PRENATAL GENETICS WITH PARTICULAR REFERENCE TO NEUROLOGICAL DISEASE

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Prenatal diagnosis, although it has been introduced only a few years ago, has already become an important branch of genetics and cytogenetics.
Metabolites of certain monogenic diseases can be discovered in the supernatant of the amniotic fluid, although reliable results are obtained in later months of pregnancy only.
Determination of fetal sex is important if the mother is a proven carrier of a severe X-linked disease such as X-linked muscular dystrophies, Hunter's, Lowe's, Lesch-Nyhan disease. It can be done by the analysis of nuclear sex or sex chromosomal complement.
Biochemical studies of amniotic fluid cells, notably cultured amniotic fluid cells, permit prenatal diagnosis of some inborn errors of metabolism such as Tay-Sachs disease, Hurler's and Hunter's disease, and some rare monogenic diseases.
Numerically of greater importance is the prenatal chromosomal analysis of high-risk women. Provided it could be done in all so-called high-risk women, a considerable number of aneuploidies could be prenatally detected and ultimately prevented.
Religious and legal implications of eugenic abortions are discussed.

1. INTRODUCTION

Progress in the biological sciences, in general, follows the development of new examination techniques and new laboratory methods. In some instances, progress ensues when already established techniques and methods are used in new combinations. The combination of amniocentesis with diagnostic methods used in genetics, notably biochemical genetics and cytogenetics, led to the development of prenatal genetics, i.e., prenatal diagnosis of diversified heritable disorders and chromosomal aberrations.

Amnioscopy or fetoscopy as a new method to detect certain malformations during fetal life is just in the beginning. By introducing a cystoscope-like tool into the uterine cavity, it has become possible to recognize such CNS anomalies as anencephaly, rachischisis, and meningomyelocele at an earlier time of gestational age than was possible with previously used radiological methods. Certain malformations could also be recognized by ultrasound exploration of the pregnant womb (Campbell et al. 1972). Very recently, it was found that increased alpha-fetoproteins in the amniotic fluid and in the maternal blood are suggestive of CNS malformations such as anencephaly, hydrocephaly, and meningomyelocele (Brock and Sutcliff 1972, Seppälä and Ruoslahti 1973). In the near future, we shall certainly hear more about these methods.

It is the purpose of this paper to briefly discuss prenatal genetics and prenatal cytogenetics with particular reference to neurological disease. A symposium on amniotic fluid, its normal

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and pathological composition, and descriptions of how to obtain amniotic fluid has been published by Fuchs (1966). Additional information is found in a monograph by Dorfman (1972).

2. TECHNIQUES OF AMNIOCENTESIS AND ITS COMPLICATIONS

Amniocentesis, i.e., removal of amniotic fluid from the pregnant womb, has been used already in the last century in women whose pregnancy was complicated by polyhydramnios. In the 1950s, amnion fluid was obtained in the third trimester to recognize fetomaternal incompatibility. In erythroblastosis fetalis, the amniotic fluid contains increased blood pigments. Serial spectrophotometric analysis of this pigment affords a new approach to the management of these pregnancies, which include fetal (intraperitoneal) blood transfusions, premature delivery, exchange transfusions, to which light therapy was added more recently. Many cases of kernicterus, mental retardation, and choreoathetosis have been so prevented.

The incidence of erythroblastosis fetalis amounted to about 1 in 200 newborns before a new method of preventing fetomaternal incompatibility was introduced. Incidence of erythroblastosis has been reduced drastically, since Rh-negative mothers receive an injection of a specific gammaglobulin soon after delivery of an Rh-positive baby.

Amniocentesis can be done per vaginam or by abdominal puncture. The former method has been abandoned; it is technically more difficult and is more often followed by complications than the transabdominal method. Complications of amniocentesis are:

1. Infections of the amnion cavity
2. Hemorrhages into the amnion cavity, placenta or uterine wall
3. Injury to the fetus
4. Induction of labor and abortion.

In the hands of the skilled obsetrician, the incidence of these complications has been reduced to less than 1 %. In point of fact, no complications were recorded in the last 200 or more amniocenteses performed in our institution.

