Prenatal Diagnosis:
Heredity Disorders, Other Biochemical Diseases, and
Disfiguring Birth Defects

There are over 250 recognized sex-linked diseases, affecting every organ system.
Of these, 95% affect males, (Emery, 1968). Despite these many sex-linked diseases, at
present prenatal diagnosis can specifically be made in fewer than 40 diseases. (Emery,
1968). These sex-linked diseases are individual rare and some are named after
physicians who described them, for example, Hemophilia A and B, Duchenne muscular
dystrophy, fragile-X syndrome, Fabry disease, Hunter syndrome, Lesch-Nyhan syndrome,
and Menkes steely-hair syndrome. The following discourse considers the reasons for the
importance of prenatal diagnosis, heredity disorders, and disfiguring birth defects.(Nora,1989).

Fabry disease is a biochemical disorder caused by a missing enzyme. (Mulinsky,
1989). A complex fatty substance accumulates in the body because of the missing
enzyme which would ordinarily break this compound into pieces.(Nora,1989). This
missing enzyme causes kidney and blood-vessel problems that lead to high blood
pressure, kidney failure and strokes.(Mulinsky, 1989). After many years of symptoms,
most patients have died in their thirties and forties owing to a lack specific treatment.

A biochemical disorder also caused by a missing enzyme is the Lesch-Nyhan
syndrome, an extremely unpleasant disorder characterized not only by profound mental
retardation and features of brain damage (stiff limbs with peculiar movements), but also
self-mutilation, (Jones, 1988). Given good care and attention however, these patients
may live on many years in their profoundly retarded state. They often require restraining,
tying their hands, to prevent them from mutilating themselves.

Another Affected children with Menkes steely-hair syndrome have hair that feels
similar to steel wool; in addition, they are retarded. The basic defect in this condition
concerns the way the body handles copper.

Only a few of these sex-linked disorders can now be diagnosed in the fetus,
(Stein, 1994). At the present time, the only recourse parents have in the case of sex-
linked diseases that are not prenatally diagnosable is to determine the sex of the fetus. If
a female fetus is found, the parents can be reassured that their child will not be affected
(a critical exception is fragile-X). However, if it is determined that there is a male fetus
present, there is a fifty percent chance that it is affected, (Milunsky, 1989). Since there is
no way of being certain, the parents must decide simply on the basis of high risk weather
to take a chance or terminate that pregnancy.

There are some unusual sex-linked diseases that are confined to females.

Disorders of this kind (such as incontinentia pigmenti, a skin disorder associated with brain damage) can be managed by determining weather the fetus is a female. In this group, virtually all females will be affected, and the parents could selective elect to have unaffected boys.

Hemophilia A and Duchenne muscular dystrophy are two of the most common sex-linked diseases that are familiar to most people. But there are so many other diseases that great care must be taken by both the doctor and the family in obtaining an accurate family history. Renpenning syndrome, in which there is mental retardation without any other physical signs, is confined to males. The only way to suspect sex-linked inheritance is for the physician to carefully analyze the family lineage. Tests are preformed to detect female carriers of such diseases. For example, almost all carriers of hemophilia and Duchenne muscular dystrophy can now be detected. A muscle enzyme, creatine phosphokinase, which leaks into the blood is also often measured to give a higher probability of recognizing a carrier. Unfortunately, because of recombination, the carrier-detection tests for both hemophilia and muscular dystrophy do not provide answers in 100 percent of cases. A negative result causes uncertainty and leaves the question of carrier detection basically unanswered. Fortunately, carrier-detection tests are steadily becoming possible in more of the sex-linked and other disorders.

