Fortnightly Review

Bone marrow transplantation

Richard L Soutar, Derek J King

Bone marrow transplantation was introduced in the early 1960s by the pioneering work of individuals like Mathe, McFarland, and Donnal Thomas. It has rapidly developed from an experimental procedure to an established treatment for a variety of serious disorders. The number of patients undergoing bone marrow transplantation increased 10-fold during the 1980s (fig 1),¹ with a similar increase in the number of transplant centres. In a survey of 111 unselected, local general practitioners we found that 14% had a patient who had had bone marrow transplantation in their practice.

The early complications of bone marrow transplantation will involve hospital practitioners from a variety of specialties other than haematology or oncology. Perhaps more importantly as patient numbers increase and survival improves, long term complications inevitably begin to involve primary care physicians. Not surprisingly, medical knowledge of bone marrow transplantation is often limited. This review is

Summary points

- Bone marrow transplantation is becoming an increasingly used medical intervention
- Allogeneic bone marrow transplantation remains a risky medical procedure, with mortality about 30%, primarily from graft versus host disease and infection; autologous transplantation has a more acceptable mortality risk of 5-10%
- If results of ongoing trials in solid tumours are favourable autologous bone marrow transplantation may become a very common form of medical treatment
- Stem cells collected from peripheral blood are increasingly being used in place of conventional autologous transplantation; they lead to more rapid engraftment, reduce duration of hospitalisation, and may help to control costs
- As patient numbers increase, general practitioners will increasingly be confronted with the long term complications of bone marrow transplantation, such as infertility, secondary neoplasms, and endocrine dysfunction
- Although most survivors of bone marrow transplantation do well after transplant, 25-50% of patients will have sexual, employment, and psychosocial problems

FIG 1—Annual (bars) and cumulative (—○—) numbers of patients receiving allogeneic or syngeneic bone marrow transplantation in Britain. Reproduced with the permission of Churchill Livingstone¹

intended to help physicians with both the donor and recipient aspects of bone marrow transplantation.

Indications

In essence bone marrow transplantation is a method of providing the patient (recipient) with a normal haematopoietic and immune system when these have been rendered defective. This may be due to either disease (aplastic anaemia, immune deficiency, inborn error of metabolism or haemoglobin synthesis, for example), or, more often, because of medical treatment—principally the effect of high dose chemotherapy or radiotherapy (box 1).

In certain tumours there is an established relation between dose of chemotherapy or radiation and response of the tumour. Escalating treatment doses are limited by the toxicity of radiotherapy or chemotherapy including irreversible marrow suppression. Bone marrow transplantation allows the doctor to overcome the problem of marrow suppression and potentially improve response rates. Dose escalation

Department of
Haematology, Aberdeen
Royal Hospitals NHS
Trust, Foresterhill,
Aberdeen AB9 2ZD
Richard L Soutar, senior
registrar
Derek J King, consultant

Correspondence to:
Dr Soutar.

BMJ 1995;310:31-6

Box 1—Disorders suitable for bone marrow transplantation

Acquired disorders

Malignant disease:

Acute lymphoblastic leukaemia—high risk patients
Acute myeloid leukaemia—consider for all patients, except perhaps those staged as FAB type M3
Chronic myeloid leukaemia—all patients, if young and there is a suitable donor
Hodgkin's and non-Hodgkin's lymphoma—selected patients at high risk of relapse
Solid tumours—selected patients with breast cancer, small cell lung cancer, testicular tumours, ovarian cancer, neuroblastoma
Severe aplastic anaemia

Inherited disorders

Haemoglobinopathies—thalassaemia major, sickle cell disease
Inborn errors of metabolism—Gaucher's disease, osteopetrosis
Immunodeficiency syndromes—severe combined immunodeficiency, Wiskott-Aldrich syndrome
Congenital severe aplastic anaemia—Fanconi's anaemia

can be applied only when haematological toxicity is the limiting factor. For certain agents dose is limited by other side effects—for example, renal toxicity with cisplatin.

