President's Address

The Pandora's Box of Antenatal Surgery

ROBERT T. SOPER, M.D. Iowa City, Iowa

Being elected President of the Midwest Surgical Association has been a source of immense satisfaction to me, as well as surprise and wonderment. The satisfaction, of course, lies in the reflected glory from the honor and prestige that comes with the office, qualities which my predecessors have earned during these 24 past years. Your previous presidents, from Loring Helfrich to Howard Glassford, have come from all walks of surgical life—from the clinical trenches of Bad Axe and Peoria to the ivied towers of Loyola and Iowa. In spite of this varied background, my predecessors have shared in common those characteristics that stamp the good surgeon: clinical acumen, technical finesse, high-personal and professional ethical standards—all blended together by a strong dash of common ordinary horse sense. These characteristics stamped them as leaders in their local and regional surgical circles and, when the vagaries of circumstance and time brought them this presidency, these qualities earned them the prestige and honor that I previously alluded to. You have wisely chosen your leadership in the past, and it is immensely satisfying to me to grab onto their coat tails and bathe in reflected glory, for at least a short, golden moment in time.

Now as to the surprise and wonderment. Why after doing so well for so long, have you picked me out of the crowd for your 24th choice? I suspect that it had much more to do with happenstance and being at the right place at the right time, than anything else. A glance at the membership roster quickly discloses many who are more worthy than I of this office—and indeed, they will be the candidates of the future. In any event, whatever peculiarities of chance and roll of the dice combined to put me here today, let me express to you my deeply felt gratitude and appreciation. It represents a high water mark professionally, as well as a pleasant and prideful personal moment to my wife Helene and me. You might have chosen more wisely for your 24th president, but you could not have chosen anyone who would savor and appreciate the honor more than we.

Further, I would like to express publicly my appreciation to those who have worked so hard this past year to make the wheels of the Midwest Surgical Association turn so noiselessly and yet so efficiently, culminating in this splendid meeting that we are enjoying on the world's longest (or is it widest) front porch. I speak specifically of the officers of the Association and those on the Executive Council, and of the members of the working committees. I would especially acknowledge those who have served on the Program and Local Arrangements Committees. Without the one, we would not have a scientific meeting worth the inconvenience and expense to attend; without the other, few would attend just because of the science, if the setting were motley or mean. Both are necessary for a successful annual meeting, and because of the efforts of these two committees, we are doubly blessed. A final tribute to all of you who sponsored or generated abstracts, because when all is said and done, abstracts are the bedrock on which any scientific meeting is built. As an association, we are fortunate to possess sufficient bedrock, which, in fact, appears to be burgeoning and proliferating in the past few years. My thanks to all the abstract submitters and the paper presenters.

And now to shift gears and explain to you the peculiar title of my address, which might better be amplified to "The Pandora's Box of Antenatal Surgery," because I wish to talk to you this morning about antenatal surgery, representing as it does the very leading edge of my special field of interest—pediatric surgery. You might wonder why I have chosen...
such an esoteric topic. I have done so first because to me the subject radiates a Buck Rogers' quality that provides a glimpse of the Brave New World on whose very threshold we now stand. Secondly, the technical and physiological advances that served as stepping stones for the surgical pioneers who now are unlocking the secrets of the womb, surely will also shed light in some of the dark corners of general surgery. Further, the survivors of today's prenatal operations surely will be some of tomorrow's challenges to adult surgeons, perhaps with new and different problems engendered by their earlier manipulations. Finally, some of us in this room will have children or grandchildren whose lives will be directly influenced as antenatal surgery evolves from its current promising state into one as mature as today's transplant service or open heart team. That this status will someday be achieved, I have no doubt. That it be achieved in a sensible and quiet manner, bathed in the light of sound physiologic principles, nourished in morally and ethically acceptable tenets, and guided by sensible judicial guidelines is my fervent hope. How much superior is this sort of scaffolding to the glare of Klieg lights, the nourishment of newspaper headlines and press conferences, and the guidelines dictated by public relations people and promotion committees!

But how did Pandora get into this title? You who are classicists will recall that in Greek mythology Pandora was the first mortal woman who not unlike her Biblical counterpart, Eve, was consumed with curiosity to know what was in her box, which she had been forbidden to open. Being mortal, she indeed opened the box, thereby allowing all human ills to escape into the world. In a later version, all the human blessings escaped and were lost, leaving only hope. More recent fairy stories suggest a mixture of blessings to have emerged into the world, some good and others bad. It is on this latter analogy that I would like to build my address this morning.

It seems to me that the field of antenatal surgery is opening a Pandora's box of mixed blessings that need to be analyzed thoughtfully and perhaps tempered by reason, common sense, and the milk of human kindness. It is my purpose this morning to review the background events that first raised this box lid a few millimeters, the current status in which the lid is opened but a few centimeters; and some of the prospects and challenges of the next 20 years when the lid will be widely ajar for its hidden treasure to go on full public display.

