Prenatal diagnosis: How fast, how far?

by Joan Lynn Arehart

Without question genetic counseling has brought joy to hundreds of parents who, without it, would not have risked having children. Genetic counseling has helped other couples decide not to have children when the possibility of a birth defect turned out to be high. With the increasing availability of counseling centers (there are now 300 in the United States), counseling should help reduce the number of infants born with birth defects, now a quarter million each year.

Yet if a baby is already on the way, genetic counseling may make use not just of pedigree studies and chromosome tests (karyotypes) of the inquiring couples, but also of prenatal diagnosis. Prenatal diagnosis allows advance detection of birth defects by withdrawal and examination of sample fetal cells from the mother-to-be's uterus. Contrary to popular opinion, it is far from routine clinical procedure.

True, amniocentesis—the withdrawal by needle of some of the fluid that bathes the fetus—has been applied late in pregnancy to detect to what extent an Rh-positive baby's blood has been destroyed by antibodies from its Rh-negative mother, so that a transfusion can be given to the baby. Tens of thousands of women have undergone

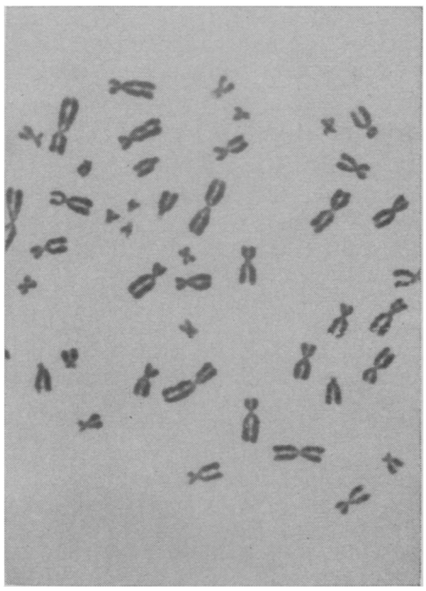
Fetal taps and tests are helping reduce birth defects, but they are far from the final answer

this procedure in the past decade, and today it is considered common medical practice in many hospitals.

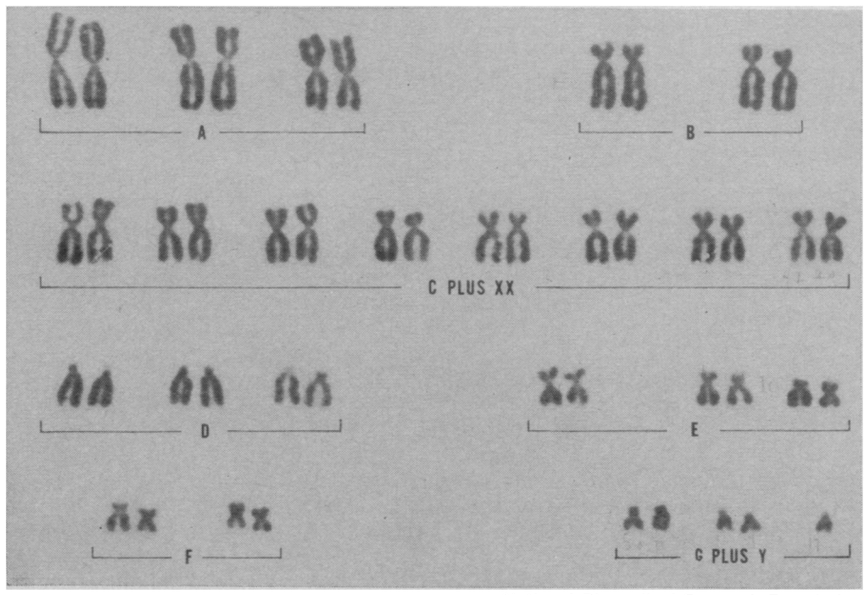
But experience with amniocentesis early in pregnancy, necessary for intrauterine diagnosis of birth defects, is limited to only several hundred patients, all in the past four years. Although any immediate serious risk to the fetus appears to be small (one percent), the long-term risks of the tap to the fetus are unknown. Taps must also be repeated 10 percent of the time to arrive at a diagnosis. Moreover, as Dr. Orlando Miller of the Columbia University College of Physicians and Surgeons points out, blood cells from the fetus pass into the maternal blood in 10 percent of the cases. This passage could pose a problem by sensitizing Rh-negative mothers with Rh-positive babies. Hence Dr. Henry Nadler of Northwestern University, and other experts at early-pregnancy amniocentesis, urge physicians to move cautiously before tapping for prenatal diagnosis and not to be swept into the procedure by public demand for it.

