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The evolving role of haematopoietic cell transplantation in radiation injury: potentials and limitations

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Abstract. Human stem cell transplantation has been performed for over 50 years. A review of radiation incident registries indicates that, during this time, 31 patients have undergone transplantation with stem cells from the bone marrow, peripheral blood, cord blood or fetal liver. Among these cases, 27 patients have expired and the remaining 4 patients have survived with a rejected allograft. Limitations to success of transplantation have included concomitant injury to non-haematopoietic organs and immunological complications of the transplantation. Selection of cases for stem cell transplantation is based upon clinical signs and symptoms, including: (1) the rate of fall and the absolute level of circulating lymphocytes, granulocytes and platelets; (2) the absence of failure of a non-haematopoietic organ or system; and (3) individual dose assessment, as determined by clinical symptoms (such as time to onset and severity of vomiting), rate of decline in absolute lymphocyte count and the appearance of chromosome aberrations. Owing to a limited amount of resources, case selection in a large-volume scenario will necessarily be modified. Recently, recommendations have been drafted by the US Strategic National Stockpile Working Group that propose a limited dose range for which transplantation should be considered as a therapeutic option for victims in a large-volume scenario. Transplantation will continue to evolve as new sources of stem cells are identified, as efficient, high-yield stem cell purification protocols are defined, and as new methods are developed to improve stem cell function post transplantation.

Introduction

Although human marrow infusion was first reported in a woman with gold-induced aplasia in 1939 [1], it was not until 1951 that a report was published indicating that protection of bone marrow from lethal radiation injury is observed after intravenous infusion of marrow into rodents [2]. Transplantation following accidental radiation exposure in man was reported for the first time in 1958, when bone marrow was infused in five patients, four of whom showed prompt improvement in haematological status [3]. Nearly a decade later, a patient with accidental exposure received a transplant from an identical twin [4] wherein rapid post-transplant recovery of haematopoiesis suggested (but did not establish) that the syngeneic cells were the source of early repopulation of the marrow.

Today, haematopoietic cell transplantation is an effective modality of treatment for individuals with haematological, oncological and non-malignant disease. Development of our knowledge of transplantation biology and advances in supportive care have resulted in dramatically reduced morbidity and mortality of transplantation. Two strategies may be used for treatment with haematopoietic cell transplantation. The first strategy aims to ablate host bone marrow with chemotherapy and/or radiotherapy in order to remove cells with a malignant phenotype. The objective of transplantation is to obtain full donor chimerism. The second strategy employs immunosuppression without myeloablation (*i.e.* non-myeloablative therapy) with the goal of attaining limited chimerism.

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Since individuals exposed to ionising radiation have received variable and somewhat uncertain doses of radiation, use of non-myeloablative haematopoietic cell transplantation could provide effective therapy. Re-institution of effective lymphohaematopoiesis during a critical time of haematopoietic failure may provide enough time for re-expansion of residual haematopoietic stem cells that may have escaped radiation exposure or that may include a small number of relatively radioresistant stem cells [5]. This manuscript will briefly review the experience of haematopoietic cell transplantation among individuals who have been accidentally irradiated. A summary of reports will show that whilst transient engraftment with partial chimerism has been achieved in nearly all patients who have undergone reconstitution of haematopoiesis from endogenous haematopoietic cells, the overall outcome has been disappointing.

Registries of victims of radiological events

The acute effects of total body radiation are detailed in registries of radiation victims that have been established primarily over the past 50 years. These include the information maintained by the Atomic Bomb Casualty Commission (currently, the Radiation Effects Research Foundation) and the International Atomic Energy Radiation Accident Registry. The Radiation Emergency Assistance Center/Training Site (REAC/TS) Registry has been cataloguing radiation accidents for the past 25 years [6]. An emphasis on clinical presentation, therapy and outcomes has been the focus of data maintained in the Moscow/Ulm Radiation Accident Clinical History Database and its successor, The International Computer Database for Radiation Exposure Case Histories [7].

Table 1. Major radiation accidents worldwide classified by device, 1944–November 2003

Criticalities	20
Critical assemblies	8
Reactors	6
Chemical operations	6
Radiation devices	315
Sealed sources	208
X-ray devices	82
Accelerators	24
Radar generators	1
Radioisotopes	91
Transuranics	28
Tritium	2
Fission products	11
Radium spills	1
Diagnostic and therapy	38
Other	11
Total	426

Source: Radiation Emergency Assistance Center/Training Site Radiation Accident Registry.

