II.

THE NATURE AND EXTENT OF RESEARCH INVOLVING THE FETUS AND THE PURPOSES FOR WHICH SUCH RESEARCH HAS BEEN UNDERTAKEN

An extensive review of the scientific literature, focusing on a period covering the last ten years, formed the basis for the Commission's investigation of the nature, extent and purposes of research on the fetus. The review was conducted under contract with Yale University, Maurice J. Mahoney, M.D., Principal Investigator. The investigation included an all-language review of published research, utilizing the MEDLARS computer indexing and search system of the National Library of Medicine, a review of selected bibliographies and abstracts, a survey of departments of pediatrics and obstetrics at medical schools in the United States and Canada to identify current research on the fetus, and a review of NIH grant applications and contracts since 1972 involving research on the fetus. In addition, the Food and Drug Administration provided information on fetal research conducted in fulfillment of its regulations.

For the purpose of summarizing the review, research involving the fetus has been considered in four general categories.

1. Assessment of Fetal Growth and Development *In Utero*. Over 600 publications dealing with investigations of fetal development and physiology were identified. In general, the purpose of these investigations was to obtain information on normal developmental processes, as a basis for detecting and understanding abnormal processes and ultimately treating the fetal patient. To this end, numerous experimental approaches were employed.

Studies of normal fetal growth relied primarily on anatomic studies of the dead fetus. Studies of fetal physiology involved both the fetus *in utero* and organs and tissues removed from the dead fetus. In some instances, this research required administration of a substance to the mother prior to an abortion or delivery by caesarean section, followed by analysis to detect the presence of the substance or its metabolic effects in blood from the umbilical cord or in tissues from the dead fetus. Information on the normal volume of amniotic fluid

at various stages of pregnancy was obtained by injecting a substance into the fluid and assessing the degree of dilution of that substance; these studies were performed before abortion, during management of disease states (Rh disease), and in normal term pregnancies. Similarly, numerous chemicals were measured in amniotic fluid to establish normal data.

Research also focused on the development of fetal behavior *in utero*. Fetal breathing movements were detected by ultrasound as early as 13 weeks after conception. Fetal hearing was documented by demonstrating changes in fetal heart rate or EEG in response to sound transmitted through the mother's abdomen. Vision was inferred from changes in fetal heart rate in response to light shined transabdominally. Increased rates of fetal swallowing after injection of saccharin into amniotic fluid suggested the presence of fetal taste capability. Observation of the fetus outside the uterus indicated response to touch at 7 weeks and the presence of swallowing movements at 12 weeks of gestation.

2. Diagnosis of Fetal Disease or Abnormality. Well over 1000 papers have been published in the last 10 years dealing with intrauterine diagnosis of fetal disease or abnormality. Much of this research involved amniocentesis, a procedure in which a needle is inserted through the mother's abdomen into the uterus and amniotic fluid is removed for analysis. Amniocentesis originally came into extensive use for monitoring the status of the fetus affected by Rh disease in the third trimester of pregnancy. Research related to treating Rh disease indicated that the yellow color of the amniotic fluid correlated with the severity of anemia in the fetus. This color index later was used as an indication of the need for intrauterine transfusion, a procedure subsequently developed to treat severely affected infants.

The knowledge that amniocentesis was safe in the third trimester of pregnancy, coupled with the demonstration that cells shed from the skin of the fetus into the amniotic fluid could be grown in tissue culture, led to application of amniocentesis to detection of genetic disease in the second trimester. The research conducted in developing this procedure focused first on demonstrating in fetal cells from amniotic fluid the normal values for enzymes known to be defective in genetic disease. This research was conducted largely on amniotic fluid samples withdrawn as a routine part of the procedure of inducing abortion.

Once it had been demonstrated that the enzyme was expressed in fetal cells and normal values were known, application to diagnosis of the abnormal condition in the fetus at risk was undertaken. The reported research documents a steady progression in development and application of amniocentesis, so that potentially over 60 inborn errors of metabolism (such as Tay-Sachs disease) and virtually all chromosome abnormalities (such as Down's syndrome), as well as the lack of these defects in the fetus at risk, can be diagnosed *in utero*, at a time when the mother can elect therapeutic abortion of an affected fetus.

