Given the potential risks, why might a woman choose a trial of labor? Women who successfully deliver vaginally generally have less postpartum discomfort, shorter hospital stays, and shorter periods of disability than women who undergo repeated cesarean section. A trial of labor may be associated with a lower risk of fever than elective repeated cesarean section. Women who plan future pregnancies may prefer to avoid repeated cesarean deliveries that further increase the risks of uterine rupture, placenta accreta, and morbidity related to multiple abdominal surgeries. Finally, there may be social and cultural reasons why some women prefer vaginal delivery.

Slovic recognized that “experts” (such as health care policy analysts, public health officials, and insurance company executives) perceive risk differently from laypeople (patients). Experts judge risk according to technical estimates of numbers of deaths. The rate of perinatal death, for example, is 5.8 per 1000 with trials of labor after cesarean section, as compared with 3.4 per 1000 with elective repeated cesarean section. The absolute difference between them is 2.4 per 1000 (or 1 per 417), a relatively small number. Patients are more apt to judge risk according to the degree to which they “dread” the unwanted outcome. “Dread,” in turn, is determined by the degree to which the outcome is irreversible, potentially lethal, and uncontrollable. By these criteria, the possibility of perinatal death resulting from a trial of labor would probably be associated with a high degree of dread.

The process of obtaining informed consent for medical care requires that physicians provide patients with the information that a reasonable person would want under the circumstances. Most reasonable women considering a trial of labor after a prior cesarean delivery would want to know that spontaneous labor is associated with a tripling of the risk of uterine rupture and that induction of labor with prostaglandins is associated with an increase in that risk by a factor of 15. Should a rupture occur, the risk of perinatal mortality increases by a factor of 10. Some reasonable persons may conclude that these absolute risks are so small that they are worth taking and are outweighed by the benefits of a successful vaginal birth. Nonetheless, these issues must be discussed with each patient, and she must make that decision for herself. After a thorough discussion of the risks and benefits of attempting a vaginal delivery after cesarean section, a patient might ask, “But doctor, what is the safest thing for my baby?” Given the findings of Lydon-Rochelle et al., my unequivocal answer is: elective repeated cesarean section.

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NEW THERAPIES FOR FABRY’S DISEASE

The treatment of a genetic disorder requires in-depth understanding of a biochemical aberration, clinical expertise in treating the target disease, and customized approaches to caring for individual patients. Recent advances in the treatment of Fabry’s disease illustrate these points and show that enzyme-replacement therapy can be safe and efficacious for certain rare inborn errors of metabolism.

Fabry’s disease, an X-linked lysosomal-storage disorder, is due to a deficiency of α-galactosidase.1 In the glycosphingolipid catabolic pathway, this enzyme removes the third sugar residue, a galactose, attached to ceramide. Without this enzyme, globotriaosylceramide (Fig. 1) accumulates within the vascular epithelium, heart, kidneys, cornea, and other tissues, causing angiokeratomata, painful acroparesthesias, hypohidrosis, renal failure, and cardiac and cerebrovascular disease. Male heterozygotes die at an average age of 41 years. Those with the cardiac variant of Fabry’s disease have residual α-galactosidase A activity (approximately 5 to 10 percent of normal), and their only symptom is myocardial dysfunction during middle age.

In this issue of the Journal, Eng et al. report the results of a multicenter, double-blind, placebo-controlled study of 58 patients with classic Fabry’s disease...
in whom biweekly infusions of recombinant human α-galactosidase A were shown to be safe and effective. Twenty weeks of therapy resulted in the clearing of deposits of globotriaosylceramide from the renal microvascular endothelium, endomyocardium, and skin. In an accompanying article, also in this issue of the Journal, Frustaci et al. describe the correction of myocardial dysfunction in a 55-year-old man with the cardiac variant of Fabry’s disease.

These accomplishments are the fruits of long and intense research efforts that have focused on the biochemistry of Fabry’s disease and other metabolic disorders. In 1967, Brady et al. identified the basic defect in Fabry’s disease as α-galactosidase A deficiency. Three years later, Krivit’s group (which included Desnick, who was involved in both studies in this week’s issue) transfused plasma that contained normal levels of enzyme into two patients with Fabry’s disease and reported supranormal levels of α-galactosidase A in the patients’ plasma. However, the half-life of the enzyme infused with the plasma was short (only 95 minutes), and thus this approach was clinically impractical. Recently, α-galactosidase A replacement has proved effective in correcting the enzyme deficiency in a mouse model of Fabry’s disease, in an open-label study involving patients, and in a phase 1 and 2 trial showing dose responsiveness.

Eng et al. made use of a passel of facts about lysosomal enzyme processing and delivery and directed mammalian cells to express α-galactosidase A so that it contained the appropriate carbohydrate moieties for uptake by parenchymal-cell receptors. Eng et al. also knew that even a small amount of α-galactosidase A could degrade stored globotriaosylceramide, making enzyme replacement feasible. Finally, an intimate knowledge of Fabry’s disease allowed them to select the correction of kidney disease — assessed as the clearing of globotriaosylceramide deposits in the renal microvascular endothelium — as an appropriate outcome measure and to perform serial renal biopsies for proof of efficacy. Thus, Fabry’s disease now joins Gaucher’s disease, which is due to a deficiency of acid β-glucosidase, as a lysosomal-storage disorder that is treatable by enzyme replacement.

