1539

remains the gold standard for assessing suitability for transplant.

Procurement personnel must always consider the possibility of litigation whenever potentially diseased or defective organs are to be transplanted. Ordinary negligence liability may result if the disease or defect is discoverable with reasonable efforts using standard medical practices. Generally, the medical history is reviewed to rule out vascular disease, infection, or cancer, but further testing (e.g., biochemical, biopsy, autopsy, slit lamp exams of corneas, or coronary angiography in patients over 40) may be required as standard practice in some locales (*21*).

Victims of cyanide poisoning have previously been described as suitable kidney (*19*) and corneal transplant donors, provided the corneoscleral tissue is rinsed thoroughly and maintained in a tissue-storage medium containing glucose (*20*). To our knowledge, however, this is the first report of successful multiple organ donation from a victim of cyanide poisoning. In this case, the lack of histological or biochemical evidence of irreversible cardiac, hepatic, or renal damage provided the basis for proceeding with multiple-organ transplantation over the objections of several surgeons.

In summary, we stress that careful donor evaluation and testing should be undertaken before excluding poisoned patients as suitable donor candidates. In the absence of transmissible disease and significant end-organ damage, mere presence or clinical effect of a toxicant should not automatically result in donor exclusion. Cyanide poisoning is only an example, and a rare one at that, of how the donor pool may be safely expanded. Brain death associated with exposure to carbon monoxide, hydrogen sulfide, azide, or oxidizing agents (causing methemoglobinemia) may also warrant evaluation for organ procurement. The nature and extent of testing required to exclude a poisoning victim will continue to evolve and will increasingly depend on what is known about mechanisms of cell injury initiated by a particular agent.

JACK W. SNYDER,[1]
DAVID W. UNKLE[2]
HOWARD M. NATHAN[2]
SHUIN-LIN YANG[3]
The Department of Medicine
The Department of Pathology
The Department of Surgery
Thomas Jefferson University
The Delaware Valley Transplant Program
Philadelphia, Pennsylvania

[1] The Departments of Medicine and Pathology, Thomas Jefferson University.

[2] The Delaware Valley Transplant Program.

[3] Address reprint requests to Shuin-Lin Yang, M.D., Department of Surgery, Thomas Jefferson University, Jefferson Medical College Building, 1025 Walnut St., Room 605, Philadelphia, PA 19107.

