

below 40 mg/dL, whereas others use the cutoff glucose level of 65 mg/dL. The authors argue that 60 to 65 mg/dL (3.3 to 3.6 mmol/L) should be used to define "hypoglycemia" whether the patient is symptomatic or not. Unquestionably, severe hypoglycemia is more frequent in adolescents than in adults, as was demonstrated in the diabetes control and complications trial. This was true whether the patients were in the intensive or conventional treatment groups. Data regarding the number of episodes of coma/seizure and also on moderate hypoglycemia per 100 patient-years were considered. The data are well worth reviewing in the original article, particularly by those who deal with diabetes frequently in their practice. The greatest frequency of severe hypoglycemia was found in children <6 years of age. By the fourth year of the study, this group had 42 events per 100 patient-years. This means that of 100 patients having the disease over a 1-year period, there would be 42 severe hypoglycemic episodes.

The authors consider under the causes errors in treating hypoglycemia, the pharmacokinetic and physiologic differences in

children with diabetes, and hypoglycemic unawareness. Considering the consequences, they discuss symptoms, changes in mental efficiency, and chronic brain dysfunction. In considering prevention, they state the key to prevention of severe hypoglycemia and associated complications is prevention of even mild episodes, which requires regular glucose monitoring, and the development of protective strategies on the part of the diabetic patient and family. Insulin regimens and diet and exercise also are considered in this section.

Becker DJ, Ryan CM. *Trends Endocrinol Metab* 2000;11:198-202.

Editor's comment: This article emphasizes the problems of insulin therapy in childhood. It follows the previous abstract (Shapiro et al) because of the potential relationship in future treatment of using islet cell transplants. If the reader has not read this article by Becker and Ryan and is treating children with diabetes, I strongly recommend that he/she do so.

Robert M. Blizzard, MD

Who Wants to Be a Tissue Engineer?

Tissue engineering is a hot topic and not foreign to *GROWTH, Genetics, & Hormones* since many genetic disorders could potentially benefit from regenerated tissues and since tissue regeneration involves local growth and its hormonal control. Successes have been limited in stimulating regeneration of

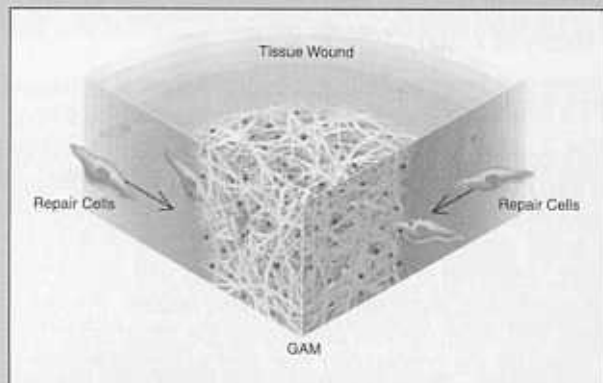
mammalian bone, skin, blood vessel, and spinal cord when bio-material scaffolds, which hopefully might bridge tissues to be regenerated and promote cell migration, proliferation, and differentiation, are used. While attractive, the use of growth factors to enhance regeneration has been hampered by difficulties in selectively delivering potential therapeutic agents at proper concentrations and for extended periods.

Bonadio and coworkers now offer a novel approach to local tissue engineering. The basic concept offered is to introduce plasmid DNA encoding the therapeutic factor into a biodegradable porous scaffold that is implanted into the region where regeneration is desired. The delivery system is called "gene activated matrix," or GAM (Figure 1). As cells grow into the scaffold, they take up the plasmid, express the plasmid DNA, and synthesize the recombinant therapeutic factor. Eventually, the scaffold is degraded as new tissue is formed.

At first glance, this seems too good to be true. However, Bonadio provides evidence that it works. Using wound healing as a model, the group has shown that fibroblasts growing into granulation tissue take up and express recombinant protein for weeks. Referring to earlier work using a canine bone defect model (Figure 2 on page 12), he notes that bone healing is much improved over controls by implantation of GAM-containing plasmids encoding BMP 4 or PTH fragment 1-34, and that the therapeutic effect is enhanced when the 2 plasmids are used together. The results suggest that GAM provides a dose-dependent, reproducible, and safe strategy for stimulating tissue regeneration.

After discussing the rationale for using GAM in wound healing and reviewing experiments with animals, Bonadio turns his attention to how GAM might be used in human medicine. He suggests that the first use of the approach may best be in situ-

Figure 1



The schematic figure shows a GAM implant in a fresh wound site (*inner area*). A GAM at its most basic consists of 2 ingredients: plasmid DNA and a structural matrix carrier. As part of the wound healing response, granulation tissue fibroblasts proliferate and migrate from viable tissue (*outer area*) surrounding the wound into the GAM. Once there, fibroblasts take up and transiently express plasmid DNA. The GAM matrix has 2 functions: It holds plasmid DNA in the wound site (until cells arrive), and it acts as scaffolding that promotes fibroblast ingrowth and accumulation near the DNA. While in the matrix, transfected fibroblasts act as local *in vivo* bioreactors, producing plasmid-encoded proteins that stimulate wound repair.

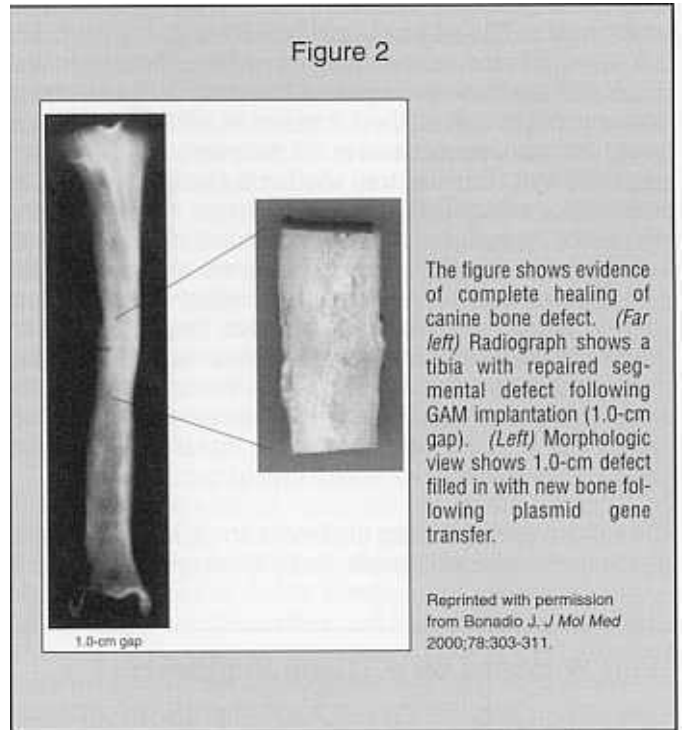
Reprinted with permission from Bonadio J. *J Mol Med* 2000;78:303-311.

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.