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Intrauterine Diagnosis and Genetic Counseling:

Implications for Psychiatry in the Future

Gilbert S. Omenn
Arno G. Motulsky

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INTRAUTERINE DIAGNOSIS AND GENETIC COUNSELING: IMPLICATIONS FOR PSYCHIATRY IN THE FUTURE[1]

Many psychological burdens are associated with pregnancy, one of the most distressing being the fear of a deformed or defective baby. The fear has some basis in the fact that approximately 3 percent of all live births are severely retarded in mental development or have serious defects. For the family in which a child or another relative is already defective, the risks may be greatly magnified. In the past two decades, genetic counseling clinics have been established to deal with the medical, genetic, and emotional aspects of such disorders.

The first requirement for genetic counseling is precise diagnosis in order to predict the course of the illness. Determination of the risk of a recurrent defect in subsequent children requires clear differentiation of heterogeneous causes of similar syndromes, often relying upon the detailed family history and upon various laboratory analyses such as radiologic studies, chromosome karyotypes, or enzyme assays. Nevertheless, even with the most detailed evaluation, families usually can be provided with only a statistical statement. For example, the risk of recurrence in subsequent children is about 1 percent for most cases of Down's syndrome (mongolism), about 5 percent for many other birth abnormalities, 25 percent for inborn errors of metabolism inherited as autosomal recessive disorders, and 50

percent for autosomal dominant conditions. Often, however, family counseling is complicated by variable severity of the illness, uncertainty of diagnosis, or the possibility that the affected child had a fresh mutation. For many common disorders, including schizophrenia and depression, for which there is good evidence of genetic factors of unknown mechanism, an "empiric risk figure" based upon reports of the frequency of recurrence in large series of families can often be given. It must be stressed that these risks for specific disorders are in addition to the approximately 3 percent risk of mental retardation or birth defects that every couple takes when having a child.

In the past few years, a dramatic development in counseling for some genetic disorders has occurred. For a small, but rapidly increasing number of diseases, it is possible to diagnose the condition *in utero* early enough in pregnancy to permit selective abortion of affected fetuses. Unfortunately, treatment is unsatisfactory for so many conditions, especially those affecting mental development, that prevention of the birth of an affected child appears highly desirable to many parents and to their physicians. Diagnosis depends on the specific determination of chromosome karyotype or enzyme assays in cells of fetal origin obtained from the amniotic fluid around the fetus and grown in tissue culture medium in the laboratory. Though much speculation exists about the potential feasibility of "genetic engineering" by manipulation of the DNA in cells, many specific disorders can be prevented by what might be called "reproductive engineering."

Amniocentesis

Amniocentesis is a procedure for obtaining amniotic fluid that contains fetal cells desquamated from respiratory and urinary tract endothelia and from skin and amnion. A transabdominal approach under local anesthesia has replaced the transcervical and transvaginal approaches, which carry a higher risk of bleeding, infection, and induced miscarriage. A small-gauge "spinal" needle is inserted under sterile conditions through the abdominal and uterine wall into the amniotic cavity. The procedure is done "blind"; success depends upon the skill and experience of the obstetrician. More accurate localization of the placental and fetal position using ultrasound techniques is being evaluated for reliability and safety. The time at which amniocentesis is carried out must be a compromise. The more advanced the pregnancy, the more fluid and the greater the likelihood of obtaining an adequate sample for study. On the other hand, amniocentesis must be carried out early enough so that laboratory studies can be completed and abortion be done safely (and legally) if termination of the pregnancy is indicated. The volume of the amniotic fluid has been measured directly with the removal of the products of conception *in toto* in pregnancies interrupted by abdominal hysterectomy between ten and twenty weeks of gestation. There is an average of 50 ml. of amniotic fluid at twelve weeks, 100 ml. at fourteen weeks, 150 ml. at fifteen weeks, and 450 ml. at twenty weeks (see Figure 27-1). Usually 10-20 ml. are removed for studies. The length of pregnancy or gestational age is calculated

by obstetricians from the first day of the last menstrual period. Thus, the actual fetal age is approximately two weeks less than the “duration of pregnancy.”

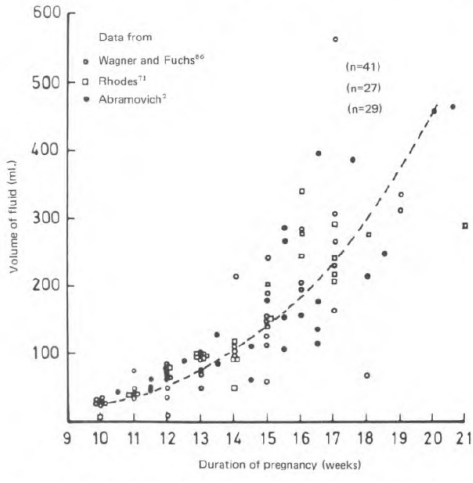

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Figure 27-1.
Volume of amniotic fluid as a function of gestational age. Note variation among individual specimens. Data from a total of ninety-seven cases. (From Emery with permission.)

The hazards of amniocentesis are not yet fully evaluated. Early reports of several hundred procedures are remarkably free of serious immediate complications’ There are no known cases of severe maternal bleeding, infection, or uterine rupture; no induced miscarriage; and no increase in the number of congenital malformations in the offspring. The fetus seems to “float away” from the amniocentesis needle, which presumably accounts for a

lack of direct puncture wounds. The potential long-term hazards of amniocentesis are much more difficult to evaluate. Careful follow-up with appropriately matched control births must be carried out to assess mental and physical development in "normal" babies subjected to amniocentesis during pregnancy. The effect, if any, of disturbing the volume and possibly the dynamics of the amniotic fluid is simply unknown. It would be a tragedy if normal babies suffered mild depression of their later IQ levels or some other subtle damage because of a diagnostic procedure aimed at detecting an abnormal fetus. For this reason, parents in the early 1970s were being counseled in pregnancies with less than 1 percent recurrence risk for a given disease that the risk of the procedure may be greater than the risk of a fetus affected with the avoidable condition. Depending on how abhorrent the disorder is to the parents, they may agree to forgo amniocentesis, or they may insist on accepting the risk of the procedure or else elect to have no more pregnancies.

Methods of Analysis of Amniotic Cells

Determination of Sex and Chromosome Karyotype of the Fetus

Not until 1956 were suitable techniques for spreading and staining the human chromosomes developed, so that the correct number of chromosomes could be established as 46 (not 48). These chromosomes occur in pairs, 23

from each parent, including 22 sets of autosomes and one set of sex chromosomes, XX for females and XY for males. Beginning with mongolism or Down's syndrome in ig5g, many clinical syndromes have been associated with specific abnormalities in number or gross structure of chromosomes (Table 27-1). In the aggregate, these gross chromosomal aberrations occur in about one of 200 births and are usually detectable at birth; thus they are congenital. However, except for unusual instances due to chromosomal translocations or mosaicism in a parent, these disorders are not "inherited"; other family members are not usually affected.