Allogeneic bone marrow transplantation (see below) may also help to eliminate residual disease by the system recognising the tumour as "non-self," with subsequent tumour destruction. This phenomenon of graft versus tumour seems to hold in the setting of allogeneic bone marrow transplantation for leukaemia (graft versus leukaemia effect²) but has not yet been established for other neoplasms.

Sources of bone marrow stem cells

The basis of bone marrow transplantation is the provision of haematopoietic stem cells to repopulate the bone marrow. Initially bone marrow was considered to be the only source of these cells, but recently alternative sources of stem cells have been recognised.

Box 2—Sources of haematopoietic stem cells

Bone marrow:

Syngeneic—from an identical twin
Matched allogeneic—from a sibling compatible for major histocompatibility complex ("HLA-identical"); each sibling has a 1:4 chance of being compatible
Mismatched allogeneic—usually from a family member, but not compatible for major histocompatibility complex
Unrelated donor—from a donor registry, donor thought to be compatible;
Autologous—patients are their own donors, thus overcoming any compatibility problems

Peripheral blood stem cells—

a relatively recent development in bone marrow transplantation. Haematopoietic stem cells are mobilised from the bone marrow and enter the peripheral blood as the marrow regenerates from chemotherapy (usually with the aid of recombinant growth factors). These cells can be collected by a cell separator and processed identically to a marrow donation

Umbilical cord blood stem cells—

the most recently identified source of haematopoietic stem cells. Due to the relatively small numbers of stem cells this source is only applicable to small children

Sources of haematopoietic stem cells are shown in box 2. Most transplants are of matched allogeneic bone marrow, autologous bone marrow, and peripheral blood stem cells.

Donating bone marrow

Before donation a full history is taken and the donor is examined and investigated (box 3). The donor marrow is obtained (harvested) by multiple aspirates from several sites on the iliac crests by using a specialised marrow aspiration needle (fig 2). The harvest is performed under general anaesthesia and lasts 30-45 minutes. In an adult 800-1000 ml of bone marrow is removed and subsequently processed by a cell separator.

The separated red cells can be returned to the donor; transfusion of homologous blood is generally not required. Meanwhile the white cells are processed into either a buffy coat or, more commonly, mononuclear cell component. Preparation of mononuclear cells overcomes the problem of potential blood group (ABO) incompatibility and at the same time results in a small volume product which can be frozen in liquid nitrogen (cryopreserved) and returned at a later date (months to years). Cryopreservation is critical in most

Box 3—Investigations performed after HLA typing and before bone marrow donation

Full blood count	Hepatitis B surface antigen
Biochemical profile	HIV serology
Virology	Blood group
Cytomegalovirus	Chest radiography
Herpes simplex virus	Electrocardiography
Herpes zoster virus	

autologous transplantation schedules as several days must elapse between donation and transplantation to permit the administration, and elimination, of the conditioning chemotherapy (see below).

Donors can expect to be in hospital for about 48 hours. Generally only mild analgesics such as paracetamol are required after donation. The practicalities of bone marrow donation have recently been reviewed by Jones and Burnett.³

Donor registries

In the vast majority of bone marrow transplantation procedures the donor is either a matched sibling (allogeneic) or the patients themselves (autologous). Unfortunately only 30% of patients requiring bone marrow transplantation will have a closely matched family donor. The plight of Anthony Nolan, who died in 1979 without having received a bone marrow transplant, was the inspiration for the creation of the first (and largest) register of unrelated potential marrow donors.

In the United Kingdom there are two donor registers, the Anthony Nolan Bone Marrow Trust in London, with approximately 125 000 potential donors, and the British Bone Marrow and Platelet Donor Panel, which is based in Bristol, recruits from blood donors, and has over 30 000 potential donors.⁴ Patients wishing to be potential marrow donors should contact either their local blood transfusion centre or the Anthony Nolan Trust, 75 Agincourt Rd, London (tel 071 284 1234).