Amniocentesis is technically not feasible before the 14th-16th week of pregnancy. Earlier amniocentesis (between the 12th to 14th week) is not advisable since it carries a higher risk for complications and a lesser chance for obtaining a suitable sample of amniotic fluid. In the 14th-16th week, the fundus uteri reaches above the symphysis pubis and the uterine cavity contains about 150-200 ml amniotic fluid. At that stage, 5-10 ml amniotic fluid can be removed without major consequences for mother and child. I mention this since animal experiments have shown that removal of larger amounts of amniotic fluid during the organogenic period may induce fetal malformations. The amniotic fluid can be used for a variety of diagnostic tests. Diversified chemical reactions are possible with the supernatant fluid. The pellet, after centrifugation, contains various cell types which are shed from the fetus and which can be used for sex chromatin, chemical and cytogenetic studies.

3. STUDIES OF SUPERNATANT FLUID

Some enzymes and catabolites, normal and abnormal, have been determined in the supernatant fluid, e.g., increased amounts of 17-ketosteroids and pregnanetriol have been detected in the amniotic fluid of fetuses affected with the adrenogenital syndrome. This,

however, is only possible during the last trimester of pregnancy. Conspicuous differences between the amniotic fluid of normal fetuses and fetuses with adrenal hyperplasia are not detectable during the first six months of pregnancy (Merkatz et al. 1969).

Nevertheless, the prenatal diagnosis can be made in the third trimester which is early enough to institute treatment for the newborn, moreso, since in the case of 21-hydroxylase deficiency, a number of days elapses before the salt-losing effect becomes apparent.

The supernatant amniotic fluid has also been used for the prenatal diagnosis of certain mucopolysaccharidoses. In some of them — notably mucopolysaccharidoses IH, IS, and II — the amniotic fluid contains very high levels (40 × normal) of acid mucopolysaccharides. A considerable fraction of the mucopolysaccharides consists of heparan sulfate if the fetus is affected. Heparan sulfate is not found in the normal. However, these mucopolysaccharides again appear rather late in pregnancy. Matalon et al. (1972) failed to detect them before the the 20th week, even when the fetus was affected. This method is no longer used since it often yields reliable results too late to perform a eugenic abortion in case the fetus should indeed be affected. (There are better methods for the prenatal diagnosis of mucopolysaccharidosis, as we shall see later on.)

Earlier reports that Pompe's disease or cardiomuscular glycogenosis type II can be diagnosed by the detection of absent alpha 1-4,1-6 glucosidase in the supernatant fluid before the 20th week of gestation (Nadler and Messina 1969) have been disproved by subsequent studies (Salafsky and Nadler 1971). Furthermore, it was found that admixture of maternal blood may dissimulate the fetal enzyme deficiency (Cox et al. 1970), which makes the method even more unsuitable for the prenatal diagnosis of cardiomuscular glycogenosis.

The study of the supernatant amniotic fluid is thus, generally speaking, of rather dubious or at least limited value.

4. STUDIES OF AMNIOTIC FLUID CELLS

Researches which have been pursued with amniotic fluid cells are as follows:

1. Fresh uncultured amniotic fluid cells
a. nuclear sex
b. enzyme deficiency (Pompe's disease, Tay-Sachs disease, Hurler's disease)
2. Cultured amniotic fluid
a. enzyme deficiency
b. metachromasia of amniotic fluid cells
c. nuclear sex
d. chromosomal aberrations.

4.1. *Prenatal Sex Determination*

The nuclear sex can be determined in the freshly sedimented amniotic fluid cells. Admixture of maternal blood is somewhat disturbing, however the drumsticks of the maternal WBCs are easily distinguished from the Barr bodies of the amniotic fluid cells. The accuracy of the method varies between 75% and 100% (Nadler 1972). We have checked our method on more than 200 cases and got correct results. In case of doubt, the results can be checked by the analysis of the prenatal sex complement in the cultured amniotic fluid cells.