*Table 27-1. Clinical Syndromes Associated with Specific Chromosomal Abnormalities**

KARYOTYPE AUTOSOMAL DISORDERS	PHENOTYPE	FREQUENCY AMONG LIVE BIRTHS	DIAGNOSED IN UTERO
Trisomy 21 D/G, G/G translocation	Hypotonia, slanted palpebral fissures, speckling of iris, simian crease, abnormal dermal ridge patterns, bony dysplasia, congenital heart disease, leukemia	l/660 (marked maternal age effect)	yes
Trisomy 18	Feeble fetal activity, prominent occiput, clenched hand, low-set ears, congenital heart defects, 10 percent survive one year, severely retarded	1/3000	yes
Trisomy 13	Defects of eye, nose, hip and forebrain, polydactyly, hyper-convex fingernails, scalp defects, cardiac anomalies, severe mental defect; 18 percent survive one year	1/5000	
Partial deletion of short arm of	Catlike cry in infancy, microcephaly, antimongoloid slant, mental deficiency, simian crease	case reports (> 30 cases)	

chromosome 5			
Sex chromosome disorders XO	Gonadal dysgenesis, short stature, broad chest, lymphedema, webbed neck, aortic and renal anomalies; normal intelligence, defect in space-form perception. (95 percent of XO fetuses are lost as spontaneous abortions)	1/3000	yes
XXY	Hyalinized seminiferous tubules, small testes, gynecomastia, eunuchoid appearance, infertility. Mental retardation and psychopathology more common	1/450 males	
XYY	Variable phenotype with increased height, gonadal anomalies, increased risk of psychopathology	1/800 males	yes

* For additional chromosomal syndromes, consult Smith.

The four chromosomal disorders of greatest interest to neuropsychiatry are mongolism, trisomy 21; Turner's syndrome or gonadal dysgenesis, 45XO; Klinefelter's syndrome, 47XXY; and 47XYY (see below).

Sex of the fetus can be determined, of course, from the full karyotype. However, it is also possible to stain fetal cells directly to detect a Barr body, which is a condensed inactive X chromosome, or a highly fluorescent Y chromosome, the "flashing Y" sign of male cells. The Barr body is found in normal XX female cells and in various sex chromosome aberrations having at least two X chromosomes, such as XXY males or XXX females. Determination of sex is useful for detection both of these sex chromosome disorders and of

males at risk for such X-linked recessive conditions as hemophilia and Duchenne-type muscular dystrophy. Technical artifacts of the two types of staining procedures can lead to errors, with obvious serious consequences in the genetic counseling. A full karyotype of cultured amniotic cells is therefore considered essential. The most important reason is that maternal cells may contaminate the amniotic fluid sample and give spurious results of a normal female. Fortunately, since adult cells have a shorter lifespan in culture than do fetal cells, the cells which grow out after two to three weeks in tissue culture appear to be exclusively of fetal origin.

Biochemical Studies

Inborn errors of metabolism may be recognized by abnormal accumulation of metabolites or by deficiency of specific enzyme activity. Amniocentesis late in pregnancy has been performed for many years to monitor bilirubin levels as a sign of hemolysis in Rh-incompatible pregnancies in sensitized mothers. Elevated concentrations of pregnanetriol and 17-ketosteroids can be detected at term in amniotic fluid of fetuses affected with adrenogenital syndrome, but not at earlier times when abortion of affected fetuses might be desired. At least two conditions have been diagnosed on the basis of deficiency of enzymes normally detectable in the cell-free fluid; these are alpha-i, 4-glucosidase for Pompe's type of glycogen storage disease and N-acetylhexo-saminidase A for Tay-Sachs disease. In both

cases, the diagnosis was confirmed with uncultured and cultured amniotic fluid cells. Tests of the uncultured fluid are hazardous, because most enzymes are intracellular and not present normally in cell-free fluid, because the cell population of amniotic fluid may be highly variable, and because maternal contamination may give a falsely normal assay.

The rule of thumb applied to enzymatic analysis of amniotic fluid cells is the following: If the enzymes can be detected in cultured fibroblasts from skin biopsies, then the enzyme should be present in cultured amniotic fluid cells. This generalization is the basis for an extensive tabulation of rare, inherited metabolic disorders for which prenatal diagnosis has not yet been demonstrated, but for which prenatal diagnosis is feasible. On the other hand, it is known that some enzymes first appear only at certain stages of development and that many others have different levels of quantitative activity at different times in fetal and postnatal life. Furthermore, the activity of certain enzymes may vary with the stage of the cell cycle in cultures in vitro. Thus, it is essential for each enzyme that rigorous controls be established with normal amniotic cells in identical culture conditions. Inasmuch as each of the inborn errors of metabolism is rare (often occurring at a frequency of one case per 40,000 births), no laboratory should be expected to assay for each enzyme deficiency. In fact, major genetic centers are actively collaborating in providing amniotic fluid samples of various ages as controls and in carrying out different, specific assays.

Consent for Amniocentesis

Because amniocentesis is still considered an investigative procedure, current knowledge about the procedure and the tests required for prenatal diagnosis should be discussed as fully as possible with the parents. They should be asked to read and sign a consent form' containing the following major points:

1. There is an unknown, but low, risk to mother and fetus.

2. More than one amniocentesis may be required to obtain sufficient fluid.

3. Cell cultures may fail to grow.

4. Chromosomal or biochemical analyses may be unsuccessful.

5. In vitro results rarely may not reflect the status of the fetus, especially if a twin pregnancy is sampled.

6. Normal chromosomal or biochemical results on the tests that are performed do not eliminate the possibility of birth defects or mental retardation from other causes or both. Any condition not ruled out by a specific test can be expected to occur with a frequency similar to that in the general population.

Types of Behavioral Syndromes Suitable for Prenatal Diagnosis

By far the greatest progress in prenatal diagnosis has come in the area

of those chromosomal and metabolic disorders that grossly disrupt the normal processes of neurological and mental development in the central nervous system. The reason is simple: The "phenotype" of mental retardation has been sorted on clinical and laboratory grounds into numerous specific etiologic mechanisms, for which specific diagnostic tests can be applied.

