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Cover: Two Young Girls at the Piano, by Pierre August RENOIR (© 1989 The Metropolitan Museum of Art; Robert Lehman Collection, 1975. 1975.1.201). Two Young Girls at the Piano is one of at least five versions of the same scene by Renoir, including a lovely pastel recently sold at auction. Renoir was 51 years of age at the time he did this work in 1892, and at the height of his popularity. This lovely presentation evokes a former era when adolescents, at least those in favored economic status, spent their leisure learning skills such as playing the piano and singing. One of the major tasks of adolescence is to develop one’s identity and sense of competence. Whether it is the charming skills so beautifully depicted in this painting or others, the task of pediatricians is to assist young people in developing skills of which they can be proud.

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Self-Evaluation Quiz
1. Of the following children who have short stature, which one presents the least convincing evidence that he or she will respond to growth hormone (GH) therapy?

2. Which of the following is the least appropriate contribution to a decision to undertake a 12-month trial of GH therapy in a child who has short stature?
   A. Assurance of some psychologic benefit.
   B. A growth velocity less than 25% of normal during the past year.
   C. Predicted height under 157 cm (62 in) in a boy.
   D. Predicted height under 152 cm (60 in) in a girl.

3. Interpretation of GH stimulation tests requires that attention be given to each of the following except that:
   A. Standards vary among laboratories.
   B. Prior thyroid tests should be done.
   C. Prior liver function tests should be done.
   D. Variability with age, sex, or pubertal status has not been determined.

Thyroid Carcinoma


Although thyroid nodules are relatively uncommon findings in the pediatric population, their detection requires careful and thorough evaluation. Several studies indicate that as many as one third of all nodules found may represent malignancies. While this incidence compares favorably with studies from the era of head and neck irradiation for tonsil or thymic enlargement, when many as 70% of thyroid nodules proved to be malignant, early detection of thyroid tumors remains an important responsibility of the pediatrician.

The thyroid should be carefully palpated to determine its size and consistency and to discover any evidence of additional nodules. In addition, cervical and axillary lymph nodes should be examined for evidence of enlargement or inflammation. The thyroid may be evaluated further using ultrasonography (to determine if the nodule is cystic or solid), by computed tomography or magnetic resonance imaging procedures, or by 131I scans. A "cold" nodule (one which fails to take up radioactive iodine) carries an increased risk of malignancy.

Although the majority of nodules are benign (most are follicular adenomas), common thyroid malignancies include papillary, follicular, and medullary carcinoma. Surgery typically includes partial thyroidectomy (except for medullary carcinoma, which requires total thyroidectomy) and dissection of involved nodes. Patients must be observed diligently postsurgery because both neck recurrence and distant metastases may be noted many years after the initial occurrence. Long-term follow-up is essential, therefore, and should include radiographic studies of the chest, tests of the serum thyroglobulin level (typically elevated in metastatic disease), and 131I total body scans. (Ron G. Rosenfield, MD, Editorial Board)
in these series. In contrast, the results of autologous transplantation with chemopurged (treated with the compound 4-hydroperoxycyclophosphamide) bone marrow are encouraging for children who have acute myeloid leukemia. Patients who have second- or third-remission myeloid leukemia have a disease-free survival rate of 30% following busulfan-cyclophosphamide conditioning and the infusion of drug-incubated autografts. The relapse rate for this group is 50%, as might be expected for recipients of syngeneic transplants.

Neuroblastoma. Children older than 12 months of age who have Stage IV neuroblastoma have a very unfavorable prognosis, with disease-free survival of less than 10% with combination chemotherapy alone. When carried out during the first complete remission, allogeneic or autologous bone marrow transplantation in children who have disseminated neuroblastoma is associated with cure rates of 25% to 40%, but children who undergo transplantation during partial or second complete remissions have much poorer disease-free survival. The possible contamination of the autograft with occult tumor cells has led to the use of ex vivo bone marrow autograft purging, especially with monoclonal antibodies directed at neuroblastoma-specific antigens or with immunomagnetic beads.

Other Malignancies. Patients who have relapsed Hodgkin and non-Hodgkin lymphoma may be cured with allogeneic or autologous bone marrow transplantation; the best results (35% to 50% cure rate) are observed with minimal residual disease or second complete remission. Patients who have bulky residual lymphoma or progressive drug-resistant disease at the time of transplant are at very high risk for tumor recurrence. More intensive pretransplant preparative regimens need to be developed that effectively eradicate a resistant or bulky residual tumor with acceptable toxicity. For example, combination pretransplant chemotherapy with combinations of busulfan, cyclophosphamide, etoposide (VP-16), or cytosine arabinoside may be useful for these kinds of patients. Autologous transplantation as part of the treatment of other solid tumors of childhood (eg, rhabdomyosarcoma, Ewing sarcoma, neuroectodermal tumors, Wilms tumor, and possibly central nervous system tumors) may lead to partial or complete response, but durable remission and prolonged disease-free survival are seen rarely. Again, the observation that patients with refractory disease or large tumor burdens at the time of transplant are at especially high risk for relapse underscores the suggestion that intensive cytoreductive therapy with bone marrow stem cell rescue should be applied during states of minimal residual disease (eg, first or second complete remission) in children at high risk for recurrence of solid tumors.

