous recombinant human granulocyte-macrophage colony-stimulating factor. *Blood* 1989;74:1905-14.
- 9 Wunder E, Sovalat H, Fritsch G, Silvestri F, Henon P, Serke S. Report on the "European workshop on peripheral blood stem cell determination." *Journal of Hemotherapy* 1992;1:131-42.
- 10 Henon P. Peripheral blood stem cell transplantations: past, present and future. *Stem Cells* 1993;11:154-72.
- 11 Peters WP, Ross M, Vredenburg JJ, Meisenberg B, Marks LB, Winer E, *et al*. High-dose chemotherapy and autologous bone marrow support as consolidation after standard-dose adjuvant therapy for high-risk primary breast cancer. *J Clin Oncol* 1993;11:1132-43.
- 12 Tepler I, Cannistra SA, Frei III E, Gonin R, Anderson KC, Demetri G *et al*. Use of peripheral blood progenitor cells abrogates the myelotoxicity of repetitive outpatient high-dose carboplatin and cyclophosphamide chemotherapy. *J Clin Oncol* 1993;11:1583-91.
- 13 Dreger P, Sutorp M, Haferlach T, Löffler H, Schmidt N, Schroyens W. Allogeneic granulocyte-colony-stimulating-factor mobilised peripheral blood progenitor cells for treatment of engraftment failure after bone marrow transplantation. *Blood* 1993;81:1404-7.
- 14 Russell NH, Hunter A, Rogers S, Hanley J, Anderson D. Peripheral blood stem cells as an alternative to marrow for allogeneic transplantation. *Lancet* 1993;341:1482.
- 15 Cassel A, Cottler-Fox M, Doren S, Dunbar CE. Retroviral-mediated gene transfer into CD34-enriched human peripheral blood stem cells. *Exp Hematol* 1993;21:585-91.
- 16 Bregni M, Magni M, Siena S, Nicola M, Bonadonna G, Gianni AM. Human peripheral blood hematopoietic progenitors are optimal targets of retroviral-mediated gene transfer. *Blood* 1992;80:1418-22.
- 17 Blaese RM, Culver KW, Chang L, Anderson WF, Mullen C, Nienhuis A, *et al*. Treatment of severe combined immunodeficiency disease (SCID) due to adenosine deaminase deficiency with CD34+ selected autologous peripheral blood cells transduced with a human ADA gene. *Hum Gene Ther* 1993;4:521-7.

Toxocara canis and human health

Greater awareness needed of its ill effects

Soil sampling shows widespread contamination of the environment, particularly parks and playgrounds, with the eggs of *Toxocara canis*, the dog roundworm.^{1 2} Human toxocariasis occurs after ingestion of infective eggs of *T canis* and migration of larvae, particularly to liver, lungs, muscle, and brain. It accounts for considerable preventable childhood illness and blindness and is often associated with pica and poor hygiene. Although the clinical features vary, three syndromes are recognised: toxocaral visceral larva migrans, ocular larva migrans, and covert toxocariasis.

Toxocaral visceral larva migrans is characterised by fever, malaise, cough and bronchospasm, abdominal pain, and occasionally failure to thrive. Hepatosplenomegaly, lymphadenitis, and bronchopulmonary signs predominate. Severe infection may cause myocarditis or respiratory failure. Focal or generalised seizures may occur. Epilepsy is associated with positive findings on serological testing for toxocara, but pica is also commoner in patients with epilepsy. Contradictory reports relate toxocara to long term defects in cognitive function. Visceral larva migrans is usually, but not invariably,