Frustaci et al. also drew from classic biochemistry in proposing a clinical study of galactose infusions for the cardiac variant of Fabry’s disease. They knew that sufficient concentrations of a ligand that binds to the active site of an enzyme could maintain the enzyme in a conformation that is resistant to degradation. This strategy has been used by scientists performing enzyme purification and by physicians attempting to maximize the residual activity of an enzyme with cofactors. Ishii et al. further showed that galactose could stabilize mutant α-galactosidase A in cultured cells. Frustaci et al. reasoned that galactose could serve the same function in vivo and yet be displaced by the natural substrate of the enzyme.

Both Eng et al. and Frustaci et al. were prompted by their understanding of Fabry’s disease to customize therapy for individual patients. In the case of Frustaci et al., galactose infusion was appropriate for a patient with sufficient residual α-galactosidase A to allow its stabilization. How much did a little more enzyme matter in this patient? It cured his cardiac disease. What would be the consequences of a little less enzyme? It would put the patient in the realm of classic Fabry’s disease, necessitating infusions of α-galactosidase A. Customized therapy reflects the traditional approach to metabolic disorders, with a range of treatments that includes chemical avoidance of oxidants in glucose-6-phosphate dehydrogenase deficiency, dietary restric-

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**Figure 1.** Globotriaosylceramide (Galactosyl-Galactosyl-Glucosyl-Ceramide).

The enzyme α-galactosidase A removes the third sugar residue, a galactose, attached to ceramide. In the absence of this enzyme, globotriaosylceramide accumulates in the lysosomes. The red arrow indicates the α-galactosyl bond normally cleaved by α-galac-

cidase, which is deficient in Gaucher’s disease. Adapted from Desnick et al. with the permission of the publisher.
tion of phenylalanine in phenylketonuria, removal of toxic copper in Wilson’s disease, and provision of biotin cofactor in carboxylase deficiencies. The strategy works.

Despite the success of therapy in these two studies, some questions about α-galactosidase A therapy and galactose treatment remain unanswered. Will the production of IgG antibodies in patients treated with α-galactosidase A continue to be harmless, as in patients with Gaucher’s disease who receive enzyme-replacement therapy? Will long-term infusion of α-galactosidase A remove the corneal deposits of globotriaosylceramide? Will the histologic and biochemical efficacy of α-galactosidase A infusions translate into functional improvements in the hypohidrosis, acroparesthesias, and renal and cardiac complications of Fabry’s disease? Will only certain types of mutant α-galactosidase A respond to galactose infusion, and if so, which types are they? Can galactose stabilize the normal α-galactosidase A enzyme, as it has in cultured lymphoblasts, allowing galactose and α-galactosidase A infusions to increase enzyme activity synergistically? Finally, how much will α-galactosidase A infusions cost, and how will the level of reimbursement be determined?

The issue of expense has ramifications beyond the treatment of Fabry’s disease. Past experience with the cost of certain orphan drugs has exposed the fragile nature of support for therapy for rare diseases. The Orphan Drug Act of 1983 offers tax credits and exclusive marketing rights to companies that develop drugs used to treat diseases that affect fewer than 200,000 people in the United States. The act was intended to encourage the pursuit of effective but low-profit treatments by pharmaceutical companies. Ten years ago, however, the act was threatened because four drugs with orphan status earned companies hundreds of millions of dollars in annual sales. This was particularly disconcerting since the bulk of the research and development for these drugs had been supported by funds from the U.S. government. The enormous cost of enzyme-replacement therapy for Gaucher’s disease—several hundred thousand dollars per patient per year—prompted a task force to conclude, “Despite the success of enzyme therapy, treatment is limited by the cost of the agent.” Although the high profits from orphan drugs may encourage their development, it also jeopardizes orphan-drug legislation and certainly militates against access for patients.

In clinical terms, the key to therapy for many metabolic disorders is increasing enzyme activity. Therapy may thus involve direct administration of enzyme, as in Gaucher’s disease and Fabry’s disease. It may also be achieved by the provision of enzyme-containing cells, as in bone marrow or stem-cell transplantation in selected patients with globoid-cell leukodystrophy (Krabbe’s disease) or certain types of mucopolysaccharidosis. The enzyme may be delivered by genes, as in vector-mediated gene therapy. The activity of an enzyme may even be manipulated by increasing its stability with chaperones that bind to the active site or by reducing substrate levels with the use of synthetic inhibitors.

To perpetuate the type of advances presented in this week’s issue of the Journal, we must encourage greater interest in a field where a little more or a little less expertise, along with a little more or a little less enzyme, makes all the difference.

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HEMIPLEGIC MIGRAINE — DOWNSTREAM OF A SINGLE-BASE CHANGE

Hemiplegic migraine (with or without cerebellar signs), spinocerebellar ataxia, and episodic ataxia can all result from changes in the gene that encodes the P/Q-type neuronal calcium channel, just one of the 35,000 or so genes that make up the human blueprint. The varied consequences of calcium-