Procedure for transplantation

Before receiving the infusion of haematopoietic stem cells the patient (host) undergoes "conditioning." The

FIG 2—Theatre requirements for bone marrow harvest: (a) modified aspiration needles, (b) syringes, (c) collection bag, (d) bag clamps, (e) heparinised rinsing fluid

first aim of conditioning is to eliminate the patient's own bone marrow and immune system, thereby creating a microenvironment suitable for marrow engraftment and preventing graft rejection by the host. A second aim in appropriate patients is to eliminate any residual malignant disease. The exact type of conditioning depends on the disease being treated but generally involves a high dose of chemotherapy frequently combined with total body irradiation.

The stem cells are infused into a central vein, and they migrate to the bone marrow space by a poorly understood mechanism. Before these stem cells engraft and produce the cellular elements of blood there is a period when the patient is anaemic (requiring regular blood transfusion), profoundly neutropenic (and prone to infection; see below), and thrombocytopenic (requiring regular platelet transfusion). The patient will also often experience other side effects of the conditioning regimen, including nausea (now generally well controlled with serotonin-3 receptor antagonists), mucositis (often severe enough to require intravenous narcotic analgesia), and diarrhoea. These factors mean that early nutritional support is required, often in the form of total parenteral nutrition.

Patients can expect to be in hospital for 4-6 weeks, although this is highly variable. The recent introduction of recombinant growth factors—for example, granulocyte colony stimulating factor—and the use of peripheral stem cells have led to more rapid engraftment and shorter duration of hospitalisation.⁵

Most patients will not return to work for at least nine months after allogeneic bone marrow transplantation, although recovery after autologous transplantation is more rapid.

Infections associated with phases of the period after bone marrow transplantation

Early (days 0-14)	Day 14 to engraftment	Engraftment to day 100	Late (after day 100)
<i>Risk factors</i>			
Neutropenia	Prolonged neutropenia	Humoral immune defect	Humoral immune defect
Central line mucositis	Antibiotic use Central line mucositis	Cellular immune defect Central line	Cellular immune defect Relapse Further treatment
<i>Infections</i>			
Gram positive and Gram negative bacteria Candida Herpes simplex virus	Resistant Gram negative bacteria Gram positive bacteria Fungi	Gram positive bacteria Fungi Cytomegalovirus Pneumocystis	Varicella zoster virus Encapsulated bacteria

Early complications

Complications may be seen in the first few weeks after transplantation, many arising from the chemoradiotherapy conditioning regimen (box 4).² Reconstitution by donor marrow generally begins 3-4 weeks after transplantation, but patients remain immunosuppressed for many months, even once blood counts have recovered, owing to factors such as lymphocyte subset imbalance and impaired mucosal defence.

Infectious disease is a major cause of morbidity and mortality in patients who have received bone marrow transplants. Distinct phases of the post-transplant period are associated with distinct infections (table). The initial neutropenic period is characterised by reactivation of herpes simplex virus and bacterial and fungal infections. These require prompt treatment with broad spectrum intravenous antibiotics and antiviral and antifungal agents. Treatment often has to be empirical, while the results of specific cultures are awaited. In the post engraftment phase, cytomegalovirus and *Pneumocystis carinii* are common infections. By 100 days after transplantation, infection rates are falling; however, late infections with varicella zoster virus and encapsulated organism are not uncommon.

Box 4—Early complications of bone marrow transplantation

Regimen related toxicity
Mucositis
Cystitis
Cardiac dysfunction
Renal dysfunction
Neurologic dysfunction
Hepatic veno-occlusive disease
Marrow graft failure
Immunodeficiency
Infection
Interstitial pneumonitis
Acute graft versus host disease

Interstitial pneumonitis is a dreaded complication—it has a mortality of about 80% and the potential for rapid progression to respiratory failure (fig 3). Its aetiology is complex, and clinically it is characterised by fever and cough. Treatment is supportive, although steroids are also commonly given.

