Biochemical Fetal Therapy

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Waves of enthusiasm for fetal therapy surrounded the earliest surgical interventions.¹ With increasing experiences as detailed in other articles in this symposium, there has been considerable sobering of expectations for such surgical procedures. Conversely, selected medical and pharmacologic alterations in the milieu of the fetus appear to be promising and ultimately will probably become quite important in fetal therapy.

Successes in medical fetal therapy have been clearly documented in two main areas: 1) the prevention of external genital masculinization in female fetuses affected with 21-hydroxylase deficiency congenital adrenal hyperplasia (CAH) and 2) the correction of fetal cardiac arrhythmias that can lead to nonimmune fetal hydrops and fetal death. In several other instances, it has been demonstrated that the pharmacology of the fetus can be altered although the usefulness of such alterations remains to be proved.

The potential effects of drugs or maternal metabolites on the fetus are well known. In many instances, as with known teratogens, adverse effects may be in part genetically determined.² Furthermore, some maternal metabolic diseases may have profound fetal effects. This is perhaps best demonstrated by the extensive fetal damage seen secondary to maternal phenylketonuria and resultant fetal hyperphenylalaninemia.³,⁴

Drugs have been administered to pregnant women for treatment of fetal disorders not typically classified as metabolic, in the hope of improving the capacity for postnatal adaptation. Well-known examples include the administration of corticosteroids for the prevention of respiratory distress syndrome in premature infants, and the administration of phenobarbital in the hope of inducing liver enzymes for postnatal reduction of serum bilirubin concentration. However, there are only a few examples of attempted prenatal treatment for genetically determined metabolic defects.

The Rh isoimmunization model provides a successful illustration for medical intervention in the developing fetus.⁵ Until the introduction of Rh-immune globulin in

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the early 1970s, thousands of infants died in utero or in the early neonatal period with acute hemolytic disease secondary to Rh isoimmunization. Many of the surviving affected infants suffered from mental retardation, incapacitating neurologic disability, or deafness. The first prenatal exchange transfusion was accomplished in the early 1960s and was complemented by the development of postnatal transfusions. Finally, complete prevention of hydrops by passive maternal isoimmunization was made possible. Unlike other surgical and medical fetal interventions that are still technically experimental, transfusion has clearly moved into the realm of standard practice for Rh isoimmunization.

**Congenital Adrenal Hyperplasia**

Recently, Evans et al. demonstrated that the fetal adrenal gland can be suppressed pharmacologically by maternal replacement doses of dexamethasone. A woman with mild 21-hydroxylase deficiency whose previous female child had classic CAH with masculinization sought genetic counseling. She and her husband wished to know if prenatal diagnosis of CAH was possible, indicating they would terminate the pregnancy if the fetus were affected. They were told of an untested technique that might suppress the fetal adrenal gland, thereby preventing the masculinization. After thorough counseling, the couple agreed to the attempt at suppression. She was given dexamethasone, 25 mg, po, qid, beginning at the 10th week of gestation. Maternal estriol and cortisol values indicated rapid and sustained fetal and maternal adrenal gland suppression. In the absence of therapy, a diagnosis of CAH is indicated by elevated levels of cortisol precursors in amniotic fluid—most notably 17-OH progesterone. Amniocentesis was performed at 17 weeks' gestation and yielded a karyotype of 46,XX. Analyses of adrenal hormones in the amniotic fluid were later found to be in the low-normal range, confirming adrenal suppression. HLA haplotypes were assayed but were not informative. Therefore, dexamethasone was continued throughout the pregnancy. The patient was followed closely and had multiple reactive nonstress tests throughout the third trimester. Fetal growth appeared adequate. At 39 weeks' gestation, the patient was delivered spontaneously of a female neonate with normal external genitalia. This study demonstrates prolonged dexamethasone suppression of the fetal adrenal gland without making the mother cushinoid and without apparent adverse effects on the fetus.

The infant was started on replacement therapy with dexamethasone and Fluorinef. ACTH challenge tests revealed that she did not have the classic disease. Subsequent analysis of the neonatal HLA haplotypes revealed a crossing over between HLA B and D loci and suggested carrier status.