Perhaps understandably, the womb and its fertility products were shrouded for centuries in mystery, mysticism, and religiosity, such as to discourage scientific inquiry. The phenomenon of procreation was duly recorded in the "begats" that are sprinkled throughout Genesis and other books of the Old Testament, but its intricacies were left to the "wisdom of Solomon." The Greco-Roman "homunculus" was a miniaturized, but fully formed human within the seed of the man, which was deposited in the womb where it grew until delivery "in the fullness of time" as a term baby. This simplistic concept was not fully mystified until one century ago, when Charles Darwin put human procreation into perspective in "The Descent of Man," by observing that "Man is developed from an ovule, about 0.125 inch in diameter, which differs in no respect from the ovules of other animals." There can be little mysticism in an ovule common to many animals. Scientific curiosity about fetal development did not surface until during the 19th century, heralded poetically by Samuel Taylor Coleridge as follows: "The history of man for the nine months preceding his birth would, probably, be far more interesting and contain events of greater moment than all the fourscore and ten years that follow it." Indeed, these events of interest and great moment were pursued scientifically in experimental animals, documenting the phenomenon of fetal movement, its requirement for warmth, and the fact that fetal breathing of air preceded its return to the uterus. Thus, the seal to the lid of this Pandora's box was first breached.

Rapidly accelerating events in scientific laboratories all over the world raised the lid several millimeters during the first half of this century. During the 1920s, experimental fetal surgery began, it was determined that maternal anesthesia anesthetized the fetus as well, that the fetus could be removed from its warm and friendly environment and then safely returned, and that the fetus could continue to term delivery after surgical manipulation. Many fetal operations were carried out during the 1930s and 1940s, including adenectomy, gonadectomy, and severance of the spinal cord.

The most important event of the 1950s was the surgical creation of fetal abnormalities that mimicked naturally occurring congenital anomalies. The work was carried out in South Africa and Minnesota by Jannie Louw and his young investigator, Christian Barnard, who subsequently was immortalized by his work publicized activities in heart transplantation. These pioneers devascularized segments of fetal canine intestine, and by varying placement of their ligatures could reproduce the many varieties of intestinal atresia. In the 1960s and 1970s, many congenital anomalies were created surgically in experimental fetuses, including biliary atresia, coarctation of the aorta, congenital hydronephrosis; more importantly, enormous strides were made in understanding fetal physiology, a hallmark of the burgeoning new specialties of perinatology and neonatology.
The final experimental step necessary for fetal surgery to be translated to the human occurred in the late 1970s, when a fetal congenital anomaly was created, which later was repaired and, after continuing on to term delivery, the animal was found to be cured of the secondary pathophysiologic changes that claimed the lives of un repaired control animals. This landmark work was carried out by Mike Harrison and his co-workers at the University of California at San Francisco, using the lamb as the model and congenital diaphragmatic hernia as the anomaly. This work subsequently has been verified at The University of Iowa by my colleague, Kevin Pringle. The final experimental prelude to human fetal surgery then was undertaken by Harrison and his group: fetal surgery in the primate.

As all of you well understand, the ultimate goal of most biomedical experimentation is to translate its beneficial spinoffs to the human. Such is certainly the case with the continuum of research on the gravid uterus that we have just reviewed. However, such translation has to await the development of a safe, noninvasive, and highly accurate method by which the human fetus could be evaluated directly. This was provided by the technological advancements that spawned pulse-echo sonography, known more familiarly as ultrasound.

The oldest fetal monitor was physical examination of the fetus through the protective apron of the maternal abdominal wall or vagina, a method as uncomfortable as it was inaccurate. Monitoring fetal heart tones with a stethoscope is also time honored, but limited in its usefulness. X-rays were eschewed because of their known potential harm, and also they provided such a paucity of information as to be limited in predicting difficult labor by measuring cephalo-pelvic disproportion. A major breakthrough in perinatology was the introduction of amniocentesis in the 1950s, which allowed a sampling of the fluid in which the human fetus was bathed. Hydroptic fetuses suffering from Rh incompatibility could be transfused in utero; a contrast dye could be injected into the amniotic fluid and the resulting x-ray amniograms outlined the fetal surfaces and, when swallowed, produced an in utero gastrointestinal series. However, the vagaries of accurately directing the needle made amniocentesis somewhat dangerous and restricted its use.

Ultrasound changed all this. It gives a highly accurate two-dimensional picture of the fetus in which its position, anatomy, and structural abnormalities are documented; as are the location of the umbilical cord and placenta. These events are recorded on a screen or on black and white photographs: with "real time" ultrasonography, a motion picture is produced, allowing us to observe the fetus rolling, kicking, thrusting its head, swallowing amniotic fluid, and periodically urinating. Fetal age, growth, and viability are documented. All this is achieved with virtually no demonstrable risk to mother or infant as determined by pilot studies numbering in the thousands.