Graft versus host disease occurs when the donated marrow recognises the recipient tissue as foreign. Acute graft versus host disease (within 100 days of

FIG 3—Chest radiograph of patient with interstitial pneumonitis, showing diffuse interstitial shadowing

transplantation) is the major life threatening complication of allogeneic bone marrow transplantation and is characterised by fever, rash, diarrhoea, liver dysfunction, and immune compromise of varying severity. The diagnosis of graft versus host disease can be confirmed histologically by appropriate biopsy. It is highly unlikely that primary care physicians would be involved in this early complication of bone marrow transplantation. Treatment consists of immunosuppressive agents such as corticosteroids, cyclosporin, and lymphocyte directed monoclonal antibodies. In vivo immunosuppression is given for three to six months after allogeneic transplantation in an attempt to prevent, or ameliorate, graft versus host disease; it is generally in the form of methotrexate and cyclosporin. Alternatively the donor marrow can be depleted of T cells in vitro. This is effective in preventing graft versus host disease, but it seems to increase relapse rates, presumably because the graft versus leukaemia effect is also lost.²

Chronic graft versus host disease (occurring later than 100 days after transplantation) is an autoimmune-like condition that affects 25-50% of long term survivors of allogeneic bone marrow transplantation.² Chronic graft versus host disease has features that can resemble systemic sclerosis, lichen planus, systemic lupus erythematosus, Sjögrens syndrome, primary biliary cirrhosis, or bronchiolitis obliterans. The principal manifestations of chronic graft versus host disease are listed in box 5.⁶ Treatment is complicated but generally consists of immunosuppression with steroids, azathioprine, and cyclosporin.

Box 5—Manifestations of extensive chronic graft versus host disease

Skin changes:	Dry eyes
Dryness	Infections
Changes in pigmentation	Weight loss
Thickening	Contractures
Abnormal liver function tests	Oesophagitis
Dry mouth or mucositis	

Long term complications

Even if they are cured of their disease, patients who have undergone bone marrow transplantation are prone to a series of long term complications (box 6). As the results of bone marrow transplantation improve, these become increasingly important. Complications include cataracts (from the radiotherapy), abnormalities of pulmonary function, endocrine abnormalities (hypothyroidism, reduced growth), secondary malignancies, and infertility.⁷

Infertility is an almost inevitable consequence of total body irradiation and very common after high dose chemotherapy. In view of the young patient age infertility, together with the fear of disease relapse, probably represents the major long term problem that

Box 6—Late complications of bone marrow transplantation

Regimen related toxicity
Gonadal dysfunction
Endocrine dysfunction
Impaired growth and development
Cataracts
Neurologic impairment
Immunodeficiency
Infection
Chronic graft versus host disease
Secondary malignancies

patients face. For men, semen donation is possible before chemotherapy, although patients are often either too ill to donate or the semen is of inadequate quality to be of use. For women, egg donation is generally not logistically possible, and it is now possible to store only human embryos, not eggs.

Although most patients adapt well after bone marrow transplantation, studies have documented that 25-50% of patients will have difficulties with sexual function, returning to employment, and psychosocial functioning.⁸⁻¹⁰ Children require revaccination after bone marrow transplantation, generally after one year, initially with inactivated vaccines. Vaccination before this time may be ineffective and possibly dangerous.

Outcome

Autologous transplants overcome the problem of graft versus host disease (and limited donor numbers) as patients are their own donor. Although allogeneic transplantation seems to be superior to autologous transplantation in reducing the risk of disease relapse, it has a much higher procedural mortality, especially in older patients.

About 30% of patients will fail to survive allogeneic bone marrow transplantation, but less than 10% do not survive autologous transplantation. The increased safety of autologous transplantation means that it is more suitable for older patients. Hence the upper age range for autologous transplantation is about 50 years but only 30-40 years for allogeneic transplantation.

Allogeneic transplantation from an unrelated, matched donor is even more hazardous than conventional allogeneic bone marrow transplantation from a sibling donor. It is generally reserved for very young patients with no other hope of cure.