Even if the fetus is not damaged, the precious few fetal cells withdrawn in the first 14 to 16 weeks of pregnancy must be cultured until there are enough of them to diagnose metabolic deficiencies or chromosome defects. It can easily require four weeks to grow enough cells to determine sex-linked birth defects such as hemophilia or a type of muscular dystrophy, and four to eight weeks to determine severe metabolic diseases such as Tay-Sach's disease (which causes progressive degeneration of the nervous system), Pompe's disease (which results in an enlarged liver and spleen and possibly mental retardation) or lysosomal acid phosphatase deficiency (which leads to vomiting, lethargy and death). If after this delay, cell culturing and diagnosis indicate the advisability of a therapeutic abortion and the parents desire one, it may by then be too late. Also, doctors have to be careful that the cells under study are really from the fetus and not from the mother.

Knotty ethical questions about prenatal diagnosis have also been raised. Some of them were discussed by prenatal diagnosis specialists at a National



Fetal cell chromosomes, unarranged.



National Biomedical Research Foundation

The arrangement shows an extra sex chromosome, or Klinefelter's syndrome.

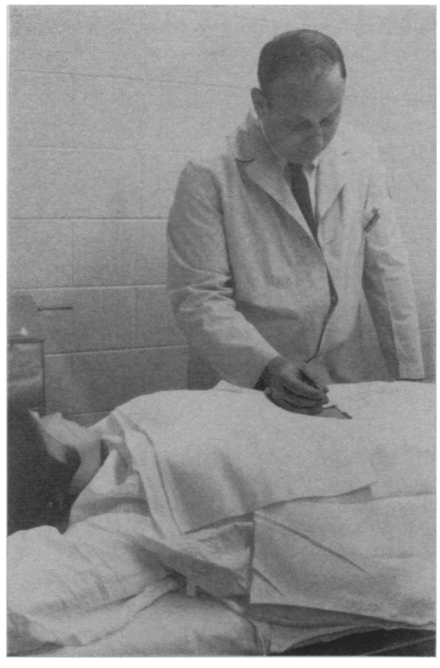
Foundation-March of Dimes conference in May. As things stand now, if a fetus is diagnosed as having a birth defect, an abortion is usually the only therapeutic recourse available. This raises a difficult question: Should a patient be allowed amniotic diagnosis if she is not willing to consider an abortion? Although some geneticists say she should not, Dr. E. James Lieberman, a Washington, D.C., psychiatrist, stresses that amniocentesis should never be tantamount to recommendation for an abortion. Amniocentesis does not mean, he says, "that the geneticist may abrogate a couple's decision by assuming that if the fetus is normal, she will carry it, or if abnormal, she will abort. The genetic component is one of many and clients must be helped to put them in perspective."

Says Columbia's Dr. Miller: "It would be unfortunate if the decision [to abort] were taken by anyone but the parents, who have their own ideas of what constitutes the optimal brood for them qualitatively as well as quantitatively. On the other hand, the decision many reach will be strongly influenced, if not determined, by what their obstetrician or genetic counselor has told them. Consequently these professionals have a responsibility to be fully informed, informed as to their patients' goals and desires, informed about the present state of the art of prenatal diagnosis and informed about genetics."

Then there is the legal aspect of amniocentesis. Dr. Lieberman points to the possibility that diagnosis by amniotic tap might be abused, as psychiatric tests have been in the past, to obtain an abortion in states where abortions are allowed only for stringent medical reasons.