Research directed at prenatal diagnosis of disease currently focuses on three main objectives. The first involves attempts to extend diagnostic capability to additional diseases, such as cystic fibrosis of the pancreas, which cannot now be detected by amniocentesis. A second approach attempts to detect fetal cells in the maternal circulation and separate these from maternal cells for chemical analysis, thus avoiding any risks and difficulties encountered during amniocentesis. The third direction is the development of fetoscopy, a process by which an instrument is inserted into the uterus and a sample of fetal blood is obtained from the placenta under direct visualization. The blood sample is analyzed to diagnose disorders such as sickle cell disease or thalassemia which cannot be detected by amniocentesis. The time needed for laboratory analysis following fetoscopy is markedly shorter than the four to six weeks required to obtain tissue culture results in amniocentesis. Fetoscopy also permits visual examination of the fetus for external physical defects.

Because of the unknown but theoretically significant risks that remained following animal studies, fetoscopy was developed selectively in women undergoing elective abortion. The first clinical applications have been reported in recent months: three fetuses at risk for beta-thalassemia, whose mothers were seeking abortion to avoid the possibility of having an affected child, were diagnosed as free of disease following fetoscopy. All three have been born and are normal.

Research has also been directed at the identification of physical defects in the developing fetus. The most handicapping defects are those of the neural tube (anencephaly or meningomyelocele). Initial research efforts were devoted to developing X-ray techniques to view the fetus for these defects by injection of radiopaque substances into amniotic fluid (amniography or fetography). These studies primarily involved women having a family history of neural tube defects

and whose fetuses were consequently at increased risk. More recently, elevated levels of alpha-fetoprotein in amniotic fluid (or maternal blood) were found to be associated with neural tube defects, and may serve as a screening test for these disorders. Ultrasound has come into use to determine internal and external structural detail of the developing fetus and thereby to detect anencephaly, meningomyelocele, and even congenital heart disease.

Amniocentesis also opened another area of fetal research: the assessment of fetal lung maturity. Studies of normal amniotic fluid in the last trimester of pregnancy provided an indication that increased concentrations of lecithin relative to sphingomyelin reflect maturation of the fetal lung; infants with mature lungs did not develop respiratory distress. This predictive test (the L/S ratio) was applied when women went into premature labor, or when induced delivery was indicated due to Rh disease or maternal diabetes, to assess the risk that the delivered infant would develop respiratory distress. When the lungs were immature, delivery could be delayed, depending on the relative risks of intrauterine versus extrauterine life. In the last three years, attempts to induce fetal lung maturation by administration of corticosteroids to the mother have added a new dimension to this clinical situation. Following animal studies indicating that this procedure was safe and effective, human studies were undertaken intending to benefit the fetus involved. Results reported to date suggest that the procedure is successful, but studies of possible long-term side effects of this intrauterine therapy are continuing.

Assessment of fetal well-being is another goal of fetal research. Ultrasound has been used to assess fetal size and gestational age, and to monitor fetal respiratory movements, certain types of which have been found to indicate fetal distress. Studies of hormones, metabolic products and chemicals in amniotic fluid (and in maternal blood and urine) identified numerous substances associated with either abnormalities of fetal growth or with fetal distress. In the last decade, monitoring the fetal heart rate and sampling fetal scalp blood during labor developed from research techniques to clinical application for indication of fetal distress.

3. Fetal Pharmacology and Therapy. Over 400 publications in the last 10 years involving fetal pharmacology were identified in the literature search;

less than 20 percent of these included research on the living fetus. Of the latter studies, the majority were coincidental studies conducted as an adjunct to clinically accepted procedures. For example, the largest category encompassed studies of transplacental drug movement or effects on the fetus of analgesic or anesthetic agents given to the mother during labor and delivery.

