III.

ALTERNATIVE MEANS FOR ACHIEVING THE PURPOSES FOR WHICH RESEARCH INVOLVING LIVING FETUSES HAS BEEN UNDERTAKEN

In the development of new medical procedures or drugs to be employed in the treatment of humans, research is usually initiated with animal models, which are used until probable effectiveness and low degree of risk are determined. Ultimately, it becomes necessary to conduct the research on humans, since initial human applications are experimental regardless of the amount of preceding animal research. In some instances, pertinent animal models may not exist or may have certain limitations, so that studies on humans begin at a relatively early stage. In all instances, however, the question may be asked whether studies on humans began at an appropriate time, or whether the information that was required could have been obtained using alternative research means, i.e., studies on animal models.

The broad nature of the survey of the nature and extent of research on the fetus (Section II) did not permit detailed evaluation of alternative means. Therefore, the Commission contracted with Battelle-Columbus Laboratories to conduct a more intensive analysis of this issue in connection with four advances in which research on the fetus played a part. The Battelle report to the Commission traces the historical development of (1) rubella vaccine, (2) the use of amniocentesis for prenatal diagnosis of genetic defects, (3) the diagnosis and treatment, as well as prevention, of Rh isoimmunization disease, and (4) the management of respiratory distress syndrome. The study identifies pertinent animal research that was conducted and attempts to assess whether the human research was necessary and appropriate, or whether animal models could have been substituted. Finally, the study evaluates the likelihood that the advance would have been achieved if all research on the fetus, both therapeutic and nontherapeutic, had been prohibited. In preparing the report and analysis, extensive bibliographies on each topic, prepared by staff of the National Library of Medicine, were utilized. In addition, a number of scientists whose research had been of greatest importance to the advances were interviewed.
1. In the case of congenital rubella syndrome, descriptions of the condition (which comprises congenital heart disease, cataracts, deafness and mental retardation) and its etiology (maternal rubella infection during pregnancy) were drawn from research on the living child and material from dead fetuses. Attenuation of the rubella virus for vaccine purposes was accomplished in tissue culture using nonhuman cells. Vaccine trials were conducted on adults and children. The vaccine was found safe and effective, and it was licensed in 1969, 28 years after the congenital rubella syndrome was first described.

No research on the living human fetus was required to develop the vaccine. A question remained, however, as to the safety of administering the vaccine during pregnancy or to women in the child-bearing years. Should a pregnant woman, without immunity to rubella, be vaccinated to prevent the risk to the fetus that would ensue if she contracted natural rubella? Some experimental animal models for the rubella condition had been developed, the rhesus monkey being the closest one to the human. Accordingly, pregnant monkeys were inoculated with either rubella virus or the vaccine virus. Subsequent study showed that five of six monkey fetuses whose mothers received slightly attenuated rubella virus were infected, but none of the six monkey fetuses whose mothers received vaccine virus was infected. Thus, the animal model suggested that the vaccine virus did not cross the placenta and was safe to administer during pregnancy, although other vaccine viruses were known to cross the human placenta.

Human studies were then undertaken. Because of the potential risk to the fetus, women requesting therapeutic abortion were employed as subjects. These volunteers received the vaccine and underwent the abortion 11 to 30 days later. Examination of tissues from the dead aborted fetuses showed that, in contrast to the results in monkeys, the vaccine virus did cross the human placenta and infect the fetus. On the basis of this research involving the fetus in anticipation of abortion, as well as subsequent reports of damage to the fetus following accidental rubella vaccination during pregnancy, administration of rubella vaccine to pregnant women or women who might become pregnant within 60 days of vaccination is proscribed.

Two alternatives to the planned testing of rubella vaccine on pregnant women in anticipation of abortion can be considered. First, more extensive animal testing of the vaccine could have been conducted. The usefulness of such a
procedure, however, would be questionable. Based on prior experience with the inconsistencies of placental passage of any agent, the human situation would remain unknown after any amount of animal testing. Testing in the human is still required even after negative results in animal models, with the same safeguards as if no animal testing had been conducted.

The second alternative would be to wait for the accidental vaccination of pregnant women and observe the outcome. This in fact occurred in several instances after the planned testing. The women involved, who had wanted pregnancies, elected instead to terminate their pregnancies by abortion due to the risk to the fetus, and studies of tissue from the dead fetuses confirmed that they had been infected by the virus. Thus, the effect in humans could have been learned in this instance by retrospective research. At issue here in the selection of alternatives is the question whether it is preferable to proceed by design with women planning abortions, or to work retrospectively with women who desire pregnancy but were accidentally vaccinated.

2. The use of amniocentesis (removal of amniotic fluid via a needle inserted into the uterus through the mother's abdomen) as a clinical procedure dates from 1882, when it was introduced as a treatment for polyhydramnios (excess accumulation of amniotic fluid). There is no evidence that animal studies were conducted prior to that time, and comparatively little research has been done on amniocentesis as a procedure apart from its applications. The Battelle study of amniocentesis thus involved evaluation of the uses to which the procedure has been put, as well as alternative means for developing the procedure. Amniocentesis has found application in three main areas of research: prenatal diagnosis of genetic disease, diagnosis of Rh disease, and assessment of fetal maturity related to respiratory distress syndrome. Its use in the latter two areas will be discussed in parts 3 and 4 of this section.