Together, these registries provide an invaluable source of information that may be used to derive therapeutic strategies for victims of radiation exposure.

As of November 2003, the REAC/TS registry lists 426 major radiation accidents since 1944 (see Table 1). Approximately three-quarters of these accidents have involved radiation devices, including sealed sources, X-ray devices, accelerators and radar generators. Of these accidents, 253 have occurred in the USA, involving 1361 individuals, 801 of whom have had a significant exposure (as defined by criteria established by the US Department of Energy/Nuclear Regulatory Commission). The remainder of accidents have occurred outside the USA, and have involved 132 441 persons (including 116 500 from Chernobyl, 249 from Brazil, 4000 from Mexico, 10 180 from Kyshytm and 27 from Spain). Among the exposed persons involved in non-USA accidents, 2252 have had significant exposures. A total of 134 fatalities (30 from accidents in the USA and 104 from accidents outside the USA) have occurred. This information is reviewed in Table 2.

Summary of outcomes of transplantation

Transplantation with stem cells from the bone marrow (22 cases), peripheral blood (1 case), cord blood (1 case) and fetal liver (7 cases) has taken place in 31 patients who have suffered a significant radiation exposure. Among these transplanted cases, 27 patients expired and 4 patients survived with rejection of the allograft. A summary of the outcome and contributing causes of death in these 31 cases is provided in Table 3. This analysis includes data compiled in the International Computer Database for Radiation Exposure Case Histories [7], the REAC/TS Registry and victims in the Tokaimura accident [8]. Significant injury to non-haematopoietic organs was evident in the majority of expired cases. Non-haematopoietic injury included radiation burns (63%), gastrointestinal syndrome (41%), documented infection (26%), graft-versus-host disease (GVHD) (22%), adult respiratory distress syndrome (ARDS) (22%), acute renal failure (7%) and host-versus-graft disease (HVGD) (4%). The majority of expired cases had more than one of these clinical findings.

Among the four patients who survived with a rejected allograft are two cases receiving transplantation with T-cell-depleted, human leukocyte antigen (HLA)-identical cells, one case transplanted with human fetal liver cells, and one case receiving cells from a syngeneic donor. It is possible that some benefit was derived from transient engraftment in these cases.

These results suggest that whilst transient engraftment is possible in the radiation victim, outcomes are poor, particularly when injury to a non-haematopoietic organ has occurred. In the absence of a control group of cases having a similar degree of toxicity, it is difficult to say whether or not transplantation impacts survival. Nevertheless, overall survival in two cases (one receiving a peripheral blood stem cell transplantation and the other receiving a cord blood transplantation) from the Tokaimura accident was possibly longer than expected considering the radiation dose and organ toxicity. In both of these cases, state of the art support therapy was provided together with immunological prophylaxis for GVHD [8].

Table 2. Major radiation accidents worldwide: human experience 1944–2003

Location	Persons involved	Significant exposures[a]	Fatalities
USA	1361	801	30
Non-USA	132441	2252	104
Total	133802	3053	134

Source: Radiation Emergency Assistance Center/Training Site Radiation Accident Registry.

[a]As defined by criteria established by the US Department of Energy and Nuclear Regulatory Commission.

Table 3. Outcome and contributing causes of death in 31 transplant cases. (Prepared with modification from [20])

Clinical finding	Number	% expired
27 patients expired		
Radiation burns	17	63
Gastrointestinal syndrome	11	41
Infection (documented)	7	26
GVHD	6	22
ARDS	6	22
Acute renal failure	2	7
HVGD	1	4

4 patients survived and rejected grafts

Type of transplant	Number
T-cell-depleted, HLA-identical transplant	2
Fetal liver cell transplant	1
Syngeneic transplant	1

GVHD, graft-versus-host disease; ARDS, adult respiratory distress syndrome; HVGD, host-versus graft disease; HLA, human leukocyte antigen.

Limitations to transplantation in radiological events

In addition to concomitant injury to non-haematopoietic organs, several barriers to transplantation limit its effectiveness. Since autologous haematopoietic cells are unlikely to have been stored prior to radiation exposure (with the likelihood approaching 0%), and because the availability of a syngeneic donor from an identical twin is limited to <1% of the population, it is overwhelmingly likely that appropriately selected patients will undergo an allogeneic transplant procedure. Successful transplantation of allogeneic cells must cross two immunological barriers, both of which are mediated by T-cells: the graft-versus-host barrier and the host-versus-graft barrier. As evident from Table 3, failure to cross either of these barriers may contribute to mortality in irradiated patients receiving allotransplantation.