Following the initial observation of Evans et al., Forrest et al. used the same protocol and demonstrated that fetuses known to be clinically affected with the severe form of 21-hydroxylase deficiency CAH were prevented from external congenital masculinization. To date, several infants with classic CAH who clearly would have been masculinized have been born with normal genitalia following the treatment. We believe that these events represent the first prevention of a birth defect through specific therapy and may serve as a model for other attempts at pharmacologic fetal therapy.

The fundamental principles addressed in the attempted prevention of masculinization can logically be extended to other medical fetal therapies. The concepts of a thorough informed consent procedure, thorough documentation of progress, and high-risk obstetric management have been followed by investigators in these fields.
Fetal Cardiac Arrhythmias

Over the past several years there has been a dramatic increase in the quality and applications of fetal ultrasound technology. One major advance has been the application of M-mode echocardiography, which when coupled with real-time analysis, allows not only rapid anatomic identification of cardiac structures but also, for the first time, accurate quantitation of time-motion relationships such as the preejuction period and ventricular ejection times.\textsuperscript{8,9}

With the use of such combinations, it is possible to study the anatomic changes in the outflow tracts and thus gain a much fuller understanding of fetal cardiac dynamics. As a by-product of such increased diagnostic abilities came the realization that many hydropic fetuses were in fact suffering from congestive heart failure; some cases of failure were associated with structural defects, and others were idiopathic. In several studies, dozens of patients with arrhythmias were studied by M-mode for cardiac rate, atrial ventricular contraction sequence, atrial ventricular valve motion, and duration of the post-ectopic pause. Kleinman et al.\textsuperscript{10} reported arrhythmias in 59 patients of whom 34 had isolated ectopic beats. Spontaneous resolution in utero was seen in 28, and in 8 patients resolution occurred in the early postnatal period. Six patients had a mild sinus bradycardia, and 8 had frequent sinus pauses—all of which resolved in utero. Sustained arrhythmias were documented in 11 patients—3 of whom had an intrauterine fetal death secondary to either hydrops or structural cardiac disease.

Attempts to cardiovert the fetuses were initially made via oral digoxin administration to the mother. Recently, Kleinman et al. reported that 13 of 14 fetuses with supraventricular tachycardia responded to digoxin alone or in combination with other agents such as verapamil, propranolol, or procainamide.\textsuperscript{11} Four fetuses that did not respond to any of the medications had either continual atrial flutter or fibrillation, and two died with atrial flutter at birth. A third fetus survived after cardioversion at birth. Stewart et al. reported 30 fetuses with cardiac arrhythmias. Of note, 4 patients with bradycardia had congenital cardiac anomalies, 2 of whom died. In this report, transplacental digoxin was only moderately effective.\textsuperscript{12}

Other possible routes of administration, such as intraamniotic injection, may ultimately be considered and would have the advantage of diminishing maternal cardiac exposure. The risks and inconveniences of such procedures, however, will have to be weighed against potential maternal toxicity from these potent cardiac medications. In all likelihood, the ability to diagnose and ultimately treat such fetuses will continue to increase, and it is anticipated that such cardiac treatments will be a mainstay of biochemical fetal therapy.

Methylymalonic Acidemia

Methylymalonic acidemia is related to a functional deficiency of a vitamin B\textsubscript{12}-dependent enzyme. Coenzymatically active B\textsubscript{12} is required for the conversion of methylymalonyl-coenzyme A to succinyl-coenzyme A. There are several genetically determined causes for methylymalonic acidemia, including defects in methylymalonyl-coenzyme A mutase or in the metabolism of vitamin B\textsubscript{12} to the coenzymatically active form, 5'-deoxyadeno-sylcobalamin. Some affected subjects may respond to administration of large doses of B\textsubscript{12}, which can enhance the amount of active holoenzyme (mutase apoenzyme plus 5'-deoxy-adenosylcobalamin).