Chromosomal Disorders Causing Mental Retardation

The most important single disorder suitable for prenatal diagnosis is Down's syndrome (mongolism). One of every 660 births is a child with Down's syndrome, recognizable at birth by the clinical features of hypotonia, slanted palpebral fissures, flat facial profile, speckling of the iris, simian crease in the palms, and congenital heart defects. The risk of mongolism increases strikingly with age of the mother, from about 1/2000 at age twenty, to 1/1000 at age thirty, 1/500 at age thirty-five, 1/100 at age forty, and 1/40 at age forty-five. More than 95 percent of cases are due to trisomy 21, meaning that 47 chromosomes are present, with the No. 21 set occurring in triplicate rather than as a pair. The mechanism of trisomy 21 is nondisjunction, that is, the pair of No. 21 chromosomes in the mother's egg failed to separate normally. The added single No. 21 chromosome from the father's sperm produces a fertilized egg with three No. 21 chromosomes. Penrose calculated that one-half of all the babies with mongolism are born to mothers over thirty-five years old. The number of children born with Down's

syndrome can be decreased simply by social practices that reduce the average age of mothers or that discourage women from having children after age thirty-five. Alternatively, it is feasible, for those couples who accept selective abortion, to prevent the birth of such children by monitoring the pregnancies of older women for trisomy 21. The age for monitoring pregnancies is now arbitrarily set at age thirty-eight to forty, but is expected to fall to age thirty-five as genetics centers develop the capacity to handle more cases and if evaluation of the potential hazards of amniocentesis indicates that the risks of the procedure are sufficiently small.

There are other circumstances in which amniocentesis should be carried out for Down's syndrome. If the family has already had one child with Down's syndrome due to trisomy 21 and the parents appear normal, the recurrence risk is estimated to be about 1 percent. The level of risk combined with the emotional, social, and financial impact of one child already affected with Down's syndrome usually leads the parents and physicians to seek prenatal diagnosis of subsequent pregnancies. About 2 to 5 percent of children with Down's syndrome have a karyotype with a "translocation pattern," 46 chromosomes that include a structurally abnormal chromosome. The "extra" No. 21 (G group) chromosome is attached to one of the "normal" G or D group chromosomes, making the equivalent of a triplicate of the No. 21 chromosome. The likelihood of the translocation pattern is relatively greater with younger mothers, so chromosome studies are particularly important in

children with young mothers. When a translocation pattern is found in the child, it is imperative to study the chromosomes of the parents. About half of the translocation cases occur *de novo* (in the formation of the egg or sperm) and have a recurrence risk similar to that for trisomy 21. The other half of translocation cases have a parent who is a healthy, balanced translocation carrier, having only 45 chromosomes, including the translocated G/D or G/G chromosome. Empirical studies have shown that the recurrence risk is 15 to 20 percent if the carrier parent is the mother and only 5 percent if the father is the carrier. One very rare form of translocation carrier (21/21) gives rise only to triplicated 21 or monosomic 21 (lethal) fertilized eggs, producing a 100 percent risk of recurrence in live-born children. These abnormalities can be recognized reliably in the karyotypes of cultured amniotic cells. If either parent is a translocation carrier, the aunts and uncles and other relatives should have chromosomal studies, since a significant proportion of relatives will also be translocation carriers with similar risk of transmitting Down's syndrome to their children.

The mean IQ for older patients with Down's syndrome is 24, with an upper limit of about 50. Many children and most adults require institutionalization; in most states, Down's syndrome accounts for half of all the patients in institutions for the mentally retarded. The annual cost to society for custodial care is so high that extensive prenatal diagnostic screening and abortion for trisomy 21 can be justified on a cost-benefit basis

alone.

Other autosomal chromosomal disorders (Table 27-1) occur much less frequently or are lethal early in life and will not be discussed further here. With new and fairly simple techniques that demonstrate specific banding patterns of human chromosomes, the list of neuropsychiatric disorders associated with less severe chromosomal alterations may be extended in the near future to include milder abnormalities than gross mental retardation.

A variety of seemingly harmless chromosomal translocations is found among "normal" individuals. Sometimes the abnormality is found first in a mentally retarded child, and then the same abnormality is identified in cells of his unaffected siblings or parents. Several such variants of uncertain significance have been discovered while testing amniotic fluid specimens for trisomy 21 or for inborn errors of metabolism. Even when there is time to test the parents and find a similar variant, it is often impossible to be sure that the fetal chromosomal findings are harmless. Moreover, one cannot offer the parents the assurance that subsequent pregnancies could be monitored with any greater certainty. Another complication arises from mosaicism, the occurrence of more than one type of cell line. For example, a pregnancy at risk for Tay-Sachs disease was monitored, and normal enzyme levels were found; however, because of the mother's advanced age, chromosomes were analyzed as well. Cultured amniotic cells were 45 XO, but studies of the aborted fetus

later showed only a normal 46 XY karyotype. Presumably the fetus had the XY/XO karyotype. Also, the possibility that twins are present and only one is sampled must be noted. In the early series of cases reported by Nadler and Gerbie, two instances of twin pregnancies were not recognized, but no untoward consequences resulted.

Inborn Errors of Metabolism

At least ten autosomal recessive and three X-linked recessive enzyme deficiencies have been demonstrated in amniotic fluid cell specimens, permitting abortion of affected fetuses (Table 27-2). Many but not all of these disorders are associated with mental retardation. As noted above, enzyme assays are feasible for many other conditions. For several of these disorders with a recurrence risk of 25 percent, pregnancies at risk (previous child affected) have been monitored, and parents were correctly informed, on the basis of normal enzyme assays, that the fetus would be unaffected. (One cannot guarantee that the child will be "normal" because of all the other untested disorders that may occur.) Each of these conditions is rare, so monitoring of pregnancies is ordinarily restricted to families in which a case has already been diagnosed. Without the option of prenatal diagnosis, most families faced with a 25 percent risk of a serious genetic disorder have elected in the past to forgo further pregnancies. Prenatal diagnosis and abortion make it possible for such parents to have a normal child without fear

of recurrence of that disease.

Table 27-2. Inborn Errors of Metabolism Already Diagnosed in utero

DISORDER	PHENOTYPE	DEFICIENT ENZYME	REFERENCE
Lipid Metabolism			
Gm2 Gangliosidosis (Tay-Sachs)	Onset age five months, apathy, psychomotor deterioration, cherry red spot in macula, blindness	Hexosaminidase A	78
Metachromatic Leukodystrophy	Ataxia, hypotonia, paralysis; "schizophrenic" onset in adult form	Arylsulfatase A (Cerebroside-sulfatase)	57
Gaucher's disease	Hepatosplenomegaly, bone involvement, anemia, low platelets, retardation	Glucocerebrosidase	24
Niemann-Pick disease	Hepatosplenomegaly, cherry red spot in macula, retardation	Sphingomyelinas e	24
Globoid Leukodystrophy (Krabbe)	Absence of myelin, presence of "globoid bodies," severe retardation	Galactocerebrosidase	24
Fabry's disease*	Distinctive rash, renal impairment, corneal opacities, peripheral neuralgias; not mentally retarded	Ceramide Trihexosidase	10
Carbohydrate Metabolism			
Galactosaemia	Hepatosplenomegaly, cataracts; severe retardation prevented by excluding galactose (milk) from diet	Galactose-1-phosphate uridyltransferase	53
Pompe's disease	Hepatomegaly,	a-i,4-glucosidase	58

	cardiomegaly, failure to thrive, glycogen storage type II		
Miscellaneous			
Lesch-Nyhan* syndrome	Hyperuricemia, choreoathetosis, self-destructive behavior, retardation	Hypoxanthine-guanine phosphoribosyl transferase	16
Lysosomal acid phosphatase deficiency	Vomiting, hypotonia, opisthotonus, infantile death	Acid phosphatase	56
Methylmalonic acidemia	Ketoacidosis, developmental retardation	Propionyl CoA Carboxylase Methylmalonyl CoA mutase	48
Hurler's syndrome Hunter's* syndrome	Mucopolysaccharidoses: hepatosplenomegaly, gargoylish skull and faces, retardation	"Correcting factors": a-L-iduronidase; Sulfa iduronate sulfatase	26

* X-linked; all others autosomal recessive.