The importance of the HLA system has been well documented in predicting outcome of allogeneic marrow transplantation. The rate of graft failure using marrows from donors who are haplotype-matched was approximately 12.3% compared with a rate of 2% in individuals receiving HLA-matched allogeneic cells [9]. Since recipient T-cells appear to mediate graft rejection [10, 11], whilst donor T-cells appear to mediate GVHD [12, 13], use of immune modulation in non-myeloablative allografts may ameliorate these complications. Results of pre-clinical studies in dogs suggest that selective inhibition of lymphocyte replication with mycophenolate mofetil (a blocker of purine synthesis in T- and B-cells) results in highly effective post-grafting immunosuppression and increased long-term, stable mixed chimerism following irradiation [13]. This approach may prove beneficial to victims of a radiological event who receive a transplant and may supplement more traditional immunosuppressive agents such as cyclosporine, methotrexate, steroids and tacrolimus.

Another barrier to performing successful allogeneic transplantation is the considerable length of time it takes to conduct a search for an appropriate donor. Although this search was unusually rapid for victims receiving a transplant in the Tokaimura incident (*i.e.* days), a typical search for allogeneic donors by the National Marrow Donor Program (NMDP) in the USA requires 1–2 weeks for cord blood selection and 2–3 months for selection of bone marrow and peripheral blood stem cells [14]. Thereafter, it may take days to weeks to procure these cells. Depending on the degree of haematopoietic toxicity, radiological victims may succumb during the time required for completion of a successful search, delivery of the product and establishment of engraftment.

Methods are therefore needed to decrease the time required for a search. Application of new technology such as molecular HLA typing of buccal cells [15] may possibly reduce tissue collection time and is potentially applicable to unrelated donor transplantation, particularly when a large number of individuals must be typed. Nevertheless, regulatory and administrative issues must still be addressed. Recently, pilot programmes have demonstrated that search time can be reduced to 1–2 weeks for high priority, unrelated donor searches by the German Deutsche Knochenmarkspenderdatei (DKMS) and the NMDP registries [14], which approaches the search time for cord blood cells. The cost for searches may be substantial, thereby adding another potential impediment to transplantation, particularly in the case of mass casualties. Whilst donor registries worldwide have enlarged to over 9 million donors, two-thirds of whom have been HLA-A, B, DR typed [16], tissue banks of significant size that include genetically diverse populations should be developed to provide product in a rapid fashion. Additional limitations to transplant include difficulty in performing HLA testing in individuals who are profoundly lymphopenic from radiation exposure, and age limitations for potential recipients.

Criteria for selection of cases for transplantation

In view of these barriers to successful transplantation, it is essential that victims of a radiological incident are carefully evaluated for eligibility to receive a stem cell transplant. The clinical decision-making process is aided by a tool developed by the Medical Treatment Protocols (METREPOL) team, which assigns a score based upon the presence and severity of clinical signs and symptoms [17]. Integration of clinical information regarding the cutaneous, haematological, gastrointestinal and neurovascular systems with laboratory information (including the absolute level of circulating lymphocytes, granulocytes and platelets) may be used to assign a physiological "response category". Patients with an advanced level of toxicity (haematopoietic grades 3 and 4) are candidates for admission to a critical care unit and treatment with growth factors and possibly stem cell transplantation [17]. Patients assigned grade 4 toxicity to the haematopoietic system are most unlikely to have autologous haematopoietic recovery, making them potentially ideal candidates for transplantation [18]. The importance of integrating clinical and laboratory methods (including time to onset and severity of vomiting, rate of decline in absolute blood lymphocyte count and the appearance of chromosome aberrations such as dicentric and ring forms) to assess individual radiation dose has been also emphasised [19].

Whilst the above approach is ideal for selecting cases for transplantation in a small-volume scenario, its application to a mass casualty event is limited by logistical issues, the potential loss of infrastructure, and a finite amount of human, technical and physical resources.

Recommendations for transplantation have been drafted by the US Strategic National Stockpile Working Group [20, 21] in the case of a large-volume scenario that of necessity must deal with these issues. These guidelines may not be applicable to a radiological event involving one or several victims. Moreover, they do not substitute for physician judgement of an individual case.