Prenatal sex determination is indicated when the mother is a known carrier of a severe X-linked condition such as severe hemophilia, X-linked muscular dystrophy, Hunter's disease, and also Lowe's syndrome and Lesch-Nyhan syndrome, which are two rarer X-linked conditions with CNS involvement. (In the Lesch-Nyhan syndrome, the enzyme defect can be discovered in the amniotic fluid cell culture.) Most important in the realm of this discussion is the problem of the X-linked muscular dystrophies, Duchenne type and its slow motion copy, the Becker type. It has been estimated that about 1 in 3000 to 5000 liveborn boys will develop Duchenne muscular dystrophy. The Becker type is five to ten times less frequent. The first case of X-linked muscular dystrophy in a given kindred — be it inherited or the result of a point mutation — will often escape prenatal diagnosis. Thereafter, however, female relatives, notably the patient's mother and sisters, can be recognized as carriers by either elevated serum creatine phosphokinase or, more reliably, by alterations of the protein synthetic activity of their muscle ribosomes. Females who are carriers proven either by genealogical studies or by elevated serum creatine phosphokinase (Zellweger et al. 1972) or by abnormal in vitro protein synthesis of muscle ribosomes would best be sterilized (Ionasescu et al. 1971). In case of pregnancy, however, prenatal sex determination is certainly indicated. Sex-chromatin-negative fetuses, i.e., fetuses with one X chromosome, represent an indication for eugenic abortion since their risk for developing muscular dystrophy is 50%. It is presently not possible to differentiate between male fetuses who inherited the mutant gene and those who inherited the wild type gene.

4.2. *Prenatal Diagnosis of Inborn Errors of Metabolism*

About 50 different enzymes have been determined in the amniotic fluid cells. Cultured amniotic fluid cells give more reliable results than freshly sedimented, not cultured, amniotic fluid cells. The disadvantage is, of course, that several weeks may pass before the results of the cultured specimens are available, which may be significant in case the results would call for a eugenic abortion. Table 1 shows a list of the diseases which have already been diagnosed

TABLE 1

HEREDITARY METABOLIC DISORDERS WHICH HAVE BEEN DIAGNOSED IN UTERO *

Disorders of carbohydrate metabolism:	Galactosemia (transferase deficiency) Cardiomuscular glycogenosis (Pompe)
Disorders of aminoacid metabolism:	Maple syrup urine disease
Disorders of mucopolysaccharide catabolism:	Hurler's disease Hunter's disease Sanfilippo's disease
Disorders of lipid metabolism:	Tay-Sachs disease (GM_2 gangliosidosis I) Fabry's disease Metachromatic leukodystrophy
Various conditions:	Lesch-Nyhan's disease Lysosomal acid phosphatase deficiency

* Many other disorders can be diagnosed as well.

in utero. The majority of these conditions is quite rare. I shall limit discussion to two of the more frequent conditions, namely, Tay-Sachs and Hurler's diseases.

The most frequent gangliosidosis is the GM_2 gangliosidosis, better known as cerebromacular degeneration or Tay-Sachs disease. Course and symptomatology are recapitulated in Table 2.

TABLE 2

TAY-SACHS DISEASE

Clinical symptoms appear by age 4 to 6 months:	Increased startle reflex Hyperakusis Early flaccidity Later spasticity Progressive dementia, seizures Optic atrophy Cherry red spot (90%)
Death at age 2 to 5 years	
Pathochemistry:	Deficiency of hexosaminidase A, an enzyme which in the normal cleaves N-acetyl galactosamine (the terminal hexoside) from the GM_2 ganglioside*. GM_2 elevated in brain ($\times$ 100-300)

* G, for ganglioside consisting of ceramide (sphingosine and fatty acid); M, for mono (one) sialic acid; 2, for trihexosides (Svennerholm 1964).

O'Brien (1969) and Okada and O'Brien (1969) a few years ago described a fluorometric method to accurately determine hexosaminidase A (Hex. A) and hexosaminidase B (Hex. B). Both enzymes — in normal controls — are present in brain, liver, kidney, serum, leucocytes, cultured skin fibroblasts, and in amniotic fluid and amniotic fluid cells. In Tay-Sachs disease, Hex. A is lacking, while Hex. B is present in normal amounts.

Table 3 shows the enzyme contents in the serum of normals, heterozygotes, and patients with Tay-Sachs disease.

Tay-Sachs disease is transmitted as an autosomal recessive trait. Individuals, homozygous for the mutant gene, have no or almost no Hex. A; in heterozygotes, Hex. A amounts to less than 45% of the total hexosaminidase, and in normal controls, Hex. A is more than 48% of the Tot. Hex.

TABLE 3

TOTAL HEXOSAMINIDASE AND RELATIVE AMOUNT OF HEXOSAMINIDASE A IN TAY-SACHS DISEASE

	I Total hexosaminidase (range in nanomol. of substrate cleaved)	II Hexosaminidase A (in % of I)
Tay-Sachs patients (N = 14)	290-1232	0-4
Parents of Tay-Sachs patients (N = 42)	270-687	24-45
Controls	382-805	48-67

Modified from O'Brien 1972.