REFERENCES

1. Gilmore A. Procuring donor organs: firm but friendly encouragement required. Can Med Assoc J 1986; 134: 932.
2. UNOS Update Sept 1991; 7: 14.
3. Report to organ procurement agencies. UNOS Statistics June 1990.
4. Nathan HM, Jarrell BE, Broznik B, et al. Estimation and characterization of the potential renal organ donor pool in Pennsylvania. Transplantation 1991; 51: 142.
5. Soifer BE, Gelb AW. The multiple organ donor: identification and management. Ann Intern Med 1989; 110: 814.
6. Darby JM, Stein K, Grenvik A, Stuart SA. Approach to management of the heartbeating "brain dead" organ donor. JAMA 1989; 261: 2222.
7. Starzl TE, Hakala TR, Shaw BW Jr, et al. A flexible procedure for multiple cadaveric organ procurement. Surg Gynecol Obstet 1984; 158: 223.
8. Hardesty RL, Griffith BP. Multiple cadaveric organ procurement for transplantation with emphasis on heart, liver, and kidneys. Surg Clin North Am 1986; 66: 451.
9. Rosenthal JT, Shaw BW Jr, Hardesty RL, Griffith BP, Starzl TE, Hakala TR. Principles of multiple organ procurement from cadaver donors. Ann Surg 1983; 198: 617.
10. Todo S, Nery J, Yanaga K, Podesta L, Gordon R, Starzl TE. Extended preservation of human liver grafts with UW solution. JAMA 1989; 261: 711.
11. Belzer FO, Southard JH. Principles of solid-organ preservation by cold storage. Transplantation 1988; 45: 673.
12. Robinette MA, Marshall WJ, Arbus GS. The donation process. Transplant Proc 1985; 17 (6, suppl 3): 45.
13. Vogel SN, Sultan TR, Ten Eyck RP. Cyanide poisoning. Clin Toxicol 1981; 18: 367.
14. Hall AH, Rumack BH. Cyanide. In: Haddad LM, Winchester JF, eds. Clinical management of poisoning and drug overdose. Philadelphia: Saunders, 1990: 1104.
15. Christel D, Eyer P, Hegemann M, Kiese M, Lorcher W, Weger N. Pharmacokinetics of cyanide poisoning in dogs, and the effects of 4-dimethylaminophenol or thiosulfate. Arch Toxicol 1977; 38: 177.
16. Sylvester DM, Hayton WL, Morgan RL, Way JL. Effects of thiosulfate on cyanide pharacokinetics in dogs. Toxicol Appl Pharmacol 1983; 69: 265.
17. Ellenhorn MJ, Barceloux DG. Cyanide. In: Ellenhorn MJ, Barceloux DG, eds. Medical toxicology: diagnosis and treatment of human poisoning. New York: Elsevier, 1988: 829.
18. Hall AH, Rumack BH. Clinical toxicology of cyanide. Ann Emerg Med 1986; 15: 1067.
19. Brown PWG, Buckels JAC, Jain AB, McMaster P. Successful cadaveric renal transplantation from a donor who died of cyanide poisoning. Br Med J 1987; 294: 1325.
20. Lindquist TD, Oiland D, Weber K. Cyanide poisoning victims as corneal transplant donors. Am J Ophthalmol 1988; 106: 354.
21. Weedn VW. Donor, donee patients. In: American College of Legal Medicine, eds. Legal medicine—legal dynamics of medical encounters. St. Louis, MO: Mosby, 1988: 355.

Received 26 December 1991.
Accepted 4 May 1992.

PARVOVIRUS B19 INFECTION CAUSING PURE RED CELL APLASIA IN A RECIPIENT OF PEDIATRIC DONOR KIDNEYS[1]

Parvovirus B19, a recently discovered single-stranded DNA virus, is a known cause of chronic anemia in immunocompromised patients. This virus has been identified as the etiologic agent of the common childhood mild febrile exanthem erythema infectiosum, or "fifth disease", as well as a chronic arthralgia in children and adults that is symptomatically similar to rheumatoid arthritis. At least one fatality from acute

[1] This work was supported in part by grants from the Iowa City Veterans Affairs Research Fund (to S.J.N.).

myocarditis in a one-year-old child has been reported (*1*). Transient aplastic anemia has been reported in infected patients with congenital hemolytic anemia such as sickle cell disease (*2*), whereas chronic anemia affects immunocompromised hosts with acquired immunodeficiency syndrome (*3*) and acute lymphocytic leukemia (*4, 5*), and it has been reported in a 14 year-old girl following bone marrow transplantation (*6*). Only one previous report of parvovirus B19–producing anemia in a solid-organ transplant, that of a cadaveric renal transplant recipient receiving cyclosporine, appears in the literature (*7*). We report the case of a pediatric en bloc renal transplant recipient on FK506 with pure red cell aplasia and peripheral pancytopenia caused by parvovirus B19 that were responsive to commercial immunoglobulin administration.