The proposed range of radiation doses for referral for consideration of transplantation is 7–10 Gy for allogeneic transplant and >4 Gy for autologous or syngeneic transplantation (see Table 4). Transplantation is recommended only for individuals who do not suffer significant injury to other body organs such as significant burns, gastrointestinal toxicity, renal or hepatic toxicity, pulmonary failure, neurovascular syndrome, systemic immune response syndrome or diffuse intravascular coagulation. As predicted by mathematical models of granulocytic cell renewal developed by Fliedner and colleagues [22],

Table 4. Recommendations of the Strategic National Stockpile Working Group for Transplantation

Group	Type	Exposure dose (Gy)
Healthy individuals (no other injuries)	Allogeneic	7–10
	Autologous	4–10
	Syngeneic	4–10
Multiple injuries (combined injury)[a]	Not recommended	

[a]Haematopoietic toxicity in the setting of failure of other organ systems.

individuals with a granulocyte count of >500/μl and a platelet count of >100 000/μl at 6 days after exposure are believed to have substantial evidence for endogenous regeneration of haematopoiesis, thereby precluding transplantation as a therapeutic option [17, 21]. Nevertheless, since some individuals receiving high radiation dose may develop a rapid decline in granulocyte count to <500/μl on days 6–8 and still undergo spontaneous recovery of haematopoiesis [23], better tools must be developed to identify exposed individuals for transplantation [24].

New directions and potentials of transplantation

Additional sources of stem cells and/or purified stem cells may by worthy of investigation as alternative therapy not only to obviate recognised barriers but also to improve recovery of the haematopoietic system (and, potentially, other non-haematopoietic systems). The embryo has been found to be one potential source of transplantable cells [25]. Embryonic stem (ES) cells are clonogenic and appear to have ''unlimited'' self-renewal capacity by symmetric division. Alternatively, ES cells may divide asymmetrically to give rise to two daughter cells, each having a distinct proliferative capacity. Technically, it is difficult to maintain human ES cells in an undifferentiated state. Recently, culture conditions have been defined to promote their isolation from the inner cell mass (ICM) and their expansion *in vitro* [26–28] (see Figure 1). Pluripotent stem cells have been found to give rise to multiple cell types found in different organs through the differentiation and clonal expansion of ''tissue-specific'' multipotent stem cells.

Human germ cells can be isolated from the fetal gonad and expanded *in vitro* under defined conditions [29]. Whilst human ES cells from the ICM have been successfully cultured, testing for their proliferative capacity in man is untenable, as re-implantation experiments into a human embryo is unethical. Moreover, rare ''abnormal'' cells such as cancer stem cells cannot be excluded. Without rigorous study, there is no assurance that human ES cells possess the same potential as murine ES cells.

During the past several years, numerous scientific laboratories have described the potential for adult stem cells from one tissue to undergo differentiation into cells of another tissue (reviewed in [30] and [31]). Table 5 provides a summary of tissue sources for stem cells that are capable of transdifferentiation. Owing to our extensive technical knowledge of isolation of bone marrow stem cells, some of which may be purified as a side population by fluorometric cytometry, it is feasible to label and track haematopoietic