Nonetheless intrauterine diagnosis is moving ahead. Although limited chromosome defects can be detected by the procedure (some dozen of which are either inherited or result from mistakes at the time the sperm and egg join, such as the scrambling in of an extra sex chromosome), more defects should become detectable, thanks to new techniques. One technique is computerized prenatal diagnosis. After a decade of steady work on computerizing chromosome analysis of both adults and fetuses, Dr. Robert S. Ledley of the National Biomedical Research Foundation, affiliated with Georgetown University Medical Center, says "we are just ready to go now."

The computer makes a chromosome karyotype in 30 seconds whereas a scientist must spend several hours doing one manually. Whether automated or manual, or applied to amniotic fetal cells or adult white blood



Northwestern Univ.

Dr. Nadler making an amniotic tap.

cells, chromosome karyotyping follows a certain procedure. Once a cultured cell is ready to divide, a drug is applied to fix it at that point, because chromosome spreads can be seen only during division. The fixed spread is then photographed under a microscope, and the images of the cell chromosomes are cut out like puzzle pieces and pasted up according to the normal human chromosome arrangement, called an "idiogram." If the pieces do not fit the normal arrangement—if certain ones are, say, missing, misplaced or added—certain kinds of anticipated birth defects can be diagnosed. "Any chromosome aberration is usually disastrous for the fetus," Dr. Miller explains. "It means a child will probably be severely retarded, and possibly have gross physical abnormalities besides."

Karyotypes of 10 to 30 cells are usually required to confirm a chromosome diagnosis. This battery of tests costs about $150 manually, but automation should slash it to $6 or $12 within a year, Dr. Ledley estimates. The computer also ensures the testing of as many cells as necessary to arrive at a diagnosis, and in plenty of time should the parent desire an abortion.

Then there is chromosome fluorescence, developed only this past year. Whereas the classic karyotype offers only a silhouette of chromosomes, fluorescent analysis reveals details on the chromosomes as well. Dr. Miller is now performing the analysis on chromosomes from abnormal children. He plans to start doing it on fetal chromosomes within several months. The analysis, he says, should reveal still more chromosome abnormalities that touch off birth defects. Meanwhile Dr. Ledley is trying to computerize fluorescent chromosome karyotyping and print-outs.

Unlike chromosomes, the genes on them elude human observation. However progress is being made in indirectly detecting, from cultured fetal cells, missing or defective genes, or rather genic expression in faulty protein or enzyme activity. Currently only 12 metabolic disorders out of some 1,400 known genetic diseases can be detected. However, thanks to increasingly sensitive biochemical tests, diagnosis should increase to 30 metabolic disorders, predicts Dr. Daniel Bergsma, vice president at the National Foundation.

Culturing of amniotic cells and their biochemical analysis is not especially difficult, but there are only 20 or so laboratories in the United States able to perform them. Sometimes these laboratories collaborate on culturing and analysis. Dr. Ledley anticipates using computers to run such biochemical tests and to compare biochemical assay results with chromosome karyotypes to see if specific chromosome-caused, and gene-triggered, birth anomalies are related.

However limited current prenatal diagnosis techniques may appear—after all, some of the most common birth defects such as sickle cell anemia and cystic fibrosis cannot be detected prenatally—these procedures are striking when one considers how new the field of human genetics is. "In 1948," Dr. Ledley recalls, "people didn't even know how many human chromosomes there were. My medical textbooks said 48 instead of the correct 46. Thus only in the past 25 years or so have we pinned down the correct number of human chromosomes, been able to see them, and known how to correlate some of their aberrations with specific birth defects."

Yet even now, as Drs. Miller and Ledley concur, researchers stand on the threshold of *applied* human genetics. Regardless of the strides made in intrauterine diagnosis of birth anomalies, the ultimate goal is prevention of birth defects before conception. Both Drs. Ledley and Miller foresee all couples having chromosome karyotypes before conceiving, just as they now have blood tests before marrying. Similarly, biochemical tests for detecting carriers of genetically linked diseases, geneticists predict, would help couples avoid identical tragedy for their children. Such assays—for detecting carriers of the rare recessive Tay-Sach's disease (SN: 10/11/69, p. 327) for example—are getting under way, and ideas on how to use them for preventive mass screening are being explored. □