The patient was a 62 year-old man with diabetic and hypertensive nephropathies and a history of gout, who underwent cadaveric renal transplantation using pediatric-donor kidneys in an en bloc fashion in February, 1990. At the time of transplant, the recipient's serologic titers were negative for hepatitis B surface antigen, anti–hepatitis B antibody, anticytomegalovirus IgM, and anti–human immunodeficiency virus antibody, while titers were positive for anticytomegalovirus IgG at 1:69, and for antihepatitis A IgG by ELISA. The donor was a 16-month-old girl who died of suspected cardiac arrest secondary to anoxia. She exhibited flu-like symptoms approximately 48 hr prior to the arrest. Donor serologic titers were negative for anti–cytomegalovirus, hepatitis, and human immunodeficiency virus antibodies. Parvovirus titers were not performed on donor or recipient sera, as they are not included in routine pretransplant serologic testing. The recipient was discharged 17 days posttransplant with a creatinine of 1.5 mg/dl and a hematocrit of 33.1% on an immunosuppressive regimen of FK506 (0.1 mg/kg b.i.d.) and prednisone (10 mg q.d.). He remained well until readmission one year posttransplant for an exacerbation of gouty arthritis affecting multiple joints, confirmed by fluid aspiration and treated by steroid injections and colchicine. At the time of admission, the patient was noted to be pancytopenic. Total WBC count was 1700/mm^3, hematocrit 22.7%, platelet count 52,000, and reticulocyte count 0.1%, with normal red cell indices. Bone marrow aspiration and biopsy at that time revealed markedly decreased erythroid maturation with normal myeloid series and megakaryocytes, and increased iron stores (Fig. 1A). No viral inclusions were present. The serum anticytomegalovirus IgG titer was positive at 1:106 and the IgM titer was equivocal at 1:15. However, urine, throat swab, and buffy coat CMV cultures and the early antigen assay remained negative. Colchicine and prophylactic trimethoprim/sulfamethoxazole were discontinued as they were thought to be likely causes of the patient's erythroid hypoplasia. His leukopenia and thrombocytopenia improved, and, following transfusion, the patient's hematocrit stabilized at 27.7%. During the subsequent month, the patient received ten outpatient transfusions of packed red blood cells. He was readmitted one month after discharge with chest pain, and subsequently a myocardial infarction was excluded by enzyme and EKG criteria. At this second admission, his hematocrit was 21.6%, his total WBC count was 1700/mm^3, his platelet count was 111,000, and his reticulocyte count was 0.1%. A peripheral blood smear revealed moderate microcytosis with rare anisocytosis and hypochromia. The serum erythropoietin level was elevated at 2820 mU/ml (normal 4–26). His chest pain resolved completely after transfusion of two units of packed red blood cells. Repeat cytomegalovirus cultures and early antigen detection were negative. Antiparvovirus IgG was detected by western blot analysis of the patient's serum (Specialty Laboratories, Los Angeles, CA)—however, antiparvovirus IgM was undetectable. Repeat bone marrow aspiration and biopsy revealed essentially complete erythroid aplasia (Fig. 1C) except for rare giant pronor-

FIGURE 1. Bone Marrow Morphology. (A) Bone marrow core biopsy on previous admission demonstrating erythroid hypoplasia. Myeloid cells and megakaryocytes are present. Intranuclear inclusions are not seen (H&E; ×400). (B) Giant pronormoblast present in the marrow aspirate on second admission (Wright-Giemsa; ×1000). (C) Bone marrow core biopsy on second admission illustrating numerous intranuclear inclusions (arrowheads) suggestive of viral infection. Infected cells are most likely red cell series precursors (H&E; ×400).

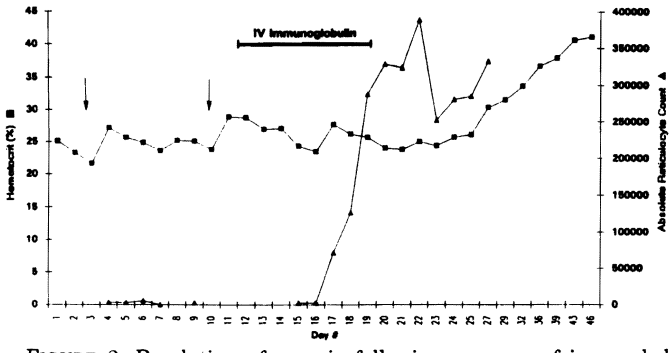

FIGURE 2. Resolution of anemia following a course of i.v. pooled immunoglobulin. Hematocrit levels are indicated by closed squares, and absolute reticulocyte counts by closed triangles. Arrows indicate transfusion of packed erythrocytes.