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Tay-Sachs disease in Askenazi Jews is excessively frequent and about 100 times more frequent than in Sephardic Jews and gentiles. Aronson and Myrianthopoulos (cf. O'Brien 1972) estimated 1 of 30 Askenazi Jews to be heterozygous for the Tay-Sachs gene. This estimate was confirmed by Kaback (1973), who screened the quasi total Askenazi population in the Washington, D.C.-Baltimore area. It was found that 1 in 25 was heterozygous. The risk of matings between two heterozygotes in this ethnic group is therefore considerable, and each pregnancy of matings of two heterozygotes carries a risk of 25% to result in a child afflicted with Tay-Sachs disease. Fortunately the disease can be diagnosed in the fetus. The enzyme deficiency can be discovered in the amniotic fluid and, more reliably, in the cultured amniotic fluid cells, although it may take 10 to 28 days until the cultures have grown enough to be harvested and successfully studied. Already over 100 pregnancies have been tested for fetal Tay-Sachs disease. In O'Brien's laboratory in San Diego, California, alone, samples of 39 pregnancies were studied. Nine fetuses were found to be homozygous for the mutant gene. Eight of them were aborted, and seven times the diagnosis was confirmed by biochemical analysis of fetal tissue. (The eighth case was not studied.) In the ninth case, the result of the amniotic fluid examination was obtained too late to legally terminate the pregnancy. The child was carried to term and developed Tay-Sachs disease.

While thousands of cases of Tay-Sachs disease have been reported, a few dozen cases of the other gangliosidoses have been described. Prenatal diagnosis of Sandhoff's disease has already been made (O'Brien et al. 1971, Suzuki et al. 1971), and can be possibly made in the other conditions (Milunsky 1973).

TABLE 4

CLASSIFICATION OF MUCOPOLYSACCHARIDOSES

Type	Eponym	Mucopolysaccharidurie	Enzyme defect
IH	Hurler	Hep. SO_4, Derm. SO_4	Alpha-L-iduronidase
IS	Scheie	Hep. SO_4, Derm. SO_4	Alpha-L-iduronidase
ISH	Hurler-Scheie hybrid	Hep. SO_4, Derm. SO_4	Alpha-L-iduronidase
II	Hunter (juvenile, late)	Hep. SO_4, Derm. SO_4	Sulfoiduronate sulfatase
III A	Sanfilippo A	Hep. SO_4	Hep. SO_4 Sulfatase
III B	Sanfilippo B		N-acetylα, glucosaminidase
IV	Morquio	Keratan SO_4	?
VI	Maroteaux-Lamy	Derm. SO_4 > Hep. SO_4	Arylsulfatase B
VII	Sly	$Ch\text{-}_4\text{-}SO_4$, $Ch\text{-}_6\text{-}SO_4$	B-glucuronidase

The mucopolysaccharidoses belong to the more frequent inborn errors of metabolism as well. Spranger (1972) calculated an incidence of 4 per 100,000 people in Germany. The mucopolysaccharidoses are cosmopolitan diseases without marked ethnic or racial predilection. Six types of mucopolysaccharidoses are well known, and a seventh mucopolysaccharidosis has been described recently (Sly et al. 1972). A summarizing outline of Hurler's disease is listed in Table 5.

Hurler's disease is transmitted as an autosomal recessive trait. Thus both parents of Hurler's patients are heterozygous for the mutant gene. Various attempts to detect heterozygosity by laboratory tests have failed. For a time, it was believed that metachromasia noticed in cultured fibroblasts could indicate heterozygosity (Danes and Bearn 1966*a*, *b*), yet subsequent studies showed that metachromasia is found in other conditions as well, e.g.,

TABLE 5

SUMMARY OF HURLER'S DISEASE

Beginning late in infancy	Hook-shaped lumbar vertebrae
Early symptoms: hernias	Angular kyphosis
Frequent upper respiratory infections	Spatulated ribs
Deceleration of growth	Thick calvarium
Progressive mental retardation	J-shaped sella
Coarse facial features	Reilly granules in peripheral lymphocytes
Thick, hirsute skin	Clear cells in connective tissue
Cloudy cornea	Ballooned neurons with glycolipids (Zebra bodies)
Hepatosplenomegaly	Swollen, vacuolated cells (Lysosomes) in parenchymal organs
Cardiovalvular involvement	
	Defective mucopolysaccharide catabolism
Dysostosis multiplex	Increased intracellular storage of sulfated mucopolysaccharides (delayed elimination)
Epimetaphyseal dysostosis	
Coarse bones	Alpha-L-iduronidase deficiency
Lack of tubulation	

cystic fibrosis of the pancreas. Most authors, therefore, discouraged from using metachromasia of the cultured fibroblasts as heterozygosity test (Milunsky and Littlefield 1969).