Two lines of research provided impetus for prenatal diagnosis of genetic disease: development of the technology for tissue culture and identification of the sex chromatin as an indicator of sex in single cells. In 1955 it was shown that fetal sex could be predicted from the sex chromatin pattern of amniotic fluid cells. Application of this technique to prenatal detection of sex-linked disorders was first reported in 1960. Rapid progress in tissue culture research
led to success in culturing fetal amniotic fluid cells in 1966, intrauterine
diagnosis of a chromosome abnormality in 1967, and the first intrauterine
diagnosis of metabolic disorders using cultured amniotic fluid cells in the
following year. Research in this area steadily expanded as chromosomal and
metabolic disorders were added to the list of conditions diagnosable in utero.
At present, virtually any chromosomal anomaly and potentially over 60 metabolic
disorders can be detected prenatally by amniocentesis. The possibility of
diagnosis and selective abortion of abnormal fetuses has enabled the birth of
normal children to families that otherwise would not have risked pregnancy,
and has permitted families to avoid the impact of the birth of a defective or
doomed child.

All research to detect genetic defects involved the living human fetus.
Much of it utilized amniotic fluid obtained in the normal course of abortion, in
order to ascertain normal values. Such research was obviously nonbeneficial for
the fetuses involved. Only research conducted on women at risk for having a
fetus with the disorder in question could be considered beneficial, in that
many of these women desired an abortion unless it could be shown that the fetus
would be normal.

An alternative means to develop the procedure of amniocentesis would have
been to conduct more extensive animal research. Animal models have numerous
limitations with regard to amniocentesis, however, including shape of the pelvis,
size and shape of the uterus, number of fetuses present (which confounds cell
analysis), and the marked irritability of the uterus in many species such that
even slight manipulation induces abortion, fetal resorption or congenital mal-
formations. Recently some animals have been found in which amniocentesis can be
performed, but even in these it is difficult in midpregnancy, when it must be done
for effective intrauterine diagnosis of genetic defects.

While animal models might have been utilized more extensively in develop-
ing the technique of amniocentesis, there is no alternative to human experimen-
tation for the purpose of developing the diagnostic tests for genetic metabolic
disorders used with amniocentesis. The conditions are unique to the human species.
Only by study of cells in amniotic fluid from pregnant humans, both normal and
those at risk for genetic disease in the fetus, was it possible to assess whether
the genetic defect was expressed in these cells, and to determine the normal and
abnormal values for the responsible enzymes in the cells as the basis for prenatal diagnosis. This research utilized only amniotic fluid and the fetal cells in it, and thus was not invasive of the fetus. In the early stages of developing the technique, however, the possible risks to the fetus were greater than those for many invasive procedures.

3. The history of Rh isoimmunization disease encompasses the description of the disorder, determination of its cause, initiation of successful treatment, and development of effective prevention, all within four decades. Characterization of this disorder, which combines hemolytic anemia, jaundice, and intrauterine death or (if delivered) severe brain damage, was accomplished in the 1930's from study of autopsy material and newborn infants. Research on blood groups, utilizing both human and animal material, led in 1941 to the demonstration from studies of mothers and newborns that Rh sensitization in an Rh negative mother to an Rh positive fetus produced hemolytic anemia in the fetus. In 1945, treatment of affected newborn infants by exchange transfusion was initiated and mortality began to decline.

Use of amniocentesis was introduced in 1956 to obtain amniotic fluid which provided an indicator of how severely the fetus was affected and, late in pregnancy, whether labor should be induced to enable treatment of the fetus outside the uterus. In 1963, treatment of the severely affected fetus by intrauterine blood transfusion was initiated, resulting in a 60 percent reduction of the stillbirth rate for affected infants. Ongoing studies of the etiology of the disease, using pregnant women, provided indications that sensitization of the mother usually occurred at the time of delivery of her first Rh positive infant, when a large volume of fetal Rh positive cells entered the mother's circulation. As the result of research conducted largely with prisoners, a vaccine was developed to prevent this sensitization. Trials of the vaccine, administered to women after delivery, began in 1964. Results indicated virtually complete effectiveness, and the vaccine (RhoGam) became commercially available in 1968.

Research on the fetus played no part in developing the RhoGam vaccine, but such research was essential in demonstrating the basic cause of the disease and in developing methods for prenatal diagnosis and treatment. All significant research on the fetus related to Rh disease was conducted on mothers and fetuses
at risk for the disease, and can be categorized as beneficial research. The size of the benefits achieved may be appreciated by reviewing statistics related to the disorder. Approximately 12 percent of couples in the United States are at risk for having an affected infant. Nearly 25,000 infants could be affected yearly. Since initiation of exchange transfusion, neonatal mortality of affected infants has dropped to about 2.5 percent. Intrauterine transfusion has reduced the annual number of stillbirths due to the disease from 10,000 to less than half that number. The entire amount of money used to support Rh disease research from 1930 through the successful development of the vaccine in 1966 is the equivalent of the present cost to society for lifetime care of six children irreparably brain damaged by the disease.