Certain autosomal recessive conditions, however, are not rare, especially when one considers particular ethnic or racial groups. Three examples are cystic fibrosis, which occurs in 1/2000 Caucasians; Tay-Sachs disease, which occurs in 1/5000 Ashkenazi Jews; and sickle-cell anemia, which occurs in 1/400 blacks in the United States. There is no reliable test on cultured cells for cystic fibrosis, so prenatal diagnosis is not yet feasible. Tay-Sachs disease causes severe mental and neurological disintegration and death by the age of four years and is due to deficiency of the enzyme N-acetyl-hexosaminidase A, which is demonstrable in amniotic cells in culture. This

enzyme can be measured accurately in human serum samples, allowing detection of the heterozygous carriers. As a result, extensive screening of the Jewish population in the Baltimore-Washington area is currently under way. The high frequency of the gene in this population has been confirmed, and young couples in which both spouses are carriers have been identified and have been offered the option of prenatal monitoring for Tay-Sachs during pregnancy. Heterozygote detection for many other autosomal recessive storage disorders is now feasible. Finally, extensive screening is in progress in many cities for carriers of the sickle hemoglobin trait. The carriers are healthy, but if two carriers marry, their children have a 25 percent risk of sickle-cell anemia. In this case, carrier detection is technically very reliable, but no method is available to obtain fetal blood cells for prenatal diagnosis. Since production of sickle hemoglobin can be detected in eighty-day fetuses, direct visualization of the fetus (amnioscopy) and sampling of even 10 /J. of blood would allow diagnosis *in utero.*

One rare X-linked recessive disorder that merits special discussion is the Lesch-Nyhan syndrome, consisting of hyperuricemia, choreoathetosis, and a compulsive self-mutilating behavior. These boys bite their lips and fingertips until the structures are destroyed. The metabolic defect is a deficiency of the enzyme hypoxanthine-guanine phosphoribosyl transferase (HGPRT), leading to overproduction of uric acid and very high concentrations of uric acid in blood and urine. This enzyme lies in what was previously

thought to be a minor pathway of purine metabolism, but the devastating effects of its deficiency reveal the pathway to be physiologically important. The highest activity of the enzyme in normal individuals is found in the basal ganglia of the brain, providing an excellent correlation with the major neurologic abnormality of this syndrome—the involuntary movements. But the basis for the compulsive behavior is beyond understanding at present. There is no very effective therapy, even though the uric acid production can be controlled to prevent damage to the kidney from uric acid stones. For families in which this disorder has occurred, the risk of recurrence is 50 percent for boys; there is essentially no risk for girls, although half of the girls will be carriers. Specific enzymatic assay allows detection of affected male fetuses *in utero.16* In the common X-linked disorders hemophilia and D11-chenne's muscular dystrophy, specific tests to distinguish affected from unaffected male fetuses are not yet available. These conditions can be prevented by abortion of all male fetuses, when the mother is a carrier for the disease. Such mothers could have unaffected daughters, though half of these girls will also be gene carriers for the disease.

Psychopathic and Sociopathic Personality

There is no doubt that familial and social milieu contribute importantly to personality disorders and criminality. Nevertheless, in similar environments remarkable individual variation is found in personality and in

the likelihood of getting into trouble with the law. Studies of twins indicate that even for indices of personality and temperament, genetic factors can be inferred, though the genetic component seems much smaller than for IQ measures. Among men imprisoned for criminal behavior, cytogenetic screening has identified individuals with sex chromosomal abnormalities at frequencies much higher than in the general population. Considerable controversy about the medical and legal interpretation of such findings has been generated with the XYY syndrome, even though little attention has been paid to the more frequently found XXY or Klinefelter syndrome.

The Klinefelter syndrome consists of testicular atrophy and infertility, occasional gynecomastia, tall eunuchoid appearance, and variable behavior, ranging from altogether normal men through individuals with mild to moderate mental deficiency or psychopathic and criminal problems. Screening for the XXY karyotype can be carried out simply with smears of the buccal mucosa and staining for the Barr body. For example, among 942 mentally abnormal inmates with a tendency to criminal behavior, 12 (1.3 percent) were found to have the XXY karyotype and 7 (0.7 percent) had the XXYY karyotype, compared with 0.2 percent and 0.02 percent, respectively, in the general population. It has been suggested that the psychopathology is secondary to mental deficiency or hypogonadism, rather than an independent result of the chromosomal abnormality. XXYY males are more likely than XXY individuals to have mental deficiency, as are persons with even greater sex

chromosome imbalance, such as XXXY. Rather than sampling a prison or psychiatrically abnormal population, Nielsen evaluated hypo-gonadal male patients of 46 XY (N=i6) and 47 XXY (N=34) karyotypes at a sterility clinic in Denmark. The XXY patients had significantly more psychiatric symptoms and were particularly differentiated from the XY patients by signs of immaturity, insecurity, boastful and self-assertive behavior, and a record of legal offenses. Differences in testis size, gynecomastia, and IQ were not related to the indices of psychopathology. With testosterone therapy, secondary sexual development like a normal male can be stimulated. However, the hyalinization of the tests cannot be reversed, and fertility is not possible. The overall frequency of XXY births is one in 450 males, with slightly increased risk with advancing maternal age. It is likely that a family in which amniocentesis is done and an XXY karyotype is found would opt for an abortion, given the likelihood of mild mental retardation and the approximately fivefold increased risk of psychopathology. Whether the frequency of this disorder or its medical and psychiatric findings warrant population screening by amniocentesis is an unresolved question that raises many social and ethical problems (see below).