Results

RESULTS OF HAEMATOLOGICAL MALIGNANCIES

Bone marrow transplantation is generally considered for patients with acute lymphoblastic leukaemia who have a high risk factor such as age > 16 years, white blood count at presentation > 50 × 10⁹/l, poor prognosis cytogenetics such as the Philadelphia chromosome, or relapse on maintenance treatment. International transplant registries indicate 39-48% disease free survival after allogeneic bone marrow transplantation for acute lymphoblastic leukaemia.¹¹ Unfortunately this is almost identical to the overall survival with chemotherapy as the higher relapse rate with chemotherapy is offset by the high procedural mortality of transplantation.¹² At present allogeneic transplantation is indicated for high risk adult patients in first remission and for other patients after a first relapse.¹³ Disease free survival rates of 20-65% have been reported after autologous transplantation; however, these results are difficult to interpret, as logistic delays in organising the treatment may have selected patients already at a lower risk of leukaemic relapse (time censoring).¹⁴

In acute myeloid leukaemia only 15-20% of patients will be cured by chemotherapy.¹⁵ Allogeneic bone marrow transplantation seems to cure about half of patients with acute myeloid leukaemia and may offer a significant survival advantage in the disease.¹⁶ However, as results with chemotherapy improve the indications for allogeneic bone marrow transplantation in acute myeloid leukaemia may change, and some clinicians reserve early allogeneic bone marrow transplantation for patients with high risk disease.¹⁷ The benefit of autologous transplantation is unclear in acute myeloid leukaemia (although disease free survival rates of 40-61% have been reported after the procedure¹⁸) principally owing to time censoring. Attempting to

overcome this, the present Medical Research Council trial in adult acute myeloid leukaemia involves a randomisation between chemotherapy alone and chemotherapy plus autologous transplantation for patients who lack a donor or are not suitable for allogeneic bone marrow transplantation.

Chronic myeloid leukaemia cannot be cured by chemotherapy and has a median survival of only three to six years. Interferon alfa may prolong the chronic phase of chronic myeloid leukaemia, but allogeneic bone marrow transplantation offers the only hope of cure. About 15% of patients with chronic myeloid leukaemia will be eligible for allogeneic bone marrow transplantation and half will be alive and free of leukaemia after five years.¹⁹

Bone marrow transplantation, principally autologous transplantation, has been used in both Hodgkin's disease and non-Hodgkin's lymphoma. The validity of transplant results in Hodgkin's disease is partially flawed by the lack of randomised trials and the possibility of selection bias; however, recent trials suggest that autologous transplantation is superior to chemotherapy in relapsed and refractory Hodgkin's disease.²⁰

Despite advances in conventional treatment about half of patients with high grade non-Hodgkin's lymphoma are not cured of their disease. Autologous transplantation seems to be able to rescue a significant proportion of patients with relapsed non-Hodgkin's lymphoma.²¹

RESULTS IN SOLID MALIGNANCIES

Unlike the haematological malignancies, the solid tumours potentially suitable for bone marrow transplantation (box 1) are much commoner and the implications for health care budgets profound. Several studies have confirmed the efficacy of bone marrow transplantation (principally autologous transplantation) in breast cancer,²² ovarian cancer, small cell lung cancer, testicular germ cell cancer,²³ and neuroblastoma.²⁴ In general the best results are obtained when the tumour is still sensitive to chemotherapy and the disease of low volume. Autologous transplantation is usually the method of choice in solid tumours, owing to the lower procedural risk and, as yet, the lack of evidence for a graft versus tumour effect. Unfortunately there are few large scale trials comparing the efficacy of bone marrow transplantation (principally autologous transplantation) with conventional chemotherapy in solid malignancies.

In most patients with metastatic breast carcinoma the tumour is sensitive to chemotherapy, but only 20% of patients respond completely to chemotherapy. Bone marrow transplantation seems to improve response rates, but the median response duration is still relatively short (5-19 months), and any improvement in survival has to be weighed against a considerable treatment related mortality (3-23%), duration of hospitalisation, treatment related morbidity, and other quality of life issues.

The situation in the other solid tumours is similar to breast carcinoma: autologous transplantation may improve tumour response, but firm conclusions cannot be stated owing to the lack of randomised controlled trials. In small cell lung cancer autologous transplantation produces good response rates (82%-55%), with a median survival of 15 months; however, this is not much better than conventional chemotherapy.²⁴ In paediatric neuroblastoma a recent randomised controlled trial failed to show benefit for autologous transplantation over standard chemotherapy.²⁵

In conclusion, many solid tumours, even those refractory to conventional chemotherapy, show response to autologous transplantation; however, improved disease free survival is harder to document.