Limited animal models were available for study of Rh disease and were utilized in some instances. Intrauterine transfusion, for example, was first conducted on animals. Extensive research has been conducted to develop an animal model of the actual disease, but the hamadryas baboon is the only species that has been found in which the disease is sufficiently similar to the condition in man for the animal to serve as a useful model. The limitations of animal models and the urgency of developing a treatment for fetuses otherwise likely to die led physician researchers to attempt experimental therapy with favorable risk/benefit ratio in human subjects. In these instances, the risk of not doing the research was approximately 50 percent intrauterine death; in the face of such odds, even such a hazardous experimental therapeutic procedure as intrauterine transfusion was considered acceptable.

4. Respiratory distress syndrome (RDS) is a major cause of infant mortality. In the United States approximately 40,000 cases occur annually; 95 percent of these cases are premature infants, and overall mortality is in excess of 25 percent. Study of the development of advances related to this condition revealed a picture of frequent interaction of animal model and clinical studies involving the living human fetus in the third trimester. In addition, advances in therapy were achieved from research involving affected premature infants. The key experimental work elucidating the basic cause of the condition involved study of the lungs of deceased infants who died of RDS or other causes. This research indicated that lungs of infants with RDS lacked a chemical
(surfactant) which acted to keep open the smallest air passages in the lung; surfactant was present in the lungs of unaffected infants. Subsequent studies, again relying primarily on autopsy material, delineated the biochemistry of surfactant, and it was suggested that amniotic fluid might provide an indicator of the presence of surfactant. Studies were then conducted of amniotic fluid obtained at various stages in the last trimester of pregnancy, solely to learn the normal values of the phospholipid components of surfactant; this research was nonbeneficial for the fetuses involved. Results indicated that a marked increase in the content of lecithin relative to sphingomyelin in amniotic fluid correlated with the appearance of surfactant in the fetal lung, and indicated that the lungs were mature enough that the fetus, if delivered, would probably not develop RDS. The report of these studies in 1971 strongly influenced obstetric management of premature labor and diabetic pregnancy, by providing an index of the time when delivery could proceed with minimum risk of RDS.

Another line of research quickly had an impact on RDS management. Animal studies in the 1950's showed that steroids were capable of inducing enzyme activity in the fetus. Studies involving the pregnant woman and the living fetus in 1961 demonstrated that cortisone crossed the human placenta. Animal studies in the late 1960's and early 1970's indicated that corticosteroids could induce enzymes and thereby increase surfactant in fetal lungs. In the species studied (lambs, rabbits and rats) the steroids did not cross the placenta and had to be administered directly to the fetus. Based on the previous demonstration that steroids crossed the human placenta, and later clinical studies of mothers receiving steroid therapy during pregnancy that had not suggested any ill effects on the fetus, clinical trials were initiated in pregnant women at risk of having infants affected by RDS. The results obtained to date indicate that corticosteroids are highly effective in preventing RDS, without undesirable side effects. Although the treatment remains experimental, it holds promise for markedly reducing the incidence of RDS.

The interplay between animal and human studies was essential in achieving the advances in clinical management and prevention of RDS. Relevant animal models were used when available, and although no extensive search for an animal model was evident before the human steroid trials, the research appeared to be a logical and carefully planned step undertaken to provide therapy for a condition of high risk to the fetuses treated.
The following conclusions are drawn from the Battelle study:

A. Animal models were utilized extensively, but adequate and appropriate models were not always available when they were needed. In some instances little or no animal research preceded human studies. In other instances intensive searches for animal models were undertaken (as in Rh disease), but investigators appear to have been reluctant to postpone therapeutic research until an animal model was found.

B. Investigators generally proceeded to clinical trials characterized by very high ratios of benefit to risk.

C. A total ban on all research on the fetus, or postponement of such research until more appropriate and exact animal models were sought and studied, would probably have significantly delayed or halted indefinitely the progress in three of the four areas that were analyzed. Only development of the rubella vaccine could have progressed unimpeded.

A more limited ban would have had less effect, depending on the nature and scope of the prohibitions imposed. For example, a ban only on nontherapeutic research on the fetus would not have affected research on Rh disease, but would have sharply curtailed research with amniocentesis, due to the resulting inability to determine normal values for abnormal enzymes in metabolic disorders. The research which developed L/S ratios, used in RDS diagnosis, might have been possible making use of fluid obtained during caesarean sections or in Rh disease studies. A selective ban on research before or after induced abortion would clearly have permitted the L/S ratio research for RDS diagnosis, but could still have severely curtailed development of amniocentesis for prenatal diagnosis by making ascertainment of normal values extremely difficult. A ban on invasive research on the fetus would have permitted development of amniocentesis, although the risks to the fetus from this noninvasive procedure were potentially greater than those from many invasive procedures.