Ampola et al. were the first to attempt prenatal diagnosis and treatment of a B\textsubscript{12}-responsive variant of methylymalonic acidemia.\textsuperscript{13} They followed the pregnancy of a patient who had previously suffered the loss of a child to severe acidosis and
dehydration at the age of 3 months. The diagnosis of methylmalonic aciduria was made only posthumously by chemical analysis of blood and urine. In the pregnancy they followed, an amniocentesis was performed at 19 weeks' gestation and documented elevated methylmalonic acid in cell-free amniotic fluid. Cultured amniotic fluid cells had defective propionate oxidation and succinate oxidation, undetectable levels of 5'-deoxyadenosylcobalamin, and normal succinate oxidation and methylmalonyl-coenzyme A mutase activity in the presence of added 5'-deoxyadenosylcobalamin. These studies established by approximately 23 weeks' gestation that the fetus suffered from methylmalonic acidemia seemingly due to deficient synthesis of 5'-deoxyadenosylcobalamin.

It was already known that fetal methylmalonic acidemia is associated with increased methylmalonic acid excretion in maternal urine.14 Ampola et al. documented increased methylmalonic acidemia in a maternal urine sample first collected at 23 weeks' gestation; the methylmalonic acid excretion/mg creatinine was approximately twice the upper normal limit and demonstrated a further rise by 25 weeks. Later the same authors showed that urinary methylmalonate excretion is not abnormal in heterozygous females carrying a normal fetus.15

At 32 weeks' gestation, cyanocobalamin (10 mg/day) was administered orally to the mother in divided doses. This only marginally increased the maternal serum B₁₂ level; however, there was a slight reduction of urinary methylmalonic acid excretion, which remained severalfold above normal. At approximately 34 weeks' gestation, 5 mg cyanocobalamin/day intravenously was begun. The maternal serum B₁₂ level rose gradually to more than sixfold normal, and this was accompanied by a progressive decrease in urinary methylmalonic acid excretion. Maternal urinary methylmalonate was only slightly above the normal range when delivery occurred at 41 menstrual weeks. Amniotic fluid methylmalonic acid concentrations were three times the normal mean at 19 menstrual weeks and four times the normal mean at term, despite prenatal treatment.

Postnatally, the diagnosis of methylmalonic acidemia was confirmed. The infant suffered no acute neonatal complications and had an extremely high serum B₁₂ level. Long-term postnatal management involved protein restriction; however, no continuous cyanocobalamin treatment was required.

In this instance prenatal treatment certainly improved the fetal, and secondarily the maternal, biochemistry. Whether there was any significant clinical benefit to the fetus by in-utero treatment cannot be adequately assessed. It seems likely that reducing the fetal burden of methylmalonic acid had some beneficial effect on fetal development and possibly reduced the risks in the neonatal period. Such, however, is only speculation.

Nyhan has suggested that there may be an increased frequency of minor anomalies associated with untreated fetal methylmalonic acidemia.15 Thus very early or perhaps even prophylactic treatment with B₁₂ before prenatal diagnosis in at-risk cases might be indicated for optimal therapy of B₁₂-responsive methylmalonic acidemia.

The report by Ampola et al. was the first example of treatment of a vitamin-responsive inborn error of metabolism in utero.13 A number of important questions raised by the study are still unresolved.

**Multiple Carboxylase Deficiency**

Biotin-responsive multiple carboxylase deficiency is an inborn error of metabolism in which the mitochondrial biotin-dependent enzymes, pyruvate carboxylase, propionyl-coenzyme A carboxylase, and
B-methylcrotonoyl-coenzyme A carboxylase, have diminished activity. Affected patients present as newborns or in the early childhood period with dermatitis, severe metabolic acidosis, and a characteristic pattern of organic acid excretion. Metabolism in patients or in their cultured cells can be restored toward normal by biotin supplementation. There have been two reports of prenatal administration of biotin to fetuses affected with this disorder.

Roth et al. treated a fetus without the benefit of prenatal diagnosis in a case in which two siblings of the fetus had died of multiple carboxylase deficiency. The first sibling had died within 3 days of birth without a diagnosis, and in the second the diagnosis of biotin-responsive carboxylase deficiency was made posthumously.

The patient was first seen at 34 weeks' gestation. Prenatal diagnosis was not attempted because of the late stage of pregnancy. The maternal urinary organic acid profile was normal throughout the final 4 weeks of pregnancy. Because of severe neonatal manifestations in the previous siblings and the probable harmlessness of biotin, oral administration of this compound to the mother was begun at a dose of 10 mg/day. There were no apparent untoward effects; maternal urinary biotin excretion increased approximately 100-fold during biotin administration.