The challenge facing oncologists is to identify patients in a high risk group at an early stage of treatment so that bone marrow transplantation can be performed earlier in the disease. This should not only improve results but lead to appropriate resources allocation and spare patients an arduous treatment when it offers them no benefit.

RESULTS IN OTHER CONDITIONS

Severe aplastic anaemia is fortunately a rare disorder; it has a five year survival of only 30-40%. For selected patients (suitable donor, young, not HLA sensitised) allogeneic bone marrow transplantation offers a 60-80% chance of cure.²⁶ Unfortunately patients in whom transplantation does not succeed generally die. Hence the decision to use transplantation for a patient with severe aplastic anaemia or to use other treatments—for example, immunosuppression—is a difficult one for the haematologist.

Several hundreds of patients have undergone allogeneic bone marrow transplantation for haemoglobinopathy, principally thalassaemia major. The overall disease free survival in this setting is 67%.²⁷ However, as conventional supportive care improves (hypertransfusion, iron chelation therapy, improved transfusion safety) it has become difficult to categorically state the best treatment option for thalassaemia major.²⁸ Several factors will be important in the decision making process, including availability of good conventional treatment, availability of a donor, compliance with treatment, acceptance of the disease, and presence and extent of iron overload.²⁹

Outcome of bone marrow transplantation in the rare immunodeficiency syndromes and inborn errors of metabolism will not be discussed. The interested reader will find articles by Vellodi *et al* and Morgan of use.^{30 31}

Future developments

If the benefit of autologous transplantation over conventional chemotherapy is confirmed in the solid malignancies, autologous transplantation may become a common medical treatment. Performing randomised controlled trials in malignant disease, however, is becoming increasingly difficult owing to both a lay and medical perception that bone marrow transplantation must be superior to conventional chemotherapy.³² Thus patients are not being randomised between bone marrow transplantation and chemotherapy in ongoing large trials such as the Medical Research Council acute myeloid leukaemia 10 trial.

The increasing use of peripheral blood stem cell transplants and the availability of haematopoietic growth factors is shortening hospital stays, permitting autologous transplantation to be performed on an outpatient basis, and reducing toxicity. Whether these new treatments will also reduce costs is still unknown, but short duration, intensive treatment may be less costly than chronic conventional dose chemotherapy. Future trials in bone marrow transplantation therefore need to assess not only disease free survival but also treatment related morbidity, patients' perception of quality of life, and relative financial costs between treatment options.

In the field of related and unrelated allogeneic bone marrow transplantation the major problem remains graft versus host disease. Improved treatment or prevention of graft versus host disease should improve results and increase the applicability of transplantation from unrelated, matched donors. Human umbilical cord blood transplantation may also increase the feasibility and safety of such transplants.³³

Expansion of bone marrow donor pools will increase the potential for transplants from unrelated, matched

donors and overcome the problem of finding a donor for non-white patients. Currently the Anthony Nolan Research Centre is recruiting donors from ethnic minorities in Britain.⁴ The development of gene therapy should result in this treatment eventually replacing allogeneic bone marrow transplantation for inborn errors of metabolism, immunodeficiency states, and haemoglobinopathies.³⁴

