Ethics and the Biology of Reproduction

by **David J. Harris**

In the reproductive cycle, death before birth is the norm rather than the exception. An analysis and better understanding of this cycle adds a new perspective to the ethical dilemmas occuring with increasing frequency in neonatal intensive care units.

Philosophical and social concern over the deaths of infants and fetuses stem from the middle twentieth century belief that once conception occurs, death normally does not follow until old age. From this point of view, medical technology gives us a welcome way to ensure that human life, however fragile or imperfectly formed, can be sustained as long as possible before and after birth.

A characteristic we share with many other species, however, is reproductive wastage. As we consider the extent to which we should or should not use technology to prolong the lives of the very young, we need to be aware that death before birth is the norm in the reproductive cycle. For twenty years, scientists have known that only approximately thirty percent of human conceptions result in term births. Most conceptions are incomplete or imperfect, and most fertilizations disappear unnoticed. In its wisdom and for the kindest of reasons, nature ensures that most of us never are born.

In order for us to gain a broader perspective on current ethical dilemmas in neonatology, we need to understand the intricacies of the reproductive cycle.

The Reproductive Cycle

Adults form eggs and sperm that unite in the process of fertilization. Fertilization is followed by early embryonic stages, later embryonic stages and finally, fetal growth. For life to pass through all three stages, genetic information must be copied and translated successfully into complex proteins that become the building blocks of growth.

Cell division requires accurate reproduction of the genetic material DNA. This molecule has two identical chains. Various enzymes facilitate the unwinding of the paired chains, bring in the building blocks of the new chains, and link the members of the new chain together. Four building blocks are linked in the chain. The chemical mechanism pairs them two-by-two so that the old chain specifies the new one.

Sometimes this order is misread or something else goes wrong so that the wrong building block is incorporated at a given location. Enzymes can recognize an incorrect sequence and remove the wrong block, but sometimes this does not work. If the error is in a critical part of the code for a protein, that protein may not work normally. For a cell to survive, certain proteins must function perfectly. In a developing embryo, excess or insufficient function may lead to structural abnormality. If these structural changes are unlucky, they can have an overwhelmingly negative influence so that the individual does not survive.

In plants, the phenomenon of each chromosome of the species being duplicated or missing was observed by scientists many years ago, but in man this was not seen until studies were done

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on embryonic and fetal material from spontaneous, and even induced, abortions in early pregnancy. In this kind of material, one can see nearly the same thing as in plants: accidents of cell division can result in abnormalities of every chromosome. Many of these produce such extensive abnormalities that these individuals die in the very early stages of development.

When chromosome studies are done after birth, examples of only three of the twenty-two chromosomes that do not govern gender were seen in anatomically abnormal newborns: those designated as numbers 13, 18, and 21. The presence of an extra copy of a chromosome is called a trisomy. The last in the list was the first to be discovered, and was found to be associated with Down syndrome. The other two trisomies in the list were described later and were associated with multiple anatomic problems, severe mental retardation, and early mortality, although, as for all biological generalizations, there are exceptions.

Collection of data from prenatal diagnosis programs has shown that the frequency of chromosomal abnormalities is between that observed in material obtained from abortions and that observed at term. The implication of this relative ordering is that loss of pregnancies occurs throughout gestation. This suggests that recognition of suboptimal phenotypes may occur at any time in a process of natural selection. The lack of instances of trisomies for many human chromosomes in term births, and second trimester amniocenteses, with recognition of those same trisomies in the early part of the first trimester adds further evidence for this theory. A population-based study using a sensitive test for chorionic gonadotropin showed that there were a number of pregnancies that spontaneously terminated before the woman had symptoms of pregnancy (Edwards 1982; French 1962).

Several studies have shown a high incidence of structurally abnormal embryos that are clearly incompatible with survival to term. There are also defects that are similar or identical to those seen in infants at birth, but once again, the incidence is higher in the aborted material than that recorded at term (Gal 1973). The large Japanese study examined embryos and fetuses obtained at elective termination of pregnancy (Nishimura 1976). In the classical Hertig and Rock studies, the embryos were obtained from hysterectomies in which there was a known interval between intercourse and the operation (Hertig 1949). This information has been used to estimate that the percentage of conceptions that survive to term is around thirty (Roberts 1975). As in most of biology, reproduction in the human species is a wasteful process. Not every conceptus has great biological value.