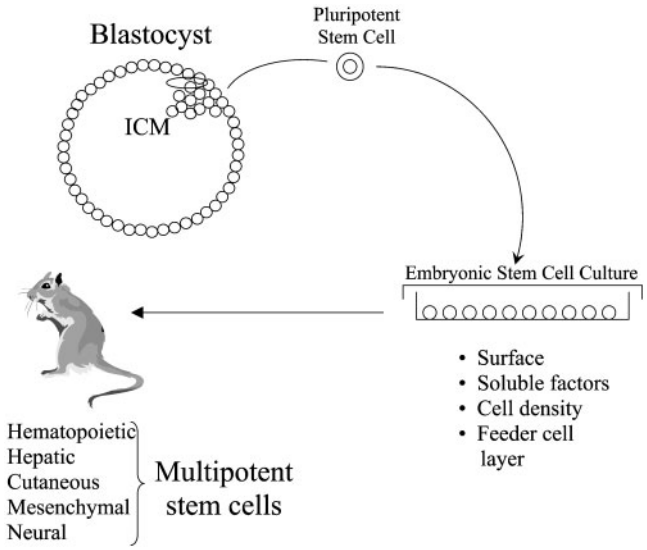

Figure 1. Origin of pluripotent and multipotent stem cells. Pluripotent embryonic stem (ES) cells reside in the inner cell mass (ICM) of the blastocyst. The ICM that forms the human embryo can be isolated and expanded *in vitro* under appropriate culture conditions that include cells cultured at an appropriate density on plastic surfaces in the presence of soluble growth factors. Recently, the requirement for a mouse feeder-cell layer has been overcome [26]. Following insertion of murine ES cells into a blastocyst from a genetically distinct mouse, a chimeric offspring develops in which some of the cultured ES cells differentiate into each tissue. Multipotent stem cells are intermediate stem cells that are thought to be generally restricted to the lineage of a specific organ.

stem cells in the circulation and target tissues [32]. This approach has identified descendants of bone marrow stem cells in multiple tissues, including the liver, lung, gastrointestinal tract and skin [33]. Bone marrow cells capable of yielding non-haematopoietic tissues (including endothelium, cardiac muscle, neurons and hepatocytes) after transplantation have been isolated from purified populations that include LIN–KIT+ cells, $CD34_{LO}$, SCA-1+KIT+

Table 5. Potential plasticity of stem cells

Location of stem cell	Type of cell generated
Brain	Neurons, oligodendrites, skeletal muscle, blood cells
Bone marrow	Endothelial cells, blood cells, cartilage, bone, adipocytes, cardiac muscle, skeletal muscle, neuronal cells, skin, oval cells, gastrointestinal tract cells, thymus, pulmonary epithelial cells
Skeletal muscle	Skeletal muscle, bone, cartilage, fate, smooth muscle
Myocardium	Myocytes, endothelial cells
Skin	Keratinocyte
Liver	Liver cells
Testis and ovaries	Gonads
Pancreatic ducts	Islet cells
Fatty tissue	Fat, muscle, cartilage, bone

Modified from reference [27] with permission.

cells, CD34+LIN– cells, LIN–SCA-1+KIT+ cells and CD34+KIT+FLK1+AC133+ cells (reviewed in [34]).

Nevertheless, caution has been urged in interpreting the broad range of stem cell versatility, as some investigators have been unable to detect an appreciable number of non-haematopoietic stem cell progeny in haematopoietic tissue [35], whilst other investigators have argued that an appropriate standard for functional transdifferentiation has not been met [36, 37]. In fact, several recent reports have indicated that rather than transdifferentiation, spontaneous fusion of transplanted stem cells occurs with cells of developed tissues [38–40].

Since adult bone marrow mesenchymal stem cells appear to be capable of differentiation into all three embryonic germ layers (*i.e.* mesoderm, neuroectoderm and endoderm) [41], use of stromal cells from adult bone marrow may provide another potential source of cells for transplantation. However, it has been estimated that >99% of marrow mesenchymal stem cells die within 4 days following transplantation into healthy nude-mouse hearts [42]. New approaches are therefore needed to overcome barriers such as peri-transplantation graft cell death [43]. For example, overexpression of Akt, a serine–threonine kinase and cell survival signal, improves viability and enhances cardiac repair after transplantation of adult bone marrow-derived mesenchymal stem cells into ischaemic rat heart [44].

Conclusions

The role of haematopoietic cell transplantation in the treatment of victims of a radiological event is in evolution. Determinants of its future will include continued technical advances in stem cell isolation and expansion, as well as application of novel approaches to improve their functionality following transplantation. Acceleration of the donor selection process, application of improved immunotherapy and use of non-myeloablative conditioning regimens may all improve outcomes of transplant victims.