Prenatal Studies for Heredity Biochemical Disorders

Many hundreds of different hereditary biochemical disorders of metabolism are known. About 1 in every 100 children born have one of these biochemical disorders. (Nora, 1989). Many of these disorders do not cause mental retardation, or impair the child's normal development or general health to any great extent, if at all. Many others, however, cause severe mental retardation, seizures, stunting of growth, and early death. Close to 150 of these biochemical disorders can now be diagnosed in the affected fetus early in pregnancy. (Nora,1989). The first diagnosis of a biochemical disorder in the fetus while in the womb was made in the late 1960's; the disorder was Tay-Sachs disease. (Emery, 1968). Diagnosis such as this are made by obtaining cells from the amniotic fluid which are placed in small dishes containing a nutrient broth, and then kept in a special warm, moist incubator. They grow slowly. After a period of two to three weeks or, occasionally, as long as six weeks, there are enough cells to work on. Each of the cells having the genetic blueprint will show the specific biochemical defect (for example, deficient activity of an enzyme) thereby enabling a diagnoses to be made. With diagnosis, physicians can treat the known disorder through the womb.

For a few disorders, such as Rh disease, treatment of the fetus directly or through

the mother has now succeeded. The first prenatal diagnosis of a biochemical disorder that was treatable in the womb was the rare disorder methylmalonic aciduria. (Milunsky, 1989). This disorder causes failure to thrive, vomiting, lethargy, biochemical disturbances, poor muscle tone, and eventually mental and motor retardation. Treatment of the fetus through the mother during pregnancy is carried out by giving her intramuscular injections of massive doses of vitamin B12. This method secures the child's health at birth, when a special low-protein diet is started. In this way serious illness, mental retardation and early death have been averted.

Another considerably more common disorder is congenital adrenal hyperplasia (CAH). This heredity disorder is inherited equally through a gene from both parents (autosomal recessive). About 1 in 5,000 to 13,000 whites and 1 in 7550 Japanese are born with CAH - nowhere near the remarkable 1 in 282 among the Yupik Eskimos. (Jones, 1988). Various forms of this disorder occur, each due to a deficient, though different enzyme along a stepwise pathway that finally results in the production of "cortisone". Symptoms of the most common form of CAH are masculinization of the female genitals, excessive growth, early appearance of pubic hair, and enlargement of the penis or clitoris. Critically important in about two-thirds of affected children is the occurrence of a life-threatening crisis one to four weeks after birth, characterized by vomiting, diarrhea, and salt loss leading to collapse and even death if not diagnosed and treated with "cortisone". Where needed, surgical correction of the female genitals is possible, and normal growth, puberty and fertility can be achieved through lifelong medical treatment with cortisone like supplements. Today, both carrier detection and prenatal diagnosis are possible for most families, using DNA techniques combined with special blood-group linkage studies.

The very first inherited biochemical disorder found to cause mental retardation was phenylketonuria.(Koiata, 1995). Since that description in 1934, it has been learned that PKU (phenylketonuria) occurs in about 1 in 14,000 newborns in the United States and as frequently as 1 in 4,500 in Northern Ireland.(Nora, 1989). Transmitted by a recessive gene from each parent, all problems are the result of a deficient liver enzyme. An affected untreated child will develop irreversible mental retardation. Therefore, in most Western countries , blood screening of newborns is done to make an immediate diagnosis and institute the special low-protein diet through which mental retardation can be avoided.

Despite the availability of effective treatment after birth, prenatal diagnosis remains a serious option for parents. This option is valuable because the special low protein diet is tasteless and very restrictive.(Mulinsky, 1989). Enforcing the

diet in early childhood is difficult, and needs to be continued for as long as possible. (Mulinsky, 1989). The usual practice has been to discontinue the diet at four to seven years of age. Recent studies show intellectual deterioration, loss of IQ pionts, learning difficulties, and behavior problems after the diet has been discontinued. (Jones, 1988). A steadily increasing number of women with PKU are entering the childbearing years. (Jones, 1988). If they become pregnant, the chemical products that accumulate in their blood damage the fetal brain and other developing organs. Their risk of having a retarded child or one with a heart defect or microcephaly approaches an incredible 100 percent. (Koiata, 1995). Only a mere handful of cases are known in which the diet was adhered to strictly before conception and a healthy child is born. Today, new DNA techniques have made both carrier detection and prenatal diagnosis of PKU possible for most families and therefore an important decision.(Koiata, 1995).