- 1 Horowitz M, Bortin M. The role of registries in evaluating the results of bone marrow transplantation. In: Treleaven J, Barrett J, eds. *Bone marrow transplantation in practice*. Edinburgh: Churchill Livingstone, 1992:367-77.
- 2 Sullivan K. Complications of bone marrow transplantation. In: Hoffman R, Benz E, Shattil S, Furie B, Cohen H, eds. *Haematology: basic principles and practice*. Edinburgh: Churchill Livingstone, 1991:242-9.
- 3 Jones R, Burnett AK. How to harvest bone marrow for transplantation. ACP Broadsheet No 134. *J Clin Path* 1992;45:1053-7.
- 4 Cleaver S. The Anthony Nolan Research Centre and other matching registries. In: Treleaven J, Barrett J, eds. *Bone marrow transplantation in practice*. Edinburgh: Churchill Livingstone, 1992:361-6.
- 5 Kessinger A. Utilization of peripheral blood stem cells in autotransplantation. *Hematol Oncol Clin North Am* 1993;7:535-45.
- 6 Mackie MJ. Bone marrow transplantation. In: Ludlam CA, ed. *Clinical haematology*. Edinburgh: Churchill Livingstone, 1990:203-14.
- 7 Deeg HJ. Bone marrow transplantation: a review of delayed complications. *Br J Haematol* 1984;57:185-208.
- 8 Hengeveld MW, Houtman RB, Zwaan FE. Psychological aspects of bone marrow transplantation: a retrospective study of 17 long term survivors. *Bone Marrow Transplant* 1988;3:69-75.
- 9 Cust MP, Whitehead MI, Powles R, Hunter M, Milliken S. Consequences of ovarian failure after total body irradiation for leukaemia. *BMJ* 1989;299:1494-7.
- 10 Andrykowski MA, Henslee PJ, Barnett RL. Longitudinal assessment of psychosocial functioning of adult survivors of bone marrow transplantation. *Bone Marrow Transplant* 1989;4:505-9.
- 11 Barrett J. Bone marrow transplantation for acute lymphoblastic leukaemia. In: Treleaven J, Barrett J, eds. *Bone marrow transplantation in practice*. Edinburgh: Churchill Livingstone, 1992:33-47.
- 12 Horowitz MM, Messerer D, Hoesler D, Gale RP, Neiss A, Atkinson K, et al. Comparison of chemotherapy and bone marrow transplantation for adults with acute lymphoblastic leukaemia in first remission. *Ann Intern Med* 1991;115:13-9.
- 13 Hoesler DF. Therapy of the newly diagnosed adult with acute lymphoblastic leukaemia. *Hematol Oncol Clin North Am* 1993;7:139-60.
- 14 Ball ED, Rybka WB. Autologous bone marrow transplantation for adult acute leukemia. *Hematol Oncol Clin North Am* 1993;7:201-31.

- 15 Tiley C, Powles R. The role of bone marrow transplantation in the management of acute myeloid leukaemia. In: Treleaven J, Barrett J, eds. *Bone marrow transplantation in practice*. Edinburgh: Churchill Livingstone, 1992:11-8.
- 16 Appelbaum F, Fisher LD, Thomas ED. Chemotherapy versus marrow transplantation for adults with acute nonlymphocytic leukaemia: a five year survival. *Blood* 1988;72:179-84.
- 17 Christiansen NP. Allogeneic bone marrow transplantation for the treatment of adult acute leukemias. *Hematol Oncol Clin North Am* 1993;7:177-95.
- 18 Geller RB. Role of autologous bone marrow transplantation for patients with acute and chronic leukemias. *Hematol Oncol Clin North Am* 1993;7:547-75.
- 19 Goldman J. Management of chronic myeloid leukaemia. *Blood Rev* 1994;8:21-9.
- 20 Bierman PJ, Vose JM, Armitage JO. Autologous transplantation for Hodgkin's disease: coming of age? *Blood* 1994;85:1161-3.
- 21 Vose JM, Armitage JO. Role of autologous bone marrow transplantation in Non-Hodgkin's lymphoma. *Hematol Oncol Clin North Am* 1993;7:577-90.
- 22 Myers SE, Williams SF. Role of high-dose chemotherapy and autologous stem cell support in treatment of breast cancer. *Hematol Oncol Clin North Am* 1993;7:631-45.
- 23 Shpall EJ, Stemmer SM, Bearman SI, Jones RB. Role of autotransplantation in treatment of other solid tumours. *Hematol Oncol Clin North Am* 1993;7:663-86.
- 24 Johnson FL, Goldman S. Role of autotransplantation in neuroblastoma. *Hematol Oncol Clin North Am* 1993;7:647-62.
- 25 Schuster JL, Cantor AB, McWilliams N, Pole JG, Castleberry RP, Marcus R, et al. The prognostic significance of autologous bone marrow transplantation in advanced neuroblastoma. *J Clin Oncol* 1991;9:1045-9.
- 26 Gordon-Smith E. Acquired aplastic anaemia. In: Hoffman R, Benz E, Shattil S, Furie B, Cohen H, eds. *Haematology: basic principles and practice*. Edinburgh: Churchill Livingstone, 1991:161-72.
- 27 Borgna-Pignatti C. Bone marrow transplantation for the haemoglobinopathies. In: Treleaven J, Barrett J, eds. *Bone marrow transplantation in practice*. Edinburgh: Churchill Livingstone, 1992:151-60.
- 28 Lucarelli G, Weatherall DJ. For debate: bone marrow transplantation for severe thalassaemia. *Br J Haematol* 1991;78:300-3.
- 29 Weatherall DJ. The treatment of thalassaemia—slow progress and new dilemmas. *N Engl J Med* 1993;329:877-9.
- 30 Velodi A, Camba L, McCarthy D. Bone marrow transplantation for inborn errors of metabolism. In: Treleaven J, Barrett J, eds. *Bone marrow transplantation in practice*. Edinburgh: Churchill Livingstone, 1992:161-76.
- 31 Morgan G. Bone marrow transplantation for immunodeficiency syndromes. In: Treleaven J, Barrett J, eds. *Bone marrow transplantation in practice*. Edinburgh: Churchill Livingstone, 1992:119-36.
- 32 Davidson NE. Out of the courtroom and into the clinic. *J Clin Oncol* 1992;10:517-9.
- 33 Nicol AJ, Hows JM, Bradley BA. Annotation. Cord blood transplantation: a practical option. *Br J Haematol* 1994;87:1-5.
- 34 Morsy MA, Mitani K, Clemens P, Caskey CT. Progress toward human gene therapy. *JAMA* 1993;270:2338-45.