The research techniques employed in investigations of this type included antepartum transfusion of the fetus with blood containing drugs, and administration of drugs or agents to the mother for therapeutic or research reasons. The ensuing studies involved assessment of effects on the fetal electrocardiogram, determination of fetal movements or structures by ultrasound, amniotic fluid sampling, scalp or umbilical cord blood sampling, and studying placental passage and fetal distribution patterns in tissues of the dead fetus. The studies were conducted either prior to abortion or in normal pregnancies, usually at the time of delivery.

In general, studies to determine the effects of a drug on the fetus were retrospective, involved the fetus incidentally or after death, or involved the infant, child or adult. Thus, all studies of the influence of oral contraceptives or other drugs on multiple births or congenital abnormalities were retrospective. Study of the effects on the fetus of drugs administered to treat maternal illness during pregnancy (including anticonvulsants, antibiotics, hormones and psychopharmacologic agents) in which the fetus was an incidental participant, were also largely retrospective. Studies of effects on the fetus and newborn infant of analgesic and anesthetic agents given at delivery also involved the fetus incidentally, but were conducted prospectively. Recently attempts were made to focus prospective pharmacologic studies of antibiotics intentionally, rather than incidentally, on the fetus. Different antibiotics were administered to pregnant women before abortion to compare quantitative movement of these agents across the placenta, as well as absolute levels achieved in fetal tissues. The results served as a guideline for drug selection to treat intrauterine infections, particularly syphilis. Studies conducted on the dead fetus after abortion showed the clear superiority of one drug over the other.

In addition to assessing effects of drugs on the fetus and measuring placental transfer of drugs, fetal pharmacologic research included attempts to

modify drug structures so that they will or will not cross the placenta to affect the fetus. Such research also included study of the effects of certain drugs (such as phenobarbital or corticosteroids) in inducing enzyme activity in the fetus (to prevent hyperbilirubinemia or speed fetal lung maturation and prevent respiratory distress syndrome).

Effects on the fetus of live attenuated virus vaccines administered to the mother were also examined. Preliminary testing of rubella vaccine in monkeys indicated that the vaccine virus did not cross the placenta. In contrast, studies on women requesting therapeutic abortion showed clearly that the vaccine virus did indeed cross the placenta and infect the fetus, indicating the danger of administering the vaccine during pregnancy. Similarly, a study conducted with mumps vaccine virus showed that the virus infected the placenta, but not the fetus.

Attempts at fetal therapy *in utero*, in addition to blood transfusion for Rh disease and corticosteroid administration to speed fetal lung maturity, were conducted recently as an adjunct to amniocentesis. Examples of this type of fetal therapy include the administration of hydrocortisone to the fetus *in utero* to treat the adrenogenital syndrome, maternal dietary therapy for fetal galactosemia, and administration to the mother of large doses of vitamin B_{12} to treat fetal methylmalonic acidemia.

4. Research Involving the Nonviable Fetus. The quantity of research on the nonviable fetus *ex utero* has been small; much of such research included the nonviable fetus only at the extreme end of the spectrum of studies of premature infants. Such studies included measurements of amino acid levels in plasma of infants with intrauterine malnutrition, administration of bromide to measure total body water in low birth weight infants, and the study of hemoglobin in blood from the umbilical cord as an indicator of fetal maturity. The purpose of this research was to gain information that could be of benefit to other fetuses and infants.

Research was also conducted involving the nonviable fetus during abortion by hysterotomy but before the fetus and placenta were physically removed from the uterus. A study conducted in the United States reported the feasibility of delivering a portion of the umbilical cord from the uterus and using it as a site

for drug administration and blood sampling. Another study, this one undertaken in Finland, employed the technique to infuse noradrenaline via the umbilical vein; study of metabolites subsequently obtained demonstrated the functional maturity of the fetal sympathetic nervous system. Several studies in Sweden used similar techniques: radiolabeled chemicals were administered to the fetus via the umbilical vessels, and metabolites were then studied in the umbilical vein and, following completion of the abortion, in the fetus. In another Finnish study, arginine and insulin were injected into blood vessels of eight fetuses (450-600 grams) with the placenta attached to the uterus, and blood samples were taken from the umbilical cord to assess fetal endocrine regulation of glucose metabolism. These studies were conducted solely to gain information on fetal metabolism for the benefit of other fetuses and infants.