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In the current developed world, population mortality rates after the perinatal period are low and do not rise significantly until middle age so that the majority will have an opportunity to reproduce. The differences in infant and child mortality between the developed and undeveloped worlds is a result of the control of epidemic infectious diseases. Analysis of the disease rates has shown that increased survival is due primarily to social changes. The provision of clean water, adequate protein and calories, uncrowded housing, and education has had more effect on childhood mortality than any medical intervention (McKeown 1979).

The major components of United States vital statistics have been summarized on an annual basis by Myron Wegman for thirty years. These reports indicate that there have been decreases in both birth and death rates during all of this century. In 1915, 44.4 infants under 28 days per thousand live births died. Of infants between 28 days to 1 year, the rate was 55.5 per thousand. By 1980,

the rates were much lower and more babies died before one month of age, with the rates being 8.5 and 4.1 respectively. In the 1983 summary, the table of selected causes of infant deaths demonstrated a higher ratio of black to white infants for all causes except congenital malformations, using data from 1981. The rate had been higher in blacks all along, but that the gap appeared to be widening between 1950 and 1965. He proposed that responsible factors included suboptimal birth weights for black infants, inadequate prenatal care, and births of black infants in suboptimal hospitals.

In the 1993 summary, the tabulation of infant mortality rates for selected years is an extension of this analysis. In 1940, the total infant mortality rate was 47.0 per thousand births while in 1991 it was 8.9 per thousand. The ratio of black to white infant deaths was 1.7 in 1940, and 2.4 in 1991. The gap between black and white infants increased. More deaths continue to be in the neonatal period under 28 days than in the post neonatal period after 28 days. In the neonatal period, the rate for white infants went from 27.2 to 4.5 per thousand, while the black rates were 39.9 and 11.2. This gives black to white ratios for neonatal deaths of 1.5 in 1940 and 2.5 in 1991. The post neonatal ratios are 2.10 in 1940 and 2.25 in 1991.

Perinatal infant mortality seems to have two components. There is a group of infants with congenital anomalies or unrecognized, severe metabolic disease that die. This group accounts for the majority of neonatal deaths in countries that have lower infant mortality rates than the United States and the affluent areas of the United States. For 1992, there are twenty-one countries that have better infant mortality rates than ours. In this country, the rates in rural areas and in the inner cities are similar to those in the "undeveloped" world. No individual state in the United States has as low a rate as Japan or the Scandinavian countries, while the District of Columbia has a rate of twenty-one, a figure close to that of white U.S. infants in 1960. The high rates continue to be associated with prematurity and low birth weight as suggested earlier (Wegman 1984, 1994).

Our willingness to deal as a society with the problems of prematurity and low birth weight demonstrates some paradoxical responses. The birth of a sick infant generates an impulse to help the helpless. The response is to use all known techniques to keep the infant alive, along with the development of new procedures. In general, neonatal intensive care has been available for babies from all socioeconomic strata. Historically, these units were first located in university medical centers or other teaching hospitals that served a high proportion of indigent persons. Costs were supported by research grants and other government funds. Undoubtedly, this care has contributed to the lowering of mortality rates discussed earlier.

On the other hand, it has been much more difficult to provide simple prenatal care to a number of poor populations, particularly in inner cities and rural areas. These services are frequently underfunded and understaffed. Often the justification of the lack of funding is that there is no money available for such allocations or that it represents socialized medicine. When one considers that the cost of prenatal care is one hundredth or less that of the care of a very small premature infant, the arithmetic suggests that the overall cost to society could be far less. The final cost appears in taxes and health insurance premiums.

After the neonatal period, in addition to a decrease in the mortality rate in advanced countries, there is also a change in the causes of death from congenital anomalies and disorders that are associated with birth to accidents and cancer. In the poorer parts of the world, childhood mortality is still largely due to infectious diseases such as gastroenteritis, pneumonia, and measles. In these areas, mortality is a result of the interaction of malnutrition with the stress of infection. Malnutrition is still seen in this country in infants who do not grow normally. In some cases this is because the families do not have food for themselves or for their infants; in other cases it is a result of an inability for the parents to nurture and interact appropriately with the developing child. The

necessity of adequate interaction for both physical and emotional development has been known for a long time (Vaux 1989).