SUMMARY

Bone marrow transplantation is a high-visibility, high-technology discipline with a growing list of potentially curative applications in neoplastic, hematologic, immunologic, and genetic diseases of children. The clinical problems experienced by children who have received bone marrow grafts involve pediatricians in both general and subspecialty practice and require a working knowledge of the applied immunobiology of bone marrow transplantation. As the transplantation procedure has evolved from a research tool to an established therapeutic modality, collaboration between basic scientists and clinicians has led to a greater understanding of the pathophysiology of the immunobiologic events that occur after allogeneic bone marrow transplantation and, thus, to improvements in the clinical care of transplant recipients. As its applications in pediatric medicine grow, bone marrow transplantation presents additional challenges for the future: expansion of the allogeneic donor pool, use of more effective or aggressive preparative regimens and autologous bone marrow-purging strategies, more effective prevention and treatment of graft-versus-host disease, and development of gene-replacement therapy by infusion of modified autologous bone marrow cells.

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SUGGESTED READING


Self-Evaluation Quiz

6. Bone marrow transplantation has been successful in the management of each of the following conditions except:
   A. β-Thalassemia major
   B. Neuroblastoma
   C. Leukemia
   D. Lysosomal storage disease
   E. Acquired immunodeficiency syndrome during infancy

7. A bone marrow transplantation between unrelated persons who have identical HLA types (class I and class II) is:
   A. Syngeneic
   B. Allogeneic
   C. Heterogeneous
   D. Autologous

8. After successful bone marrow transplantation, each of the following cells of the recipient will be of donor origin except:
   A. Platelets
   B. Macrophages
   C. Osteoblasts
   D. Gial cells
   E. Kupffer cells
9. In successful bone marrow transplantation, the cell of the donor marrow most critical to repopulation of the recipient is the:
   A. T cell.
   B. B cell.
   C. Stem cell.
   D. Monocyte.
   E. Erythrocyte.

10. The incidence of clinical graft-versus-host disease following bone marrow transplantation between apparently entirely histocompatible non-twin (sibling) persons is closest to:
   A. 5%.
   B. 15%.
   C. 35%.
   D. 65%.
   E. 85%.

11. A pretransplantation regimen designed to ablate the recipient's bone marrow and bone marrow-generated cells is required prior to bone marrow transplantation in each of the following patients except the patient who has:
   A. Wiskott-Aldrich syndrome.
   B. Severe combined immunodeficiency.
   C. Leukemia.
   D. Neuroblastoma.
   E. Chronic granulomatous disease.

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EDUCATIONAL OBJECTIVE

E. The pediatrician should be aware that gastroesophageal reflux has been reported in several children with cystic fibrosis. In addition, pulmonary disease due to gastroesophageal reflux during infancy may mask a diagnosis of cystic fibrosis. (Recent Advances, 90/91)

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Gastroesophageal Reflux (GER) and Cystic Fibrosis during Infancy: Don’t Blame GER for Everything


Gastroesophageal reflux (GER) frequently is found in association with recurrent episodes of pulmonary disease, although the precise causal relationships are not clear. Some children (and adults) with recurrent pneumonia or asthma together with GER improve with therapy directed at the GER. These three studies present data concerning cystic fibrosis and GER.

Bendig et al review seven patients, aged 8 to 31 years, with previously diagnosed cystic fibrosis who complained of pain in the upper abdomen. All had GER documented by esophagram, endoscopy, and pH probe. Therapy included medical management or surgery, depending on the severity of involvement and the degree of respiratory reserve. No improvement in lung function was shown, although there were varying degrees of relief of the abdominal symptoms.

Frates and Cox discuss two infants who had recurrent vomiting and failure to thrive. One had documented GER, the other had presumed GER. The failure to thrive was ascribed initially to the GER, but subsequent sweat tests revealed cystic fibrosis.

Thomas et al present two infants with respiratory distress and documented GER. Both infants developed respiratory failure and required mechanical ventilation. After the respiratory failure and growth of Staphylococcus aureus from the airways, cystic fibrosis was suspected and confirmed. Both babies had received bethanechol as part of the management of their GER before the development of the respiratory failure.

Comment: These studies provide an analysis of the relationship of GER and cystic fibrosis from two perspectives. The study of Bendig et al suggests that there may be an increased incidence of GER in patients who have cystic fibrosis. They point out the importance of considering GER in the differential diagnosis of upper abdominal pain in such patients. Specific therapy may reduce symptoms and gastrointestinal complications, although there may be no effect on the respiratory complications of cystic fibrosis.

The other two studies serve to remind pediatricians to continue including cystic fibrosis in the differential diagnoses of failure to thrive and recurrent pulmonary disease. Such patients have an increased incidence of asthma and possibly of GER. When either of these diseases is diagnosed in an infant or toddler, cystic fibrosis must also be considered. Sweat tests should be performed by a reliable laboratory, one with high volume and good quality control. Liberal use of the sweat test laboratory is mandatory, particularly given the improved outlook for patients with cystic fibrosis if they receive early diagnosis and institution of appropriate therapy. As Dr Robert Wood of the University of North Carolina says, “There is no reason for not doing a sweat test.” (Michael R. Bye, MD, Albert Einstein College of Medicine/Montefiore Medical Center, Bronx, NY)