Galactosemia is another treatable hereditary biochemical disease where prenatal diagnosis is possible. If the fetus is affected, special lactose-free dietary treatment of the mother started early enough will almost always avert early death or mental retardation, cataracts, and liver damage.(Jones, 1988). There are a few other very rare disorders where prenatal diagnosis and early treatment may be critical to save life or prevent mental retardation or other consequences. Some of these diseases are: tyrosinemia, homocystinuria, maple-sirup urine disease, and propionicacidemia. (Jones, 1988). A few other disorders are now being conquered by early diagnosis and treatment in the womb. (Jones, 1988). Continued support for medical research will undoubted provide more and more opportunities for early treatment or prevention, reducing the need for abortion, which is a major option and issue today. Progress in actual prenatal treatment for genetic disorders can be anticipated, provided that fetal research is not interdicted by state legislation. (Nora, 1989).

The fact that mental retardation is more common in males has been a known fact for about a century. (Emery, 1968). The major reason for this excess became clear in the mid-1970's, when studies from Australia focused attention on an unexpectedly common disorder with striking features: the fragile -X syndrome. (Nora, 1989). This disorder, caused by a single defective gene on the X chromosome, has highly variable signs that usually include mental retardation and distinctive facial features. (Milunsky, 1989). Special studies have revealed the location of the defective gene on the X chromosome: a vulnerable spot that tends to break, hence, the term "fragile-X syndrome." (Milunsky,

1989). Because of the remarkable variability of the physical, behavioral, and developmental features of fragile-X syndrome and the delayed appearance of some major features, definitive recognition of this disorder eluded researchers for many years. (Milunsky, 1989). Confusion was also generated by the fact that although males were primarily affected, within the same families mildly affected females were also observed. It is now known that about 1 in 1,060 males are born with fragile-X syndrome, and that the disorder accounts for about 25 percent of all male cases of mental retardation and about 10 percent of mild to moderate mental retardation in females.(Nora,1989). The main signs of this disorder are on Table 1.

Transmission of the fragile-X disorder was initially thought to conform to other sex-linked disorders. Quite unexpectedly, a unique pattern that does not conform exactly to sex-linked inheritance has been discovered only recently. The current knowledge, as studied by Dr. Milunsky, allows certain risk predictions:

1. An intellectually normal female who inherits the fragile-X gene from her carrier mother has a 50 percent risk of having an affected son, whose risk of being retarded is 40 percent . Half her daughters will carry the gene, but only 16 percent will be retarded.

2. If such a daughter is retarded, her risk of having an affected and retarded son is 50 percent. If she has a daughter herself, the risk is 28 percent that the will also be mentally impaired.

3. Men who are seemingly entirely normal and do not even show the fragile-X chromosome when tested may nevertheless transmit the gene to all their daughters. These females are usually intellectually normal. However, when they reproduce, 50 percent of their sons will be affected, and 40 percent will be retarded. Half their daughters will be carriers, among 16 percent will be retarded.

4. Normal-but-transmitting males may account for 20 percent of all cases of the fragile-X syndrome. Unfortunately, they will remain undetectable until new technology revels their ominous burden or until one of their children or grandchildren is diagnosed as having this fateful flaw.

5. Curiously, women carriers who bear a son who is a normal-but- transmitting male have a 50 percent risk of having an affected male, who has only a 9 percent risk of being retarded. This carrier female also has a 50 percent risk of having carrier daughters, and these girls have only a 5 percent risk of being intellectually impaired.

Further research inth this devistating disorder and it's complex heridaty pattern may significantly reduce the amount of congenital mental retardation.

Heredity, biochemical and other disfiguring birth defects must be a top priority with expectant parents. A knowledge of these concerns will alolow them to make wise

decisions regarding prenatal diagnosis and decisions and availability of treatment to
prevent birth defects, thereby saving lives.