Several methods have been explored to recognize Hurler's disease in the fetus. That the presence of acid mucopolysaccharides, notably heparan sulfate, in the supernatant of the amniotic fluid did not yield reliable results in early pregnancy has already been mentioned.

Fratantoni et al. (1969) measured uptake and degradation of radioactive sulfates by the amniotic fluid cells and found an abnormal accumulation and delayed elimination of tagged sulfates from these cells. This appears to be a fairly reliable test for prenatal diagnosis, which can be checked by the study of the so-called corrective factor. What is the corrective factor? Neufeld and Fratantoni (1970) found that the metabolic defect of cultured Hurler cells could be corrected if the latter were mixed with normal cell cultures or with cells of patients afflicted with another mucopolysaccharidosis. Correction of the metabolic error occurred, even if the culture medium in which cells of other mucopolysaccharidoses grew was added to the Hurler cells. The method has proved to be reliable for the prenatal diagnosis of Hurler's disease and other mucopolysaccharidoses. The whole procedure, including cell culture, may take up to five weeks. This long duration is disadvantageous, notably when the amnion fluid is obtained late in the second trimester.

A still better method has since been developed. Matalon and Dorfman (1972) found that absence of alpha-L-iduronidase in cell cultures of Hurler's patients represented a reliable test which now has been applied successfully in amniotic fluid cell cultures (Matalon, personal communication). Corresponding enzyme deficiencies have been found also in Hunter's and in Sanfilippo's disease. The brief review presented here illustrates the progress which has been made in the prenatal diagnosis of monogenic disorders. Further progress is expected as the causative enzyme defects of many inborn errors of metabolism are unraveled. Most of these conditions are decidedly rare or very rare. The number of amniotic fluid examinations, which we foresee for our population — provided all cases at risk would be tested — are perhaps in the neighborhood of 10 samples per year (for prenatal sex determination and prenatal diagnosis of monogenic disease). In contrast, requests for prenatal chromosome analysis for the same population are at least 100 times more frequent (again, if all high risk cases are considered).

4.3. *Prenatal Chromosome Analysis*

The incidence of the better known and well defined chromosomal aneuploidies (conditions with abnormal numbers of chromosomes) is listed in Table 6. The figures were computed from three serial karyotype analyses of over 10,000 newborns (Sergovich et al. 1969, Lubs and Ruddle 1970, Ratcliffe et al. 1970), and adjusted to 100,000 livebirths per year corresponding to the yearly birth rate of a population of 6 million.

If it were possible to perform amniocentesis and fetal chromosome analysis for every pregnancy, chromosomal aberrations would be eliminated at once. This, however, would mean

TABLE 6

ESTIMATED NUMBER OF LIVE NEWBORNS WITH ANEUPLOIDIES FOR A POPULATION OF 6 MILLION WITH A BIRTH RATE OF 100,000 LIVEBIRTHS PER YEAR

Mongolism	120
Trisomy D and E	50
Monosomy X	40
Trisomy X	70
Klinefelter, mostly XXY	80
Double Y syndrome	100

for that given population of 6 million, 100,000 amniocenteses and chromosomal analyses per year. One technician cannot handle more than 200 chromosomal analyses per year, which means that a minimum of 500 technicians would be needed to cope with the task. Cost of such an operation would be at least in the neighborhood of 15 million dollars per year. This is technically not feasible and, from an economical point of view, probably unsound at the present time. Moreover, many pregnant women would be included whose risk of having a chromosomally abnormal child is smaller than the risk of experiencing one of the complications connected with amniocentesis. There are then several reasons to limit prenatal chromosomal analysis to pregnancies which carry a high risk of a karyotypically abnormal child. What is a high risk pregnancy? We shall limit the discussion in the following to the problem of mongolism which has been best studied. A risk of 1 % to having a mongoloid child is considered high. There are several categories of high risk women with respect to having a mongoloid child. By far the largest group of high risk women are mothers over 40 years of age (Table 7). Of 100,000 pregnancies, approximately 2000 would be in women aged 40 and above. Their risk of having a mongoloid child is higher than 1 %. A smaller group represents mothers aged 35 and over who had a previous aneuploid child and thus shift in the high risk category, since a previous mongoloid or otherwise aneuploid child increases the risk by a factor of 3.