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References

1. Osgood EE, Riddle MC, Mathew TJ. Aplastic anemia treated with daily transfusions and intravenous marrow: case report. Ann Intern Med 1939;13:357.
2. Lorenz E, Uphoff D, Reid TR, Shelton E. Modification of irradiation injury in mice and guinea pigs by bone marrow injections. J Natl Cancer Inst 1951;12:157.
3. Jammet H, Mathe G, Pendic B, Duplan JF, Maupin B, Latarjet R, et al. Etude de six cas d'irridation totale aigue accidentelle. Rev Fr Etud Clin Biol 1959;4:210–25.
4. Gilbert MV. The 1967 radiation accident near Pittsburgh, Pennsylvania and a follow-up report. In: Hubner KF, Fry SA, eds. Medical basis for radiation accident preparedness. Amsterdam, The Netherlands: Elsevier North Holland, 1980:131–40.
5. Inoue T, Hirabayashai Y, Mitsui H, Sasaki H, Cronkite EP, Bullis JE, et al. Survival of spleen colony-forming units (CFU-S) of irradiated bone marrow cells in mice: evidence for the existence of a radioresistant subfraction. Exp Hematol 1995;23:1296.
6. Ricks RC. The radiation-accident patient in the new millennium: past history and future threats. In: Ricks RC, Berger ME, O'Hara FM, eds. The medical bases for radiation-accident preparedness: the clinical care of victims. Boca Raton, FL: The Parthenon Publishing Group, 2002:1–9.
7. Densow D, Kindler H, Baranov AE, Tibken B, Hofer EP, Fliedner TM. Criteria for the selection of radiation accident victims for stem cell transplantation. Stem Cells 1997;15(Suppl. 2):287–97.
8. Maekawa K. Overview of medical care for highly exposed victims in the Tokaimura accident. In: Ricks RC, Berger ME, O'Hara FM, eds. The medical bases for radiation-accident preparedness: the clinical care of victims. Boca Raton, FL: The Parthenon Publishing Group, 2002:313–8.
9. Anasetti C, Amos C, Beatty PG, Appelbaum FR, Bensinger W, Buckner CD, et al. Effect of HCA compatibility on engraftment of bone marrow transplants in patients with leukemia or lymphoma. New Engl J Med 1989;320:197.
10. Kernan NA, Flomenberg N, Dupont B, O'Reilly RJ. Graft rejection in recipients of T-cell-depleted HCA-non-identical marrow transplants for leukaemia. Transplantation 1987;43: 842–7.
11. Bosserman LD, Murray C, Takvorian T, Anderson KC, Freedman AS, Fitzsimmons J, et al. Mechanism of graft failure in HLA-matched and HLA-mismatched bone marrow transplant recipients. Bone Marrow Transplant 1989;4: 239–45.
12. Simpson E. Minor transplantation antigens: animal models for human host-versus-graft, graft-versus host, and graft-versus-leukemia reactions. Transplantation 1998;43:611–6.
13. Georges GF, Storb RF. Experimental and clinical experience with hematopoietic stem cell transplants. In: Ricks RC, Berger ME, O'Hara FM, eds. The medical bases for radiation-accident preparedness: the clinical care of victims. Boca Raton, FL: The Parthenon Publishing Group, 2002:73–93.
14. Confer DL. Use of hematopoietic stem cell transplants: cord blood, peripheral blood and bone marrow. Presented at Conference on Medical Planning and Care in Radiation Accidents; Oak Ridge; 2003 March 3–7.
15. Saftlas AF, Waldschmidt M, Logsden-Sackett N, Triche E, Field E. Optimizing buccal cell DNA yields in mothers and infants for human leukocyte antigen genotyping. Am J Epidemiol 2004;160:77.
16. Updated online at http://www.bmdw.org [accessed 18 January 2005].
17. Fliedner TM, Friesecke I, Beyrer K. Medical management of radiation accidents: manual on the acute radiation syndrome. London, UK: British Institute of Radiology, 2001.
18. Dainiak N. Hematologic consequences of exposure to ionizing radiation. Exp Hematol 2002;30:513.
19. Fliedner TM, Graessle D, Reimers K, Weis M, Paulsen C. Stem cell transplantation in radiation accidents. In: Medical aspects of radiation emergency: the criticality accident in Tokaimura. Chiba, Japan: National Institute of Radiological Sciences, 2000:228–35.
20. Dainiak N, Waselenko JK, Armitage J, Farese AM, MacVittie TJ. The hematologist and radiation casualties. Hematology (Am Soc Hematol Educ Program) 2003: 472–95.
21. Waselenko JK, MacVittie TJ, Blakely WF, Pesik N, Wiley AL, Dickerson WE, et al. Medical management of acute radiation syndrome: recommendations of the Strategic National Stockpile Radiation Working Group. Ann Intern Med 2004;140:1037–51.