Nonidentical twins were subsequently delivered at term. Cord blood and urinary organic acid profiles, and cord blood biotin concentrations were 4–7 times greater than normal. The neonatal course for both twins was unremarkable.

Subsequent study of the cultured fibroblasts of both twins compared under biotin-rich and biotin-depleted growth conditions indicated that in biotin-depleted medium, the cells of twin B (but not of twin A) had virtual complete deficiency of all three carboxylase activities. Genetic complementation studies confirmed that despite the normal clinical presentation during the newborn period, twin B was homozygous for the disease mutation.

Packman et al. have also reported prenatal diagnosis and treatment of biotin-responsive multiple carboxylase deficiency in a mother who had previously given birth to a boy with the neonatal-onset form of this disease. In the next pregnancy, maternal urine organic acid profiles were normal. The three carboxylase activities were assayed in cultured amniotic fluid cells obtained by amniocentesis at 17 menstrual weeks. In biotin-restricted medium, the amniotic cells demonstrated the characteristic severe reduction in carboxylase activities.

At 23.5 menstrual weeks, the mother started receiving 10 mg/day oral biotin. After birth, the term female exhibited no clinical or gross chemical abnormalities. Postnatal biotin administration was begun on day 4. The diagnosis of multiple carboxylase deficiency was confirmed in fibroblasts derived from the neonate. Postnatal development of the infant was normal.

These two cases provide compelling evidence that biotin administration effectively prevented neonatal complications in certain patients with biotin-responsive multiple carboxylase deficiency. No toxicity from treatment was observed.

In the patients with methylmalonic aciduria and biotin-responsive multiple carboxylase deficiency discussed previously, the traditional approach would be treatment immediately after birth. At this time, it is not possible to definitively assess the relative advantages or disadvantages of prenatal treatment, although such therapy appears both effective and logical.

**Abnormalities of Mineral Metabolism**

Specific prenatal mineral supplementation has yet to be reported for prevention of human fetal disease. However, such
additives have been used in animals with genetic deficiencies. Animal studies are of considerable interest and suggest the possibility of analogous human treatment.

**Manganese**

The effects of prenatal manganese supplementation on the prevention of otolith defects in mice affected with the pallid mutation have been investigated.\textsuperscript{18,19} Pallid mice have defective pigmentation, including an absence of pigment from the membranous labyrinth. This pigmented characteristic is fully penetrant in the pallid homozygous recessive, whereas another manifestation, impaired otolith formation, is variably expressed. Lyon reported a significant correlation of litter size and the expression of the otolith abnormalities in the offspring and speculated that the otolith defect may be influenced by competition in utero for an unidentified substance.\textsuperscript{20}

Hurley et al. reported that development of the inner ear in normal rats and mice was affected by decreased manganese. In mice, experimental manganese deprivation in utero induced a defect of the inner ear that was morphologically and behaviorally indistinguishable from pallid, although manganese deficiency did not mimic the effect of the mutant gene on pigmentation. Subsequently these investigators observed that manganese supplementation of pallid mice throughout gestation with a diet containing 45 to 2,000 parts/million of manganese yielded a dose-dependent decrease in the percentage of abnormal otoliths.\textsuperscript{18}

These data have been extended to a genetic basis for susceptibility. In several studies of prenatal manganese restriction, the percentage of otolith abnormalities is influenced by the strain of mice studied. Thus, interactions of manganese intake and genetic predisposition influence otolith development in several strains.\textsuperscript{18} These observations invite the speculation that at low or borderline levels of dietary intake of other nutrients, fetal responses may vary substantially depending on the genotype of the fetus.

There are a number of genetic defects in animals with associated pigmented and inner-ear abnormalities. Hurley and colleagues have suggested that a sex-linked form of ocular albinism in humans, associated with labyrinthine dysfunction, may be analogous to some of these animal models. We are unaware of any studies of manganese metabolism in human ocular albinism, or of attempts to administer manganese prenatally in the hope of ameliorating expression of any associated labyrinthine defects.