In order for the reproductive cycle to repeat, the individual must survive to reproduce, produce gametes, in turn, and for those gametes to unite to form new potential individuals. In the developed world, there are few illnesses that kill young adults, and the incidence of those disorders is low. Most of the mortality is environmental in origin: accidents, homicide, and suicide. Some have proposed studying genetic factors in violence to be able to control the increase in frequency of violent behavior. The frequency of genes that might predispose to violent behavior cannot change in twenty years or so. These factors must have had something to do with the biological survival of the human species. I would like to quote from a talk by Dr. James Bowman in St. Louis September 1994:

> "Reminiscent of the heyday of eugenics in the United States, there are recent attempts to link genes with abusers of alcohol, drugs, and per petrators of violent crime. Interestingly, how ever, the perpetrators of white collar criminal activities, such as embezzlement, insider trading in the stock market, and the Savings and Loan Association's 160 billion dollar fiasco have not been objects of study—which suggests that classism, or racism, or both are contributory factors to the linking of genes with crime. Holzman and Rothstein (1992) perceptively alluded to an example of the selectivity of eugenicists. They quoted Lancelot Hogben, in referring to hemophilia in the royal families of Europe, saying: 'No eugenicist has publicly proposed sterilization as a remedy for defective kingship.' Apparently, not only kings and queens, but Fortune 500 executives are exempt from genetic scrutiny."

Acquired diseases may limit fertility. A number of sexually transmitted diseases may scar the fallopian tubes, thereby preventing the ovum from making its way to the uterus. In males, rotation of the testis from its normal position may cut off its blood supply. When mumps was prevalent, infection of older boys and young men could result in inflammation of the testis which then stopped sperm production. In females, sexually transmitted diseases scar the fallopian tubes and mechanically interfere with the developmental stages of fertilization through implantation. Such acquired infertility can be addressed technologically with the procedures of modern reproductive technology.

Ethics and the Reproductive Cycle

This litany of the life cycle lies between the endpoints of life and death. There are multiple solutions to the problem of how to view the process. The endpoints may not be eliminated, but our responses to them and the forces that govern the nature of our responses may influence the success with which we as individuals and as a society are able to use these experiences constructively. The conflicts arise because of our desire to have a different outcome than that suggested by the biologic realities. The wish to improve things may start altruistically, but scientific and technologic progress complicates the equations. Finally, economic interests may also distort the decision-making process, for profit for a number of interests may result from intervention at an stage of life from birth through death.

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People want children and want then to be perfect in every way. Success in reproduction has great psychological value. If one has no children, one's ancestral line and genetic contribution come to an end. Childlessness has been a cause of pro-

found sadness over the millennia, as seen in classical literature including a number of biblical narratives. Adoption agencies have difficulty placing babies with minor congenital anomalies or a family history suggesting that they are at risk for physical disease or mental illness. This goal supports genetic research and its application, even though environmental factors are important in the development of behavioral characteristics that are far more important in the welfare of our society.

The drama of the development of genetic technology is an example of the commodification of medicine. When one cannot intervene, the values of caring, sharing, and support for the confrontation of suffering emerge. These constitute what Vaux termed the "perennial philosophy" behind the professional relationship of the physician to the ill person. The development of successful intervention currently means economic rewards for production of the materials for that intervention, the distribution network, and the individuals who apply the technique. Our medical economic system rewards the provision of technical services far more than the interactive personal processes. Scientists and venture capitalists are ready to take advantage of genetic techniques for provision of genetic testing on a large scale.

Cystic fibrosis is the disorder that has been given the most attention as it is the most prevalent autosomal recessive disorder in the white population. Since the estimate is that one in twenty persons is a carrier for this disorder, the potential market is very large. The only reason that mass testing has not started yet is that there are nearly three hundred disease producing mutations that have been discovered, with the more frequent ones only accounting for ninety percent of the population. This would result in an unacceptably high false negative rate under conditions of mass screening. However, even now, families at high risk could use in vitro fertilization and testing at an early embryonic stage before the attempt at embryo implantation, to ensure a "normal" outcome without requiring a midtrimester termination of pregnancy (Holtzman 1989).

There is a substantial list of disorders for which the previously described techniques could be used. That list will be enlarged by information generated in the Human Genome Project (Kevles 1992). A major question will be to what extent that knowledge should be applied, and will such interventions be available for varying attributes of human diseases as opposed to debilitating diseases. The potential danger is enforcement of uniformity, with a significant risk for the limitation of creativity in a number of areas.

Much of the success of this country has been attributed to the diversity of the people coming into it. Our civilization will continue to require creativity that may be coupled with some less desirable traits. Our challenge will be to be able to enhance rather than to control one another in order to improve our collective lot.

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