moblasts (Fig. 1B). Numerous eosinophilic intranuclear inclusions were noted in marrow cells (Fig. 1C, arrows) suggestive of viral infection. The presence of parvovirus B19 DNA was detected in the patient's serum by polymerase chain reaction (PCR), screening by dot-blot DNA hybridization, and finally by Southern blot analysis (University of Iowa, S.J.N.). The patient was treated with a ten-day course of an intravenous commercial pooled human immunoglobulin preparation with subsequent elevation of his reticulocyte count and resolution of the anemia (Fig. 2). He was discharged home seven days after completion of immunoglobulin therapy in good condition. Hematocrit rose to 30.3 and 37.9% at the time of discharge and twelve days later, respectively. Four months later, the patient's hematocrit slowly drifted down to 29.9%. Repeat bone marrow biopsy showed no evidence of viral infection. While on oral iron therapy, his hematocrit stabilized at 36.1% two weeks later, and remains at 42.1% one year after immunoglobulin therapy.

Bone marrow biopsy specimens obtained from the patient two months prior to treatment, one week prior to treatment, and four months after treatment were removed from paraffin blocks under sterile conditions for PCR, dot-blot, and Southern Blot analysis. Parvovirus B19 DNA was detected by Southern analysis of PCR product from both bone marrow specimens obtained before immunoglobulin therapy, but it was not detected in the posttreatment specimen.

Parvovirus B19 disease is now a recognized cause of aplastic crisis and anemia in patients who are immunocompromised by leukemia, hemolytic anemia, and acquired immunodeficiency syndrome. However, few cases of such infections have been reported in solid-organ transplant recipients. The shortage of available kidneys for transplantation has prompted many transplant centers to search for means of expanding the donor pool. At our institution we have utilized en bloc transplantation of pediatric cadaver kidney grafts for adult recipients. This technique uses both donor kidneys with donor aorta and vena cava intact for anastomosis to recipient iliac vessels. Periaortic and pericaval lymphatic tissue is carefully removed during preparation of the grafts for transplant. We report the case of a pediatric-donor renal transplant recipient who had pure red cell aplasia secondary to parvovirus B19 infection one year after transplantation, confirmed by PCR and Southern analysis. Serology demonstrated the lack of an IgM response, a finding that is not uncommon in immunosuppressed patients infected with this virus (*8, 9*).

In the case reported here, the infant donor exhibited a viral prodrome prior to sudden death, and, since at least one case of death from myocarditis caused by parvovirus in an infant has been reported (*1*), this case raises the question of whether parvovirus B19 was transmitted from donor to recipient via the allograft. We retrieved autopsy specimens of myocardium and bone marrow from the infant donor in this case, both of which were tested by PCR and Southern-blot hybridization and found to be negative for parvovirus DNA. These tests do not, however, completely rule out the possibility of the presence of the virus in donor tissues. Further investigation into the prevalence of parvovirus B19 disease in transplant patients is warranted, as this infection may prove to be a common cause of anemia and aplastic crisis in the solid-organ transplant recipient.

Acknowledgments. We thank Susan Hays-Goldsmith and Cheryl A. True for technical assistance.

DAVID A. CORRAL[2]
FRANK S. DARRAS[2]
CHRISTOPHER W. B. JENSEN[2]
THOMAS R. HAKALA[2]
STANLEY J. NAIDES[3]
JOHN R. KRAUSE[4]
THOMAS E. STARZL[5]
MARK L. JORDAN[2]
Division of Urologic Surgery and Renal Transplantation
Department of Hematology
University of Pittsburgh School of Medicine
Presbyterian-University Hospital
Pittsburgh, Pennsylvania 15213
Division of Rheumatology[3]
University of Iowa College of Medicine
Iowa City, Iowa 52242

[2] Division of Urologic Surgery and Renal Transplantation, University of Pittsburgh School of Medicine.
[3] University of Iowa College of Medicine, and Iowa City VA Medical Center.
[4] Department of Hematology, University of Pittsburgh School of Medicine.
[5] Division of Transplantation, Department of Surgery, University of Pittsburgh School of Medicine.