Incidentally, we perform prenatal chromosomal analysis in younger mothers who had a previous mongoloid child, even if the risk is below 1 %. Such mothers are notoriously apprehensive, and fear that they could have another aneuploid child. Their fear and anxiety alleviate if we assure them after prenatal chromosomal analysis that the fetus is karyotypically normal.

An increased risk of having a child with mongolism exists in normal individuals — males and females — who are chromosomal mosaics with a 21 trisomic clone. The risk of having

TABLE 7

DOWN'S SYNDROME AND MATERNAL AGE

Maternal age (yrs)	Risk of Down's syndrome per 1000 births	
	Iowa [1]	New York [2]
15-19	0.71	0.43
20-24	0.67	0.62
25-29	0.66	0.83
30-34	1.06	1.15
35-39	3.04	3.50
40-44	12.35	9.93
45-49	50.00	22.00

[1] Zellweger and Simpson 1973
[2] Stein et al. 1973

a mongoloid child is not exactly predictable, but is sufficiently great to call for prenatal chromosomal analysis.

Females with monoclonal trisomy 21 also carry a risk of having a mongoloid child. About 50% of the ova of a mongoloid female are disomic for the 21 chromosome and lead to a 21 trisomic zygote after amphimixis with a karyotypically normal sperm. The ratio mongoloid: nonmongoloid offspring is less than 1:1 because the fetal wastage of aneuploid fetuses is considerably increased. Reproduction of mongoloid females was mentioned only since mongoloid males are presumably not reproductive. So far, no mongoloid male has been reported who has sired a child.

A fifth and final indication for prenatal chromosomal analysis represents maternal or paternal translocation. Pregnancies of mothers with a balanced 15/21 or 21/22 translocation carry an empirical risk of 10% that their offspring will be translocation mongoloid. The risk is below 5% but still high when the father carries the balanced translocation. All living offspring of a parent, either father or mother, with a balanced 21/21 translocation will be mongoloid. Offspring of a parent with a balanced 21/21 translocation will either inherit the translocation and thus become translocation mongoloids or will inherit no 21 chromosome from the parent with balanced translocation and thus a monosomy 21 will result which is a nonliveable condition.

Summarizing then, the indications for prenatal chromosomal analysis in order to recognize mongolism during gestational life are:

1. Maternal age over 40 years
2. Previous aneuploid child
3. Parental mosaicism with an aneuploid (21 trisomic) clone
4. Maternal aneuploidy (mongolism)
5. Parental balanced translocation

In a study done recently in the state of Iowa, Zellweger and Simpson (1973) found that 24.8% of all mongols were born by mothers aged 40 years and more, and 35.7% by mothers

over 34 years of age. Stein et al. (1973) in the state of New York found 16 and 35.3% for the respective maternal age groups. In other words, then, if all women aged 40 years and over in the population listed in Table 6 had amniocentesis and prenatal chromosome analysis, 20 to 30 mongols could be recognized prenatally and ultimately prevented.

High maternal age obviously accounts for the largest group of examinations and would also give the highest yield. The other 4 indications for the same population would amount to less than 100 examinations per year, yet the yield, i.e., the finding of mongoloids would be relatively higher than for indication 1.

With respect to other aneuploidies, trisomies D, E, X and XXY Klinefelter are likewise maternal age dependent indicating that a relatively high number of these conditions could also be discovered by amniocentesis of mothers aged 40 and above. Monosomy X and double Y syndrome are not maternal age dependent, thus the number of such cases detected by the examination of older mothers would be less promising.