The nonviable fetus was the subject of research to develop a life-support system ("artificial placenta") for sustaining very small premature infants, as well as to obtain data on normal fetal physiology. Some of this life-support system research was conducted only with larger infants (viable by weight criteria) who had failed on respirators and were tried on experimental systems as an ultimate therapeutic effort to achieve survival. Of the published studies with clearly nonviable fetuses, one was conducted in the United States. Published in 1963, this research involved 15 fetuses, obtained following therapeutic abortion at 9-24 weeks gestational age. The fetuses were immersed in salt solution containing oxygen at extremely high pressure, in an attempt to provide oxygen for the fetus through the skin. The longest survival was 22 hours. In an earlier study in Scandinavia, seven fetuses weighing 200-375 grams, from both spontaneous and induced abortions, were perfused with oxygenated blood through the umbilical vessels. Longest survival was 12 hours. A third study, conducted in England, utilized a similar method and included eight fetuses obtained following hysterotomy abortion and weighing 300-980 grams. Longest survival was 5 hours. No other studies of this type involving nonviable fetuses were found in the literature review.

Studies of fetal physiology conducted on the delivered fetus utilized several experimental approaches. In a study conducted in Sweden, the intact fetal-placental unit obtained by hysterotomy abortion was removed and utilized for perfusion studies. A study performed in England involved cannulating the

carotid and umbilical arteries of the aborted fetus and measuring fetal glucose levels in response to administration of growth hormone. Four fetuses from hysterotomy abortions at 16-20 weeks gestation were perfused via the umbilical vessels in a study in Scotland which demonstrated that the fetus could synthesize estriol independent of the placenta. A similar study by the same investigators involving six fetuses demonstrated that the 16-20 week fetus could synthesize testosterone from progesterone. To learn whether the human fetal brain could metabolize ketone bodies as an alternative to glucose, brain metabolism was isolated in eight human fetuses (12-17 weeks gestation) after hysterotomy abortion by perfusing the head separated from the rest of the body. This study, conducted in Finland, demonstrated that the human fetus, like previously studied animal fetuses, could modify metabolic processes to utilize ketone bodies.

These studies of the nonviable fetus represent the total number reported in the world scientific literature, as well as could be ascertained from review of the most comprehensive bibliographic search ever undertaken of research involving the human fetus. The total number of citations involving fetal research was well in excess of 3000; the reports of research on the nonviable fetus that were found numbered less than 20. Certainly some reports of such research may have been missed even by this thorough review, but it is safe to conclude that the amount of research conducted on the nonviable fetus has been extremely limited. Of the principal investigators conducting this type of research, three were from the United States; two of these investigators conducted their research abroad. The only research conducted in the United States on the nonviable fetus *ex utero* was the study involving attempts to develop an artificial life-support system. The literature survey disclosed no reports of research conducted in the United States on the nonviable fetus intended solely to obtain information on normal physiologic function.

In summary, research involving the fetus includes a broad spectrum of studies of the fetus both inside and outside the uterus. The research may be as innocuous as observation, or involve mild manipulation such as weighing or measuring, or more extensive manipulation such as altering the environment, administering a drug or agent, or noninvasive monitoring. Diagnostic studies may involve sampling amniotic fluid, urine, blood, or spinal fluid, or performing

biopsies. The most extensive or invasive procedures include perfusion studies and other attempts to maintain function.

The extent of research on the fetus is reflected by the more than 3000 citations included in the literature review of such research. Most involved the fetus *in utero*; less than 20 articles involved the nonviable fetus.

The purposes for which research on the fetus has been undertaken include obtaining knowledge of normal fetal growth and development as a basis for understanding the abnormal; diagnosing fetal disease or abnormality; studying fetal pharmacology and the effects of chemical and other agents on the fetus, in order to develop fetal therapy; and developing techniques to save the lives of ever smaller premature infants.