The story of the XYY syndrome is one of the most curious in behavior genetics. XYY karyotypes were first reported in association with a variety of gonadal abnormalities. In 1965, an excessive incidence of XYY males was described after screening very tall men in maximum-security prisons in

Scotland. Presumably because males are considered more aggressive than females and because an extra Y seemed to be an intuitively reasonable basis for greater height and greater aggressiveness, stories from Australia and France about accused murderers having XYY karyotypes made front-page news in the United States. A mass murderer of eight Chicago nurses was publicized, wrongly, as a (possible) XYY. Behavior geneticists have taken increased interest in the XYY syndrome for another reason. A psychosocial evaluation with family data on nine XYY and eighteen XY prisoners at the maximum-security prison at Carstairs in Scotland indicated that XYY criminals could be distinguished from XY counterparts by a lack of broken families, a lack of criminal records among their siblings, a tendency to get into trouble with the law earlier in their teens with crimes against property rather than people, and a greater lack of concern about their criminal behavior. In other words, such individuals seemed to represent chromosomal accidents that made them “black sheep” of otherwise upstanding families. The analogy to mental retardation syndromes was obvious: a severely mentally retarded child in a family of normal parents and siblings is often the result of a particular chromosome or metabolic abnormality, while a mild or moderately retarded child in a family with parents and siblings of similar IQ reflects the interplay of multiple genetic and environmental influences. Unfortunately, subsequent studies have failed to confirm this striking differentiation between XYY and XY criminals. Furthermore, population screening by the

laborious preparation of full chromosomal karyotypes demonstrated that 1/800 male births is XYY, many times the frequency of tall criminals in Western society. At present it appears that the XYY karyotype is associated with a several-fold increased risk of psychopathology and criminality. No parent populations are known to have an increased risk of producing XYY children. While screening women of age forty or older for Down's syndrome, Nadler encountered one case of the XYY syndrome as well as three cases of Down's syndrome, among 104 pregnancies. Should the family desperately want a baby or disapprove of abortion, the knowledge that the child is born with an XYY karyotype may interfere with normal attitudes toward child-rearing. It is obvious that moral, ethical, and legal problems arise from such situations, especially when knowledge of the natural history of the chromosomal syndrome is incomplete or biased. Screening of all pregnancies for XYY fetuses appears inappropriate at the present state of knowledge, but the fortuitous finding of an XYY fetus seems a reasonable indication for abortion.

Disorders of Sexual Differentiation of Behavioral Interest

Genetic and chromosomal disorders affecting every stage of differentiation and function of the gonads and the sex hormone-responsive tissues have been described. Several excellent reviews are available. Federman, for example, has divided the syndromes into three categories:

ambiguity of genital development without infertility; infertility without ambiguity; and both ambiguity and infertility. Patients range from true hermaphrodites (containing functioning ovarian and testicular tissue) to those with gonadal dysgenesis (having no functioning germ tissue). Evidence in rats, guinea pigs, monkeys, and man demonstrates that sex hormones have important influences in the development of attitudes and many specific behaviors in addition to those directly involved in reproductive behavior. Money and his colleagues have investigated in detail a variety of chromosomal disorders and inborn errors affecting sexual development, as well as other behavioral patterns for which no biological basis is yet known (homosexuals; transsexuals). The most intriguing findings are those from studies of patients with gonadal dysgenesis (Turner's syndrome). These girls have short stature and lack functioning ovarian tissue, hence lack menstruation or breast development. Nevertheless, they have essentially normal intelligence and normal female gender identity. IQ testing revealed that scores for verbal performance regularly exceeded those for nonverbal subtests, but the difference lay in the tests of space-form perception, in which at least 80 percent of these girls are remarkably deficient. Similarly, the draw-a-person or figure-copying tests elicit bizarre and poorly formed outlines. It is not at all clear how a chromosomal abnormality present in all cells could so strikingly affect one particular cognitive function. There is some analogy to the constellation of signs known as Gerstmann's syndrome (right-left

disorientation, dyscalculia, finger agnosia, and dysgraphia) that can occur with tumors or strokes affecting the left (dominant) parietal region of the brain. The 45 XO karyotype can, of course, be recognized in amniotic cells; however, nearly half of the cases of gonadal dysgenesis are mosaics, leading to problems in diagnosis. Furthermore, the proportion of mosaic lines may be quite different in vitro than in vivo and may be variable between tissues, making a decision about the prognosis very difficult. A couple's decision about abortion of a 45 XO fetus will be influenced by their attitudes about abortion and their willingness to accept a "less than perfect" child.

Another interesting category of disorders is congenital adrenal hyperplasia, due to enzyme deficiencies at one of the several steps in the biosynthesis of cortisol and stimulation of the adrenal by pituitary ACTH to make more cortisol precursors. The resulting high levels of androgens cause the external genitalia of a female fetus to become masculinized, leading to mistaken identification of the baby as a boy. When the metabolic abnormality is recognized, sex is reassigned to female. Fifteen girls with the adrenogenital syndrome treated early with cortisone, compared with a control group matched for age, sex, IQ, and father's occupational level, had a much higher incidence of interest in masculine-associated clothing and toy preference and very little interest in infant care and feminine-associated clothing and toys. They considered themselves and were considered by others to be tomboys. It was postulated that the tomboyish traits are a product of androgenization of

the hypothalamus or related areas of the brain *in utero.* There was considerable individual variation, suggesting an interplay of social conditioning and fetal androgenic effects. Surprisingly, IQ testing of 70 patients with adrenogenital syndrome gave a mean IQ of 110 ± 19, with 60 percent of the patients above IQ 110, instead of the expected 25 percent of a control population. Better control data, using unaffected sibs as controls, are needed to evaluate the significance of these findings. Because the enzymes responsible for steroid biosynthesis are not normally expressed in fibroblasts or amniotic fluid cells, direct assay in early pregnancy for these enzymes is not feasible. The accumulation of steroid precursors can be demonstrated late in pregnancy, but not in time to intervene with abortion. In these disorders, treatment is quite effective and reasonably simple, so many families would be willing to accept the birth of an affected child, especially if diagnostic and therapeutic measures were instituted promptly. Other families, in our experience, have decided against further pregnancies, because they would not consign 25 percent of their children to lifelong treatment with cortisone.

Other evidence that androgens during pregnancy can affect the psychologic development of girls comes from cases in which synthetic progestational agents have been administered to pregnant mothers to prevent threatened miscarriages. (Note that a high percentage—at least 25—of such threatened miscarriages reflect chromosomal aberrations and represent nature's way of avoiding some defective babies.) Of ten girls with

progestin-induced hermaphroditism studied at ages three to fourteen years, six had IQ scores above 130, with a mean of 125 ± 12 and no significant difference between verbal and performance IQ, and nine of the ten were considered tomboys.