**Copper**

Hurley and coworkers have studied the effects of prenatal copper administration on mice with the recessive mutant "crinkled" gene.\textsuperscript{21} These investigators have suggested that the "crinkled" gene produces many phenotypic characteristics common to patients with Menkes kinky-hair syndrome. Dietary supplementation of pregnant mice with copper sulfate partially ameliorated the effects of the crinkled gene in the offspring. Different prenatal copper regimens have resulted in varying degrees of success. Copper triacetate appeared to be superior to copper sulfate in increasing postnatal survival and body copper content of the mutant offspring of heterozygous dams. Postnatal supplementation with copper did not increase survival of the mutants.

These studies may possibly lead to insights relevant to prenatal treatment of Menkes syndrome, a sex-linked disorder characterized by progressive degeneration of neurologic function in infants. Alterations suggestive of functional copper deficiency are present in affected infants. In Menkes disease, fibroblasts accumulate excess copper, probably present in an ab-
normally bound form. Menkes syndrome can be diagnosed in utero by demonstrating abnormally increased copper uptake in Menkes-cultured amniotic-fluid cells incubated in a high-copper medium, and possibly in chorionic villus samples (CVSs). Menkes disease has been refractory to postnatal therapy with copper, and it is conceivable that by analogy to the crinkled mutation, prenatal treatment might be of greater benefit.21

Despite apparent responses to prenatal mineral administration of pallid and crinkled mutations, the relationships of these mutants, if any, to ocular albinism and Menkes disease, respectively, remain quite speculative. While animal studies have proved encouraging, they do not yet justify trials of prenatal mineral supplementation in genetically defective human beings.

Galactosemia

Galactosemia is an inborn error of metabolism caused by diminished activity of the enzyme galactose-1-phosphate uridyl transferase. It is an autosomal recessive disorder that results in cataracts, growth deficiency, and ovarian failure. Prenatal diagnosis is possible by study of cultured amniocytes. Clinical symptoms appear in the neonatal period and can be largely ameliorated by elimination of galactose from the diet. Cellular damage in galactosemia is probably related to accumulation of galactose-1-phosphate intracellularly and of galactitol in the lens.

There are suggestions that even the early postnatal treatment of galactosemic individuals with a low galactose diet may not be sufficient to ensure normal development. There has been speculation that prenatal damage to galactosemic fetuses could contribute to subsequent abnormal neurologic development and to lens cataract formation.22,23 Furthermore, it has been recently recognized that female galactosemics, even when treated from birth with galactose deprivation, have a high frequency of primary or secondary amenorrhea due to ovarian failure. Subtle abnormalities have also been suggested for male gonadal function.24

Exposure to a high-galactose diet has been considered to represent an animal model for human galactosemia. Chen and associates have observed a reduction in the oocyte content of rat ovaries after prenatal exposure to a 50% galactose diet.25 However, analogous alterations in the testes were not observed in prenatally treated males. Experiments in rats suggest that toxicity to the female gonads from galactose and its metabolites is most obvious during the premeiotic stages of ovarian development.

These observations in animals and humans have led to speculation that galactose restriction during pregnancy may be desirable if the fetus is affected with galactosemia. In the human female, ovarian meiosis begins at 12 and is complete by 28 menstrual weeks. Thus, ovarian damage, and perhaps neurologic or lens abnormalities, might occur before the usual time at which prenatal diagnosis by amniocentesis can be accomplished. Diagnosis at 10 weeks by chorionic villus sampling might allow therapy to be pursued only in early diagnosed cases. Anticipatory treatment in pregnancies at risk for a galactosemic fetus might best be initiated very early in gestation or even preconceptionally.

Despite these experiments and speculations, we are unaware of studies that adequately assess the impact of prenatal administration of a low-galactose diet to galactosemic infants. For obvious reasons, such data, especially controlled, will be difficult to obtain. Nevertheless, prenatal galactose restriction is probably desirable in galactosemia and should be harmless. There is little reason to suppose that galactose restriction would have adverse consequences, since galactosemic and normal fetuses are both capable of some endogenous galactose synthesis.
Future Developments

Only the most preliminary steps have been taken toward the therapy of genetic metabolic disorders in the fetus. Certain categories of diseases may be candidates for future attempts at treatment, especially if some new approaches are developed.

Vitamins

Prenatal therapy has been reported for two vitamin-responsive genetic errors of metabolism. Many vitamin-responsive defects are known and have responded to postnatal treatment. Antenatal treatment of some of these may be anticipated, especially for those with neonatal manifestations.

