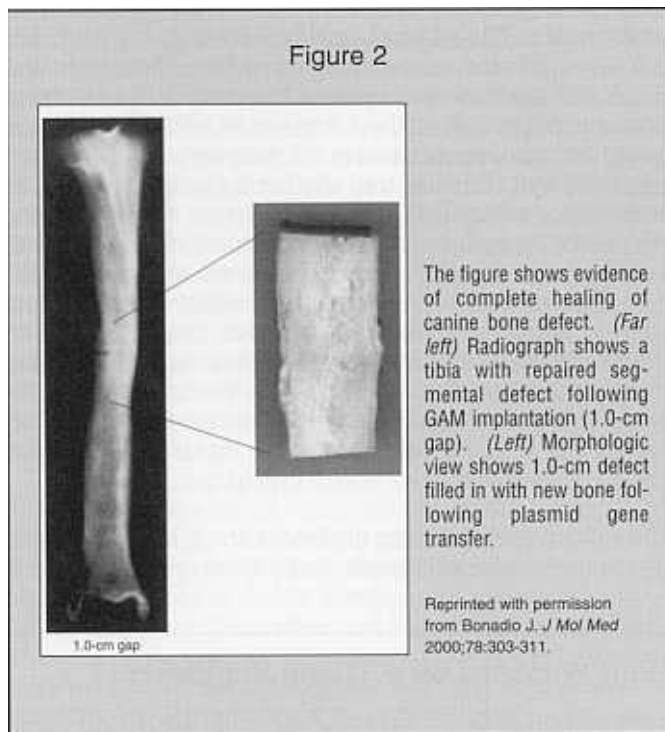


ations in which wound healing is inadequate. He describes the rationale and strategy for using GAM containing PTH 1-34 plasmids to treat hip fracture in elderly individuals with osteoporosis—an exciting postulate.

Bonadio J. Tissue engineering via local gene delivery: update and future prospects for enhancing the technology. *J Mol Med* 2000;78:303-311.

Editor's comment: *It is a long way from elderly osteoporotic patients with hip fractures to children with growth disturbances, but the principles involved in locally delivering plasmids encoding potentially therapeutic genes, as outlined in this article, may be applicable to a variety of disorders of interest to the GGH readership, especially for treatment of localized growth disturbances. The GAM technology is still in its infancy and remains to be proven safe and effective in humans, but the results presented to date are very encouraging. It is important to stress that determining which growth factors or, more likely, which combinations of growth factors are most effective for different clinical situations remains as big a challenge as developing the means to deliver such factors. The concept of being a tissue engineer may have much potential. After you read Bonadio's review you may agree.*

William A. Horton, MD



Long-Term Effect of Bone-Marrow Transplantation for Childhood-Onset Cerebral X-Linked Adrenoleukodystrophy (X-ALD)

The authors report that bone marrow transplantation (BMT) undertaken at the inception of neurologic symptoms in children with X-linked adrenoleukodystrophy (X-ALD) often can halt or reverse the progressive neurologic disease characteristics of this illness. However, the component of primary adrenal failure progresses. Eighteen boys aged 5.3 to 11.8 years with the slowly progressive form of cerebral disease or the advanced form of cerebral disease of X-ALD underwent BMT.

Six transplanted subjects died: 2 of complications of BMT, 2 with advanced cerebral disease, and 2 with slowly progressive cerebral disease that accelerated to advanced cerebral disease after BMT.

Twelve patients survived. Eight patients are in regular school classes; 1 has graduated from high school and attends college. The plasma concentrations of very long chain fatty acids (VLCFAs) decreased in all subjects after BMT. Magnetic resonance imaging (MRI) revealed decreasing myelinization for 1 to 2 years after transplantation; it then stabilized and even increased in 3 patients. Clinically, in 5 patients with mild corticospinal signs, resolution occurred in 3 and remained stable in the other 2. In 2 subjects, seizure control was greatly improved. Vision deteriorated in 3 patients. Verbal IQ (VIQ) scores remained stable after BMT in 10 of 12 subjects. In 5 of 11 patients tested, performance IQ (PIQ) increased by >10 points. In 4 of the 11, PIQ decreased significantly but then stabilized. Language skills, auditory processing, and motor performance increased appropriately over time in most patients. In the majority of a similar population of 13 boys with X-ALD

for whom no compatible marrow donor could be found, 7 have died, 4 are in a vegetative state, and 2 became stable after an initial period of deterioration. The investigators conclude that BMT early in the course of neurologic disease can alter the natural history of X-ALD.

Shapiro E, et al. *Lancet* 2000;356:713-718.

Editor's comment: *The mutated gene (ALD, OMIM 300100) in boys with X-ALD encodes a peroxisomal membrane ATP-binding transporter protein that, when inactivated, impairs β -oxidation of fatty acids, resulting in accumulation of VLCFAs with 24 to 30 carbons. Esterified to cholesterol in the CNS and adrenal cortex, these compounds prove injurious to these tissues. Present data suggest that bone marrow cells cross the blood-brain barrier and attenuate the process(es) that lead to demyelination and neurologic deterioration in children with X-ALD.*

The authors made an additional educational contribution by classifying the severity of X-ALD patients into 4 clinical categories. This classification currently exists in general for X-ADL and goes beyond the characterizations in the 12 patients reported. There is clinical value in this classification, which is repeated here.