Yet another instructive syndrome, determined by abnormality at a single gene locus, is testicular feminization. These genetic males have a 46 XY karyotype, two intraabdominal testes, and produce testosterone, but their target tissues are "insensitive" to the action of testosterone. Phenotypically, these males appear at birth and through puberty to be females, then seek medical attention in their teens for amenorrhea or infertility. The external genitalia are those of a normal female. The vagina ends blindly. Breast size varies as in normal women. Psychologically, a series of ten such patients showed unmistakably feminine behavior and outlook with regard to marriage and maternalism. For four married patients, interviews of the husbands confirmed these conclusions. The treatment of choice is to inform the "woman" that she is infertile, that the "gonads" in the inguinal hernia should be removed because they are not functioning normally and may become malignant, and that any difficulty with intercourse may be improved by plastic surgery procedures. It is unwise to advise such a person that "she" is cytogenetically a male, since physiologically, psychologically, socially, and legally she is a female. If the syndrome is recognized in a family, it is possible for a couple to avoid having affected children. Since the trait is inherited as an

X-linked or sex-limited disorder, amniocentesis and determination of fetal sex would permit the parents to abort male fetuses, which have a 50 percent risk of being affected.

The indications and results of monitoring pregnancies, based upon published experiences, are summarized in Table 27-3.

Psychiatric Disorders Not Now Feasible for Prenatal Diagnosis

Depression (Affective Disorders)

There is considerable evidence from twin and family studies that depression and especially manic-depressive psychosis is conditioned by genetic factors. Among the relatives of a patient with manic-depressive psychosis, approximately 10 percent of parents, 10 percent of children, and 12 percent of sibs will have affective disorders. When more knowledge is gained about the biochemistry of depression, it may be possible to assay specific enzymes or use pharmacologic challenges in in vitro systems to identify healthy individuals or even fetuses at higher-than-normal risk of developing depression later in life.

Schizophrenia

Table 27-3. Summary of Data on 387 Monitored Pregnancies24 55

INDICATION FOR AMNIOCENTESIS	NUMBER OF CASES	NUMBER AFFECTED
For Down's syndrome		
Maternal age ≥ 38 years	138	5
Previous Trisomy 21	91	2
Translocation carrier	42	11
Other chromosomal abnormalities	29	5
Sex determination for X-linked disorders	35	18
Autosomal recessive metabolic disorders	52	11
	387	52

Statistical analyses of family and twin data and comparisons of the incidence of schizophrenia in biological and adoptive relatives of probands who were adopted early in life suggest a major role for genetic factors in schizophrenia,''' though the exact mechanism or mechanisms of inheritance are unknown. No specific metabolic abnormalities have been discovered as the basis or bases of such a predisposition in the vast majority of cases. Genetic counseling for relatives of a schizophrenic patient, therefore, rests on empirical risk figures.

One sure sign of heterogeneity is the mimicking of schizophrenia by specific inborn errors of metabolism, such as the adult form of metachromatic Leukodystrophy. The onset of metachromatic Leukodystrophy has been recognized in at least nineteen patients over twenty-one years; their mental

and emotional changes were so severe that they were institutionalized, usually with a diagnosis of schizophrenic illness. Only years later did neurological deterioration become manifest and lead to the pathological demonstration of sulfatide storage in the brain. Probably these patients have a less severe deficiency of the same enzyme that is deficient in the infantile presentation of metachromatic Leukodystrophy, cerebroside sulfatase.

It would not be surprising if many other enzymes whose complete deficiency grossly disrupts the development of the central nervous system function were found to be causes of late-onset dysfunction manifested as psychoses, either as a result of a different mutation causing less severe deficiency or as the half-deficient heterozygous carrier of the gene causing infantile onset. Very few studies have been made of the parents (obligate carriers) or siblings (two-thirds are carriers) of children affected with autosomal recessive inborn errors of metabolism. A disease like phenylketonuria, in which the abnormality lies in a liver enzyme with only secondary toxic effects on the brain from accumulated metabolites, would not be a good choice for such studies. Instead, a disorder in which the affected enzyme normally has high activity in the brain should be selected for study. Such a disorder is homocystinuria, in which there is a deficiency of cystathionine synthetase. Cystathionine is normally present in remarkably high concentrations in brain, though its function is unknown. It is one of many amino acids now considered possible neurotransmitters. Individuals affected

with homocystinuria have skeletal abnormalities, ectopic lens, marked tendency to venous and arterial thromboses, and about half are retarded. Why only half are retarded is not at all clear. Those who are considered of normal intelligence might have had higher IQs if not for the homocystinuria. Among the unaffected relatives in certain families, a seeming excess of schizophrenia has been noted, but no systematic studies have been carried out with carriers of the homocystinuria gene. Homocysteine and methionine are involved in methylation reactions in the brain, offering another possible connection to schizophrenia, if methylated neurotransmitter metabolites are involved in the pathogenesis of schizophrenia. Cystathionine synthetase deficiency can be demonstrated in amniotic fluid cells, and recent studies of stimulated peripheral lymphocytes indicate that detection of heterozygotes may become feasible. Even for this rare recessive condition (disease frequency about 1/40,000) the frequency of heterozygous gene carriers is 1 percent in the general population.

Another rare autosomal recessive condition that can be present with schizophrenic-like symptoms in the early stages is progressive myoclonic epilepsy, or the Unverricht-Lundborg syndrome. Centrencephalic epilepsy with petit- and grand-mal seizures is accompanied by deposition of amyloid-like Lafora bodies in the brain, retina, nerves, muscle, heart, liver, and fibroblasts. With elucidation of the biochemical abnormality, this condition should become diagnosable *in utero.*

Autosomal Dominant Disorders

Unfortunately, the biochemical basis for dominantly inherited disorders is still unknown. Often, the manifestations of the disease are not present at birth, and their appearance may be delayed even for decades into middle life. Also, it is characteristic of dominant conditions that the clinical manifestations vary considerably from patient to patient. The more severe the disorder, the less likely that the affected person will reproduce; thus, the more severe the disorder, the higher the probability that individual cases are due to fresh mutations (often associated with advanced paternal age), rather than transmitted from parents. Autosomal dominant disorders that may cause mental retardation include neurofibromatosis, tuberous sclerosis, and myotonic dystrophy. Genetic counseling depends on making the diagnosis, then informing an affected parent that his children have a 50 percent risk of getting the abnormal gene and a variable risk (about 10 percent) of being retarded as a result of the genetic disease. Prenatal diagnosis for these conditions must wait for the development of specific biochemical tests or for the discovery of linkage of the gene for the disease to another marker gene, whose product can be detected *in utero.*

Two dominant disorders can present with depressive psychoses, indicating genetic heterogeneity for affective disorders. The porphyrias are metabolic disorders of hepatic heme biosynthesis, vertically transmitted

through families as autosomal dominant traits. Episodes of colicky abdominal pain with constipation (due to autonomic neuropathy) occur together with variable central nervous system involvement, including flaccid paralysis, agitated and paranoid depression, or schizophrenic behavior. In the Swedish type, or intermittent acute porphyria, biochemical diagnosis during the acute attack is highly reliable. However, the increased urinary excretion of porphyrin precursors may not be present before puberty or between attacks. Increased production of delta-aminolevulinic acid (ALA) and porphobilinogen is caused by higher than normal activity of the rate-limiting enzyme, ALA-synthetase, in the liver. The mechanism of the increased activity is not yet clear.- Several common drugs induce higher activity of the ALA-synthetase and may precipitate attacks in predisposed individuals. These drugs include barbiturates, certain sulfonamides, and the antifungal agent griseofulvin. Hepatic cells are required to demonstrate ALA-synthetase activity; either liver biopsy or some as yet unknown means of "turning on" the gene for ALA-synthetase in amniotic cells would be needed to attempt prenatal diagnosis.