REFERENCES

1. Saint-Martin J, Choulot JJ, Bonnaud E, Morinet F. Myocarditis caused by parvovirus. J Pediatr 1990; 116: 1007.
2. Conrad ME, Studdard H, Anderson LJ. Aplastic crisis in sickle cell disorders: bone marrow necrosis and human parvovirus infection. Am J Med Sci 1988; 295: 212.
3. Frickhofen N, Abkowitz JL, Safford M, et al. Persistent B19 parvovirus infection in patients infected with human immunodeficiency virus type 1 (HIV): a treatable cause of anemia in AIDS. Ann Intern Med 1990; 113: 926.
4. Van Horn DK, Mortimer PP, Young N, Hanson GR. Human parvovirus-associated red cell aplasia in the absence of underlying hemolytic anemia. Am J Pediatr Hematol Oncol 1986; 8: 235.
5. Kurtzman GJ, Cohen B, Meyers P, Amunullah A, Young NS. Persistent B19 parvovirus infection as a cause of severe chronic anemia in children with acute lymphocytic leukemia. Lancet 1988; 2: 1159.
6. Niitsu H, Takatsu H, Miura I, et al. Pure red cell aplasia induced by parvovirus during allogeneic bone marrow transplantation.

Rinsho Ketsueki 1990; 31: 1566.
7. Neild G, Anderson M, Hawes D, Colvin BT. Parvovirus infection after renal transplant. Lancet 1986; 2: 1226.
8. Naides SJ. Parvovirus B19 infection. In: Andriole VT, ed. Mediguide to infectious diseases. Vol. 10, issue 4. New York: Della Corte, 1991.
9. Naides SJ, Scharosch LL, Foto F. Rheumatalogic manifestations of human parvovirus B19 infection in adults: initial two year clinical experience. Arthritis Rheum 1990; 33: 1297.
10. White DG, Woolf AD, Mortimer PP. Human parvovirus arthropathy. Lancet 1985; 1: 419.

Received 25 July 1991.
Accepted 4 May 1992.

RAPID ANALYSIS OF TUMOR NECROSIS FACTOR–ALPHA mRNA EXPRESSION DURING VENOOCCLUSIVE DISEASE OF THE LIVER AFTER ALLOGENEIC BONE MARROW TRANSPLANTATION[1]

Venoocclusive disease (VOD)* of the liver is a life-threatening bone marrow transplantation–related complication that may occur secondary to high doses of chemotherapy and radiation. VOD of the liver results from fibrous obliteration of the terminal hepatic venules, and involves jaundice, hepatomegaly, weight gain, and ascites (*1*, *2*). The overall incidence of VOD after bone marrow transplantation ranges from 10 to 30%, with a mortality rate over 40%. The incidence of VOD varies according to the conditioning regimen; the incidence of VOD in patients administered cyclophosphamide (Cy) plus total-body irradiation (CyTBI) and busulfan (Bu) (4 mg/kg for 4 days) plus Cy (50 mg/kg for 4 days) (BuCy4) was 21–24% (*3*, *4*), compared with 9% with BuCy2 (Cy 60 mg/kg for 2 days) (*5*). The pathogenesis is considered to be secondary to endothelial damage of the terminal hepatic venules, followed by activation of the coagulation cascade. More recently, it has been suggested that the dysregulation of cytokines such as tumor necrosis factor–alpha is implicated in transplant-related complications. It is also reported that serum TNF-alpha is increased prior to transplant-related complication such as acute graft-versus-host disease (aGVHD), interstitial pneumonitis (IP) and VOD (*6*, *7*).

In two patients (one with chronic myelogenous leukemia, a 30 year-old man [case 1] and one with acute lymphoblastic leukemia L2, a 17-years-old boy [case 2]) jaundice, hepatomegaly, right upper abdominal pain, weight gain, ascites, and hepatic coma developed after allogeneic BMT using BuCy2 as a conditioning regimen and cyclosporine and methotrexate as immunosupressants, respectively. Ultrasonographic studies of the abdomen revealed ascites, thickening of the gallbladder wall, and a failure to visualize the major hepatic veins. The diagnosis of VOD of the liver was confirmed from these clinical features. Both patients were treated with pulse therapy with methylprednisolone, continuous infusion of heparin as an anticoagulant, and prostaglandin E_1 as a vasodilator. After intensive therapy, liver function of the patient with CML improved, ascites diminished within 10 days, and jaundice resolved within 30 days, and the patient was alive more than four months after transplantation with no acute GVHD. On the other hand, although the liver function of the patient with ALL improved temporarily, it deteriorated from day 60 and the patient died of hepatic failure. Localized skin eruption of acute GVHD grade 1 was present from day 46 (Fig. 1). Autopsy of this patient revealed the typical pathological features of VOD, with fibrous obliteration of the terminal hepatic venules.