22. Fliedner TM, Tibken B, Hofer EP, Paul W. Stem cell response after radiation exposure: a key to the evaluation and prediction of its effects. Health Phys 1996;70:787–96.
23. Baranov A, Guskova A, Nadejina N, Nugis VY. Chernobyl experience: biological indicators of exposure to ionizing radiation. Stem Cells 1995;13(Suppl. 1):69–77.
24. Dainiak N, Sorba S. Early identification of radiation accident victims for therapy of bone marrow failure. Stem Cells 1997;15(Suppl. 2)275–85.
25. Nagy A, Rossant J, Nagy R, Abramow-Newerly W, Roder JC. Derivation of completely cell culture-derived mice from early-passage embryonic stem cells. Proc Natl Acad Sci USA 1993;90:8424–8.
26. Xu C, Inokuma MS, Denham J, Golds K, Kundu P, Gold JD, et al. Feeder-free growth of undifferentiated human embryonic stem cells. Nat Biotechnol 2001;19:971–4.
27. Amit M, Carpenter MK, Inokuma MS, Chiu CP, Harris CP, Waknitz MA, et al. Clonally derived human embryonic stem cell lines maintain pluripotency and proliferative potential for prolonged periods of culture. Dev Biol 2000;227:271–8.
28. Schuldiner M, Yanuka O, Itskovitz-Eldor J, Melton DA, Benvenitsy N. Effects of eight growth factors on the differentiation of cells derived from human embryonic stem cells. Proc Natl Acad Sci USA 2000;97:11307–12.
29. Shamblott MJ, Axelman J, Littlefield JW, Blumenthal PD, Huggins GR, Cui Y, et al. Human embryonic germ cell derivatives express a broad range of developmentally distinct markers and proliferate extensively in vitro. Proc Natl Acad Sci USA 2001;98:113–8.
30. Rosenthal N. Prometheus's vulture and the stem-cell promise. New Engl J Med 2003;349:267–74.
31. Kuehnle I, Goodell MA. The therapeutic potential of stem cells from adults. BMJ 2002;325:372–6.
32. Goodell MA, Rosenzweig M, Kim H, Marks DF, DeMaria M, Paradis G, et al. Dye efflux studies suggest that hematopoietic stem cells expressing low or undetectable levels of CD34 antigen exist in multiple species. Nat Med 1997;3:1337–45.
33. Kraus DS, Theise ND, Collector MI, Henegariu O, Hwang S, Gardenr R, et al. Multi-organ, multi-lineage engraftment by a single bone marrow-derived stem cell. Cell 2001;105:369–77.
34. Graf T. Differentiation plasticity of hematopoietic cells. Blood 2002;99:3089–100.
35. Morshead CM, Benveniste P, Iscove NN, vander Kooy D. Hematopoietic competency is a rare property of neural stem cells that may depend on genetic and epigenetic alterations. Nat Med 2002;3:268–81.
36. Morrison SJ. Stem cell potential: can anything make anything? Curr Biol 2000;11:R7–9.
37. Anderson DJ, Gage FH, Weissman IL. Can stem cells cross lineage boundaries? Nat Med 2001;7:393–5.
38. Wagers AJ, Sherwood RJ, Christensen JL, Weissman IL. Little evidence for developmental plasticity of adult hematopoietic stem cells. Science 2002;297:2256–9.
39. Vassilopouos G, Wang PR, Russell DW. Transplanted bone marrow regenerates liver by cell fusion. Nature 2003;422:901–4.
40. Terada N, Hamazaki T, Oka M, Hoki M, Mastalerz DM, Nakano Y, et al. Bone marrow cells adopt the phenotype of other cells by spontaneous cell fusion. Nature 2002;416:542–5.
41. Jiang Y, Jahagirdar BN, Reinhardt RL, Schwartz RE, Keene CD, Ortiz-Gonzalez XR, et al. Pluripotency of mesenchymal stem cells derived from adult marrow. Nature 2002;418:41–9.
42. Toma C, Pittenger MF, Cahill KS, Byrne BJ, Kessler PD. Human mesenchymal stem cells differentiate to a cardiomyocyte phenotype in the adult murine heart. Circulation 2002;105:93–8.
43. Zhang M, Methot D, Poppa V, Yasushi F, Walsh K, Murry CE. Cardiomyocyte grafting for cardiac repair: graft cell death and anti-death strategies. J Mol Cell Cardiol 2001;33:907–21.
44. Mangi AA, Noiseaux N, Kong D, He H, Rezani M, Ingwall JS, et al. Mesenchymal stem cells modified with Akt prevent remodeling and restore performance of infarcted hearts. Nat Med 2003;9:1195–201.