Huntington's chorea is a degenerative neurologic and psychiatric disorder that is one of the major problems in counseling in medical genetics. Over a period of ten to twenty years, the affected person undergoes progressive deterioration of personality and of mental function, eventually requiring institutional care because of psychotic behavior or dementia or both. Irresponsible social behavior may lead to psychiatric evaluation and

diagnosis of affective or schizophrenic processes before the neurologic signs become manifest or before the importance of the family history is appreciated. The age of onset of involuntary movements is usually in the thirties or forties, but may be delayed even longer. Thus, individuals at risk (50 percent if a parent is affected) have the dual misery of not knowing whether they will be transmitting the disease to their children and of worrying that any "normal" twitches or behavioral problems may be the early signs of the disease. The pathophysiology of the disease is unknown, and no specific diagnostic test is yet available. Since L-Dopa administration to patients with Parkinsonism may induce involuntary, choreiform movements, it has been speculated that carriers of the gene for Huntington's chorea might manifest such movements at a lower dose of L-Dopa than do normal people or Parkinson patients. However, individuals at risk for this untreatable disease certainly will differ in their desire to know or to not know whether they will become affected later.

Possible Diagnosis by Genetic Linkage for Dominant Disorders

The gene for Huntington's chorea might be closely linked to some other gene whose product is easily tested, like a blood group. It is now feasible in suitable pedigrees to use linkage to the secretor locus to make an early, even a prenatal, diagnosis of myotonic dystrophy, another autosomal dominant disorder of late age of onset. Although myotonia and other complications of

this disease may not appear until middle life, it has been possible to identify gene carriers before age twenty by slit-lamp demonstration of a particular type of cataract. Thus, two- and three-generation data suitable for linkage analysis could be obtained. The locus that controls secretion of blood group substances into saliva and other body fluids, including the amniotic fluid, happens to be closely linked on one of the chromosomes to the gene for myotonic dystrophy. Although linkage is sometimes mentioned as a powerful indirect diagnostic approach, even for this seemingly ideal example of close linkage (recombination only 8 percent), very few pedigrees are suitable. The carrier of the gene for myotonic dystrophy must also be heterozygous for secretor status (probability 0.5) and the spouse must be homozygous negative for secretor function (probability 0.25); in addition, the "phase" of the myotonic dystrophy and secretor genes on the two homologous chromosomes must be inferred from study of other relatives. Even then, incorrect conclusions will result 8 percent of the time due to crossing-over (recombination) between the two linked loci.

Computer-assisted programs to seek evidence for linkage of a postulated dominant gene for schizophrenia to some genetic marker have been proposed. Because of the likely heterogeneity of mechanisms underlying so complex a phenotype as schizophrenia, individual large kindreds should be used for such studies.

Anticipated Technical Developments

As enzymatic assays are adapted to micro-methods, the delay between the time of amniocentesis and the report of results should be shortened, relieving some of the tension of the wait and making abortion, if necessary, safer. As biochemical mechanisms of more diseases are elucidated, the list of conditions for which prenatal diagnosis will be feasible should continue to grow. Detailed evaluation of the potential hazards of amniocentesis will make more exact the patients' and physicians' balancing of benefit and risk in undertaking amniocentesis for disorders of low frequency. Hopefully, better methods of terminating pregnancies in mid-gestation may be developed.

For the common psychiatric phenotypes, it is expected because of heterogeneity that the mass of cases will be attacked only gradually, as in the case of mental retardation syndromes. Promising approaches include the application of new staining methods for abnormal chromosomal banding patterns, the evaluation of heterozygous carriers of genes that cause mental retardation in the homozygous state, the possibility of demonstrating linkage to easily tested genetic markers, and the development of *in vitro* methods for pharmacogenetic differentiation of cellular responses. Many biochemical functions or responses that are characteristic of the nervous system may not be expressed in amniotic fluid cells. Progress must then depend upon "turning on" the unexpressed genes in the amniotic cells and upon harmless

methods for biopsy of superficial tissues or organs of the fetus. Certain neurological conditions may be associated with congenital anomalies visible through a fiber-optic amnioscope. Other sensitive instruments may be able to detect fetal physiological and neurophysiological parameters. Monitoring of pregnancies will become more widespread and applicable to more diseases. Population screening for heterozygous carriers will be initiated, requiring computerized data evaluation and regional or national networks for counseling family members.

Special Issues Involving the Psychiatrist in Genetic Counseling

Stresses of Monitoring a Pregnancy

With the popularization of amniocentesis and prenatal diagnosis in magazines, many families have initiated contact with their physicians or counseling centers with the unfortunate expectation that tests can assure them of a normal baby or that many specific conditions can be tested, for which no tests are available. Sometimes a couple has tried for years to have a child or has waited many years after an affected child for the possibility of such prenatal monitoring. The many weeks of waiting before amniocentesis can be performed and before test results are available can be exceedingly stressful, especially when the hazards of a late abortion loom as a distinct possibility and the couple realizes that mistakes can be made in the testing

procedures. Occasionally a couple will seek amniocentesis in the hope that something will be found to be wrong with the baby, so that they can justify to themselves terminating the pregnancy. For example, Epstein et al. described a couple who previously had a child with translocation Down's syndrome; when karyotypes of the amniotic cells indicated a 46 XY fetus, they requested an abortion anyway, for reasons of mental health. Husband and wife may have basic disagreement about abortion or child-rearing, of course, and in most states they still must contend with archaic laws restricting abortion. In states like California, Oregon, New York, Hawaii, and Washington, where liberalized abortion statutes are in effect, the genetic counselor and the family can deal more directly with the medical and psychological problems of the individual family. It is highly desirable that counseling be provided before the woman is pregnant. Sometimes extensive arrangements for specific enzymatic assays must be made or complicated testing of the woman for possible carrier status with regard to an X-linked disorder must be carried out. In any case, the stress is bound to be less if the couple can consider the genetic information and plan the pregnancy.