[1] This work was supported by Grants-in-Aid from the Ministry of Education, Science and Culture, Japan.

* Abbreviations: Bu, busulfan; Cy, cyclophosphamide; PCR, polymerase chain reaction; VOD, venoocclusive disease.

In the present study, we investigated the expression of TNF-alpha mRNA and IL-2 mRNA in peripheral mononuclear cells using the semiquantitative polymerase chain reaction (PCR) (*8*) to analyze the interaction of cytokines and VOD. The total RNA (5 μg) prepared from peripheral mononuclear cells separated by centrifugation with Ficoll-Hypaque gradient was reverse-transcripted by 600 U murine Moloney leukemia virus reverse transcriptase (BRL) with 150 pmol of random hexamer, and 1/20 th of the resulting cDNA was used for PCR. The primers (IL-2A 5′CAACTCCTGTCTTGCATTGCACTA3′, IL-2B 5′TGTTGAGATGATGCTTTGACAAAA3′ [*9*], TNF-alpha A 5′AGTGACAAGCCTGTAGCCCATGTT3′, TNF-alpha B 5′AGACTCGGCAAAGTCGAGATAGTC3′ [*10*], beta-actin A 5′TTCGAGCAAGAGATGGCCACGGTC3′, beta-actin B 5′ATACTCCTGCTTGCTGATCCACAT3′ [*11*]) were synthesized on a 380B DNA synthesizer (Applied Biosystems). The primer sequences were chosen from separate exons of the genes.

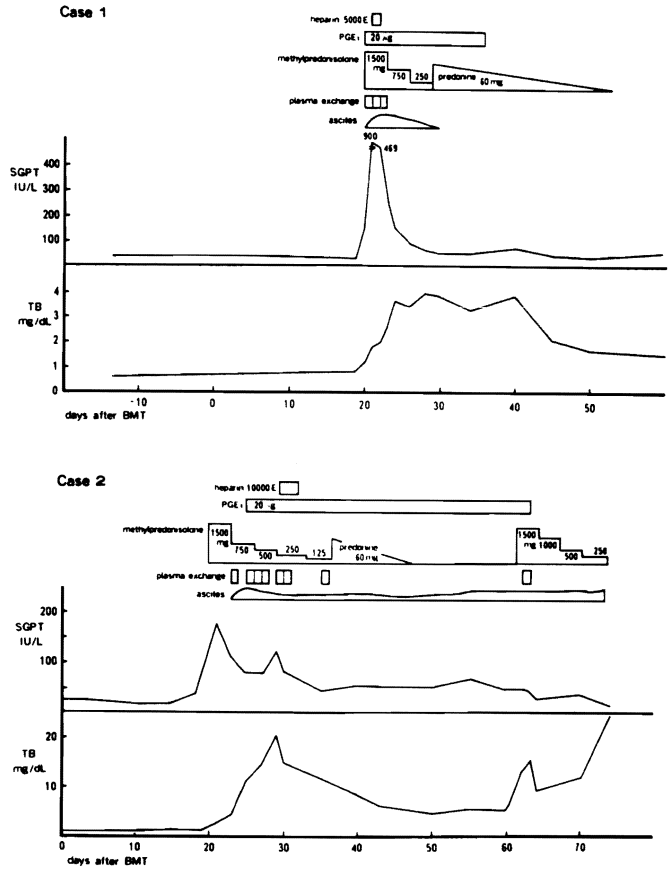

FIGURE 1. The clinical course of patients who developed venoocclusive disease of the liver.