1. Patients with no cerebral disease, with or without Addison's disease, in whom MRI and neuropsychological tests are normal. These are not candidates for BMT. About half of this group will develop neurologic signs involving the spinal cord in adulthood.

2. *Patients with slowly progressive cerebral disease, with or without Addison's disease. MRI shows slow progression of demyelination. BMT is to be considered. Disease severity is evaluated by scoring the extent of demyelination on the MRIs and performance on neuropsychological tests. MRIs are scored using a demerit scale ranging from 0 to 34 devised by Loes et al. BMT is recommended for patients whose cognitive abilities exceed a VIQ or PIQ of 80.*
3. *Patients with stable cerebral disease. Included are patients with MRI and neuropsychological abnormalities at diagnosis and in whom follow-up shows no evidence of MRI and neuropsychological deterioration. Close monitoring is required to detect change that may signal decline. (Not stated, but implied, is that those who are declining but whose IQ remains >80 might be candidates for BMT.)*
4. *Patients with advanced cerebral disease. These include patients with rapid progression of disease who decline rapidly to a vegetative state and have marked VIQ or PIQ dysfunction (<80) and neurologic signs. Current methods of BMT are not beneficial.*

The authors also state: "The absence of any correlation between the clinical phenotype and the ALD gene mutation or the biochemical defect, and the effectiveness of BMT ONLY at an early stage of the disease, lead us to recommend careful planning and frequent observation of all boys biochemically identified with X-ALD with normal brain MRI. No biological marker predicting the onset of cerebral demyelination is as yet available. Therefore continued MRI and neuropsychological testing are the only tools allowing the identification of patients who will benefit from BMT. Similarly no existing marker predicts whether or when a patient with a "slowly progressive cerebral disease" will enter into the "advanced cerebral disease" stage. Observations raised the hope that VLCFA could be decreased or even normalized by new pharmacological approaches. BMT, however, remains the only effective therapeutic approach in the cerebral form of X-ALD. The opportunity to recommend BMT at an early stage of cerebral X-ALD should not be missed."

Allen W. Root, MD

Loes DJ, et al. *Am J Neuroradiol* 1994;15:1767-1771.

Transmission of BSE (Bovine Spongiform Encephalopathy) by Blood Transfusion in Sheep

Houston et al published an early warning report before completion of a study that they were doing to look at cross-species transmission of bovine spongiform encephalopathy (BSE) through blood transfusion. This study was aimed at answering the question of whether there is a concern about blood transfusions transmitting the variant Creutzfeldt-Jakob (vCJD) disease in Britain from anyone living in Britain or who traveled in Britain between 1980 and 1996. Several countries have banned blood donations from people who spent time in Britain during the time of potential exposure to BSE.

Houston et al were engaged in a study to see if it is possible to transmit BSE between sheep by blood transfusion after the blood donor sheep had orally ingested the infecting agent. It turns out that sheep blood types are very complex, so this study was not a simple matter. It had been thought that there was a barrier to cross-species transmission of infectious agents. BSE-infected sheep harbor infection in peripheral tissues (tonsils, for example) prior to becoming symptomatic and thus are similar to humans infected with vCJD. A group of sheep were orally challenged with 5 g of BSE-affected cattle brain. At a later time, their blood was taken and transmitted into scrapie-free sheep. For the most part, whole blood was used for the transfusions and only a single transfusion was made. BSE clinical signs and pathologic changes have occurred in 1 of the sheep who received blood from a BSE-infected animal who was asymptomatic at the time of the transfusion. The donor had been challenged by oral BSE cattle brain 318 days before whole blood was taken. The BSE developed in the recipient animal 629 days after the transfusion. This suggests that the blood was taken from the orally challenged sheep halfway through the incubation period and yet it was nevertheless able to infect the recipient sheep.

This experiment does indicate that BSE can be transmitted between individuals of the same species by whole blood transfu-

sion and thus has implications for the blood transfusion system in general. The United Kingdom has been utilizing leukocyte-depleted blood; however, this may not be sufficient to avoid the problem.

A number of models have been utilized to predict the incidence of vCJD in the United Kingdom. There has been concern that as many as 500,000 individuals could become affected. The models have varying lengths of incubation and various calculations as to the number of people who would become infected and symptomatic after eating meat from an infected cow. The observed number of cases affected in early 2000 was 75 (Table). There appears to be a susceptible prion genotype, which is present in about 40%

Table
Annual Number of Onsets, Classifications, and Deaths From vCJD in the UK

Year	Onsets	Classified as vCJD	Deaths
1994	8	0	0
1995	10	7	3
1996	11	8	10
1997	14	12	10
1998	16	17	18
1999	16	17	14
2000	0	14	14
Total	75	75	69

Based on current classification criteria, applied retrospectively where appropriate.

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