Severity of Disease and the Indications for Abortion

If the risk of recurrence is high and the disorder severe, such as the autosomal recessive conditions listed in Table 27-2, most couples will desire amniocentesis, unless they seek no more children. But when the risks are low,

as in the cases of advanced maternal age and previous trisomy 21, the couple must decide whether to take the high probability (about 99 percent) that the fetus will not have trisomy 21 or whether to take the unknown risks associated with the procedure. Couples differ in their responses to this predicament. Therefore, it is important that detailed genetic counseling be offered before the obstetrician performs the amniocentesis. In one series, twenty-seven of eighty-three couples decided against amniocentesis after receiving counseling. Many were reassured by the low recurrence risks; in three cases the condition could not be detected by available tests; one woman had no desire to have her pregnancy terminated whatever the outcome; and in another there was not time to do all the necessary tests because of the advanced stage of pregnancy. With the behavioral disorders of adult onset, the definition of "genetic disease" and of tolerable severity is complicated. The available information from population, family, twin and adoption studies suggests that genetic factors predispose to affective disorders or schizophrenia, but do not indicate the probability of such a predisposed person developing severe disease. Similarly, in the cases of sex chromosomal abnormalities, for which prenatal detection is already feasible, most men with XYY karyotype are not psychopathic criminals and most individuals with XYY or XXY or XO karyotypes do not suffer serious mental impairment. Is the infertility associated with XXY or XO karyotypes a basis for the parents to insist upon abortion? Or the possibility of behavioral problems associated

with XXY? The problem is vexing, because firm data on the absolute risks of such behavioral problems are not available and there is no basis for predicting which offspring will be affected later in life. The physician is then faced with the dilemma of giving or withholding information that the parents cannot evaluate either. By analogy, the discovery of Huntington's chorea in a patient brings a pall over the family, because there is no treatment for the disease and no advantage of early diagnosis except the prevention of further offspring and the establishment of a diagnosis that saves the family fruitless medical inquiry. On the other hand, vigorous investigation of the family with polyposis of the colon is considered essential, since prophylactic removal of the affected colon will prevent fatal colonic carcinoma. Although genetic counselors seek to provide detailed information and meaningful advice, the responsibility for deciding the course of action rests with the individual couple. It is our impression that families fear behavioral disorders even more than somatic anomalies and that the majority of families would request abortion of a XYY or XXY or XO fetus if informed of the results of the chromosomal tests.

Abortion nowadays is discussed as a simple and innocuous matter. Psychologically, of course, it is not: each couple must be evaluated and assisted. Surgically, abortion for conditions diagnosed in mid-pregnancy requires special techniques and carries substantially higher risks of maternal mortality or morbidity than does abortion before eight weeks of gestation. At

present, abortion between twelve and twenty weeks is being done primarily by saline infusion or by hysterotomy, though newer agents, such as prostaglandins, may prove helpful. If the couple lives in a state that does not allow legal abortion for such indications, they face the ignominy of "fleeing" to another, more liberal state for the abortion, seeking a physician who will twist or violate the law, or taking no action. If no abortion can be obtained, amniocentesis can be justified only in exceptional circumstances. For instance, after the birth of one child with Down's syndrome an occasional couple who would not allow abortion may still seek amniocentesis for reassurance that the fetus is unaffected.

An alternative to selective abortion of affected fetuses is detection and counseling of unmarried teenagers and young adults who are heterozygous carriers for such diseases as Tay-Sachs and sickle-cell anemia. These young people could avoid the birth of affected children by avoiding marriage with carriers for the same disease. Most authorities agree that a massive educational effort would be required to affect mating patterns. It is not known whether the knowledge that one is a carrier for such a disease would influence a person to avoid marrying someone who is also a carrier, and it is not known how such an educational effort should be mobilized to properly inform, and yet not frighten, these healthy carriers. Several screening and educational programs have been started for sickle-cell anemia, since intrauterine diagnosis is not feasible for this disease. When feasible, the

identification of couples who are both carriers and who wish to avoid the birth of affected children by selective abortion seems more practical. However, affected children would continue to be born of out-of-wedlock matings in such a program.

With abortion on demand in certain states and with increasing family planning, some families have sought to use the technology of intrauterine chromosome karyotyping to learn the sex of the fetus and assure themselves the birth of either a boy or girl. Obviously, the "risk" of the "wrong" sex is 50 percent, but a couple must have an overwhelming desire to select the sex of the child in order to accept the unknown risks of amniocentesis and a late abortion. A request for amniocentesis and chromosome karyotyping of cultured amniotic fluid cells for sex may be dismissed as a frivolous attitude or may be considered a coldblooded approach to an "ideal" family of one son and one daughter, according to the attitudes of those involved. To many physicians in genetic counseling, the prevention of devastating disease provides moral justification for abortions, while the selection of the sex of one's children raises moral, social, and political issues far beyond the medical clinic.

Society's Position with Regard to Genetic Diseases

With the decrease in deaths from acute infections and the recognition of

so many specific inherited conditions, the medical profession and lay people are becoming increasingly aware of the nature and variety of genetic diseases that require hospitalization, cause deaths, and influence the lives of people in contact with those affected. Until recently, society has disapproved of abortion as a means of preventing unwanted children. Now most people approve of abortion to prevent the birth of defective children, if not simply "abortion on demand." Will amniocentesis be required for women above a certain age, just as testing for phenylketonuria is required by law in most states? How will society look upon the couple who refuse abortion and deliver a child with severe mental retardation who is dependent upon the society for his existence? Many of these questions transcend the realm of medicine.

One may ask, also, what effect intrauterine diagnosis and selective abortion will have on the frequency of inherited diseases. The impact of several types of public-health programs has been projected by Motulsky et al. The total number of cases will be reduced slightly if intrauterine diagnosis is initiated only after the birth of an affected child, as for the rare autosomal recessive conditions listed in Table 27-2. Maximal case reduction requires detection of high-risk mothers or high-risk matings before marriage, as is feasible for Tay-Sachs and other lipid storage disorders and for sickle-cell heterozygous carriers. There is a slight "dysgenic" effect of selective abortion, in that an individual who would not have survived to pass on the deleterious

gene is likely to be replaced in the sibship by another child with a substantial risk (two-thirds for autosomal recessive traits) of being a carrier. However, since changes in gene frequencies are significant only over many generations, medical and social efforts should be directed to the intrauterine diagnosis and prevention of affected cases, especially of the common genetic diseases.

Concluding Remarks

Intrauterine diagnosis is possible for chromosomal disorders and many rare inborn errors of metabolism. Most common birth defects and genetic diseases, however, cannot yet be diagnosed *in utero.* Diagnosable disorders of particular interest to psychiatrists and the directions of anticipated future developments are stressed. Since intrauterine therapy of genetic disorders is not feasible in most cases, abortion of affected fetuses is usually practiced. Psychiatric and social problems surrounding abortion for genetic and chromosomal diseases affecting behavior merit further attention.

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Notes

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