We also speculate that in addition to the usual vitamin-responsive errors, there may be genetic defects for which prenatal vitamin E administration may be justifiable. Postnatally, vitamin E administration prevents abnormalities of leukocyte function and improves the shortened red cell survival in glutathione synthetase deficiency. Because grossly lowered intracellular glutathione levels in this mutant state seem to predispose to oxidant-mediated cellular damage, it might be desirable to consider prenatal antioxidant therapy with vitamin E. Most patients with glutathione synthetase deficiency have neurologic impairment, which can be progressive. Functioning as an antioxidant, vitamin E might inhibit the development of neurologic abnormalities. Such speculations can be confirmed or denied only by future clinical studies.

Very low serum vitamin E levels are also seen in abetalipoproteinemia. Progressive and fatal neurologic impairment gradually develops. It is now known that high-dose vitamin E supplementation can retard or prevent neurologic damage. While patients with abetalipoproteinemia, like glutathione synthase–deficient patients, appear not to manifest gross neurologic abnormalities at birth, prenatal damage is possible. Antenatal treatment with vitamin E might be justifiable on an experimental basis.

Miscellaneous Pharmacologic and Nutritional Possibilities

 Suppressing excessive cholesterol production prenatally in severe familial hypercholesterolemia would be desirable if a safe and effective agent for accomplishing this were available. No clear evidence for hypercholesterolemic prenatal damage is yet available, but it would seem that the less exposure the better.

If cysteamine or related agents were to prove effective treatment for lethal variants of cystinosis, prenatal therapy might be considered because excessive and possibly harmful cystine accumulation is already demonstrable in cystinotic fetuses. Cystine levels have been measured in normal chorionic villi, and significant elevations, even at 10 weeks' gestation, have been detected in a cystinotic CVS.

Inhibitors of gammad glutamyl transpeptidase, if safe, would elevate intracellular glutathione levels and inhibit oxoproline production in glutathione synthase deficiency, thereby averting the characteristic neonatal acidosis.

In theory, it would be desirable to minimize copper accumulation in Wilson disease as early as possible. If and when reliable prenatal diagnosis of Wilson disease is possible, cautious prenatal administration of penicillamine might be considered. Such would be a double-edged sword, however, as the teratogenic and lathyritic potential of penicillin would demand careful evaluation. Recently, Batshaw et al. treated certain urea-cycle defects by the administration of arginine and benzoate. Since some of these neonates develop acute hyperammonemia immediately after birth, it might be desirable to consider pretreating the fetus with these
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compounds just before or during labor to minimize postnatal hyperammonemia.

Conversely, drug avoidance may be desirable as an approach to fetal treatment. For example, fetuses with glucose-6-phosphate dehydrogenase deficiency are sensitive to a variety of drugs that can induce hemolysis. It would probably be appropriate to avoid administering such agents to women carrying or known to be at risk for carrying fetuses deficient in glucose-6-phosphate dehydrogenase.

Chronic villus sampling or umbilical cord catheterization under ultrasound guidance may lead to the development of other types of fetal treatment that at present may seem rather futuristic. Systems such as gene replacement for certain disorders will be the subject of much experimental work in the next decade. Progress is being made in postnatal experimental models on administration of thymic cells for certain immune deficiency states, bone marrow transplantation for a variety of genetic disorders, and gene transfer. The development of better and earlier techniques for prenatal treatment will be complex, especially with regard to gene transfer, but progress will be made, and access to the fetal vasculature may be required for these methods to have a chance for success.

Bone marrow transplantation or thymic cell infusion is only a specialized example of organ transplantation. In the future, fetal organ transplantation may become possible and open many prospects for surgical treatment of certain biochemical genetic disorders.

One can also speculate about therapeutic possibilities involving compounds administered directly into the amniotic fluid or into the fetal intestinal tract. It is possible, for example, to administer thyroid hormone in this fashion. It might someday be possible to prevent meconium ileus in cystic fibrosis by instilling yet to be deter-

mined substances (probably enzymes) into the fetal intestinal tract.

References

12. Stewart TA, Tonge HM, Vladimiroff JW.