LEGAL AND RELIGIOUS CONSIDERATIONS

So far, the mere scientific aspects of prenatal diagnosis of genetic and cytogenetic diseases were discussed. Presence of any one of these diseases represents — scientifically speaking — an indication for termination of pregnancy. There are, however, several nonmedical aspects to the problem of religious, ethical, and legal nature. Thus, before confronting an expectant mother and her family with the problem of amniocentesis and possible eugenic abortion, their religious attitudes with respect to the latter has to be explored. If the family belongs to a religious group which forbids abortion, one has to know how strictly the respective family adheres to the rules of its church. Many couples are willing to accept the procedure in spite of the opposition of their church. Their spiritual advisor may be consulted by the parents and by the physician as well, in case of doubt. If the spiritual advisor is opposed to abortion, the physician should abstain from it. One should never create a religious, or ethical conflict for a given family on top of the already existing or arising tragedy, which the presence of an affected child may cause for that family.

Finally there is the legal situation which differs from country to country. The Supreme Court of the United States of America on January 22, 1973, took a clear and unmistakable decision: Abortion within the first six months of pregnancy — eugenically indicated or not indicated — is entirely a problem of the woman and her physician. The Supreme Court's document incidentally contains an excellent historical study of concepts and opinions concerning abortion through the centuries. It demonstrated " that the restrictive criminal abortion laws in effect in the majority of the states [*of the U.S.*] today [*22 January 1973*] are of relatively recent vintage. Those laws generally proscribing abortion or its attempt at any time during pregnancy except when necessary to preserve the pregnant woman's life, are not of ancient or even of common law origin. Instead, they derive from statutory changes effected, for the most part, in the latter half of the 19th century. "

Even in ancient times, attitudes toward abortions were predominantly permissive. The statement of the Hippokratic oath: "I will not give to a woman an abortive remedy " was rather the exception. Greeks and Romans, in general, did not bar abortions. And also in the early Christian era, a difference was made between embryo inanimatus (prequickening fetus) and embryo animatus. St. Augustine even considered abortion of the former not as an indictable offense. This is quite in contrast to the opinion of some contemporary ecclesiastics.

Even scientists may be opposed to the purely scientific approach. For instance, Lejeune, the famous French cytogeneticist, stresses the continuum of human existence from the time of fertilization. In his view, there is no point at which abortion does not terminate a human existence. No valid argument can counter this statement. However, the presence of a severely damaged fetus should be considered in the total context of the family and of the society as a whole. The tragedy which such a child may create for a family should be weighed against the moral burden of an abortion. A. Schweitzer, one of the world's foremost ethicists, stated that there are situations where the minor of two evils has to be chosen and where decisions which, per se, violate his principle, reverence for life, can be ethically acceptable.

Justification for eugenic abortion derives furthermore from the observation of what Nature does. It has been shown that approximately 1 in 200 livebirths shows a serious chromosomal aberration. If, however, spontaneously aborted fetuses are karyotyped, chromosomal aberrations are found in 1 of 4 or fewer aborted fetuses. Boué, in a recent study, found chromosomal abnormalities in 892 (i.e., 61%) of 1457 spontaneous abortions (Boué and Boué 1973). The earlier the spontaneous abortion occurs, the higher the incidence of chromosomally abnormal fetuses. This then means that the great majority of karyotypically abnormal fetuses is eliminated by a, so to speak, cathartic principle of Nature. Abnormal fetuses who reach the end of gestation are really exceptions and may possibly represent an oversight of Nature. Less than 25% of the 21 trisomic zygotes are liveborn. And of 20 X0 monosomic zygotes, 19 are spontaneously aborted and only 1 reaches the end of gestation. It would be wise, therefore, that the physician watches carefully what Nature does and would not obviate its wise decisions.

A final point to be considered concerns the change of the human gene pool. Many monogenic diseases are or can be treated with more or less success, for example, phenylketonuria, galactosemia, one variant of homocystinuria, maple syrup urine disease, to name but a few conditions which, if untreated, induce possible brain damage and mental retardation. Patients afflicted with these diseases were rarely reproductive in earlier times, but nowadays, after being treated with more or less success, may be able to reproduce. This necessarily leads to the augment of the respective mutant genes, which is probably of lesser importance for autosomal recessive diseases, yet may have disastrous consequences for autosomal dominant disease. Howell (1972) calculated that retinoblastoma would increase 100-fold in 100 generations if all presently affected individuals could be cured and would reproduce in the usual manner. One wonders how much one should worry for our progeny of 100 generations from now. Nevertheless, prenatal prevention of genetic disease as discussed here will counterbalance the propagation of mutant genes at least to some extent.

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