Controversies in Management

Should obstetricians see women with normal pregnancies?

Obstetricians should be included in integrated team care

Patrick Walker

This is the fifteenth in a series of articles examining some of the difficult decisions that arise in medicine

The expert maternity group which suggested that obstetricians should not see normal pregnancies¹ was, perhaps, unrepresentative. About 700 000 women each year in England and Wales are booked for care under a named consultant obstetrician. Yet the expert committee did not request formal input and had no representative from the Royal College of Obstetricians and Gynaecologists.²

Normality with respect to pregnancy, especially first pregnancy, is a retrospective diagnosis.³ If it could be confirmed that a woman would not require medical advice or help at any stage in a pregnancy, an obstetrician might not be strictly necessary. But this is not possible. In addition, unless obstetricians attend normal pregnancies they will have nothing to judge against when they look after women whose pregnancies are progressing abnormally. Women with abnormal pregnancies must be looked after by a someone who is regularly exposed to the full range of physiological and pathological patterns of pregnancy and labour. Would you be confident to be looked after by a cardiologist who had not listened to a normal heart for 20 years or a surgeon who had not seen normal anatomy since medical school?

The midwife alone cannot be gatekeeper. A team

approach is needed, including the midwife, general practitioner, and consultant. This ensures lateral as well as longitudinal continuity of care whatever arises.

Fire fighting obstetricians

The obstetrician as a fire fighter is also an untenable proposition. It does not make common or clinical sense and it is inappropriate for the empathic care of pregnant women. Even if we accept that midwives are always as good as doctors at spotting problems in pregnancy and labour at an early and appropriate time, the fire fighter strategy remains inappropriate. When problems arise in pregnancy, many of which require emergency treatment, it is one of the most stressful moments of a women's life. If it is important that women are cared for in labour by someone they know—as asserted by those arguing for midwife only care—surely it is even more essential that they know their obstetrician if more dangerous and interventional procedures are required.

In genuine team midwifery women whose pregnancies in retrospect are normal may have met the obstetrician only at booking and then received an informal courtesy visit in early labour from the

Royal Free Hospital,
London NW3 2QG
Patrick Walker, consultant
obstetrician

BMJ 1995;310:36-8