Understandably, ultrasound revolutionized perinatology, transforming amniocentesis from an art to a science. With ultrasound guidance of the needle, mid-trimester amniocentesis has become an eminently safe way to evaluate pregnancy, and in the past decade thousands of these combined maneuvers have been undertaken with virtually no maternal morbidity and only a 0.5% chance of triggering abortion. At the present time, about 25,000 of these procedures are performed annually in this country, and yet it is estimated that this comprises only 10% to 20% of the "at risk" pregnancies that might benefit by its use. By combining these two techniques, fetal viability and age can be determined; chromosomal analysis can detect fetuses afflicted with Down's or Turner's syndrome or translocation abnormalities; fetal sex is verified, which is vital when evaluating certain X-linked disorders as hemophilia and certain forms of muscular dystrophy and mental retardation; nearly 100 metabolic disorders can be verified and alpha-fetoprotein elevations can predict the presence of major neural tube defects. Finally, ultrasound has allowed fetoscopy to develop, whereby the fetus is directly visualized; fetal skin can be sampled for cell culture, and fetal blood can be drawn to detect sickle cell anemia, classic hemophilia, beta-thalassemia; and chronic granulomatous disease.

But much more germane to us as surgeons has been the rich harvest that ultrasound and amniocentesis have yielded in detecting structural congenital anomalies and providing us with tools to manipulate, alter, and even correct certain of these abnormalities. The potential of cost effectiveness in preventing or correcting congenital anomalies is, of course, absolutely mind boggling. In this country alone, 100,000 to 150,000 babies are born each year with chromosomal abnormalities, single gene heredity disorders, and structural congenital anomalies. The improvements in other parameters of medical care have elevated congenital anomalies to the second most common cause of death up to the age of four years and the third most common from 15 to 19 years of age. They account for 30% of children who are hospitalized in this country, and cause half of our mental retardation. Their hospital care costs $1,000,000 a year and their institutional care costs $350,000,000 per year. But this is trifling when compared to the psychosocial cost of congenital anomalies in terms of stigmatization, altered lifestyle, parental anxiety and guilt, and family disruption.

First, let us acknowledge the many anomalies that today defy any known remedy, whether it be pharma...
ological, enzymatic replacement, or surgical manipulation. Into this category fall fetuses with severe chromosomal abnormalities, bilateral absent or polycystic kidneys, anencephaly and microcephaly, or other conditions that destroy the central nervous system. For these disorders, there is but one intervention possible—abortion. Even if these conditions are recognized during the first two trimesters of gestation when it is legal, the decision to abort is agonizing to both parents and physicians as it is loaded with ethical, moral, religious, and psychological implications. If the diagnosis is not made until the third trimester, then the crushing realization of the defective fetus weighs on all parties until delivery, at least in those states where third trimester abortions are prohibited. If the afflicted fetus is one of twins, the decision then is burdened further with considerations for the well-being of the normal twin. These are but a few of the negative blessings yielded upon opening this Pandora's box.

A large group of prenatally detectable congenital anomalies simply require alterations in the time, place, or method of delivery. Again, the agony of knowing about the defective fetus falls heavily on the parents, especially, but being forewarned allows the parents and medical team to forearm themselves appropriately.23

Arrangements can be made for delivery to be achieved in a pediatric surgical center for many anomalies that are best corrected after term delivery: atresias of the gut from esophagus to anorectum, cysts and duplications of bowel, ovarian cysts, cystic hygroma, omphalocele, and meningocoele to name a few. Under these circumstances, the uterus is the safest and most physiologic vehicle in which to transport the fetal patient.

Preterm delivery and neonatal surgical repair likewise can be arranged for such problems as obstructive hydrocephalus and hydronephrosis, midgut volvulus, gastrochisis, and ruptured omphalocele; early delivery also is advisable for fetuses suffering from hydrodrops fetalis or intrauterine growth retardation. This cluster of abnormalities has in common the fact that morbidity and mortality are worsened the longer the pregnancy is maintained. Early delivery when the fetus is viable prevents this progression and reduces morbidity and mortality.

Cesarean delivery can be arranged for certain anomalies that produce dystocia, or difficult delivery: conjoined twins, giant omphalocele, ruptured omphalocele, giant hydrocephalus, large teratomas or cystic hygromas, and large or ruptured myelomeningoceles. Both mother and infant are spared the morbidity of attempted vaginal delivery, and the infant's anomaly can be corrected promptly by the waiting pediatric surgical team.

In addition, there are a handful of fetal deficiency states that can be ameliorated by prenatal replacement therapy once their presence has been documented. In utero transfusions can be administered to the hydropic fetus. Thyroid hormone can prevent the ravages of Cretinism, and steroids can stimulate surfactant production in the fetus requiring preterm delivery. Also, there are a few metabolic deficiencies that are correctable by replacement therapy today, and literally dozens more are potential candidates for treatment in the future.

Finally, there are a few structural abnormalities of the fetus that are amenable to prenatal manipulation. If they are allowed to go unchecked to term, they could irreparably damage vital body systems to cause death or severe disability: obstructive uropathy, diaphragmatic hernia and obstructive hydrocephalus are current examples. To date, in four or five centers in this country, 20 to 25 such prenatal surgical corrections have been undertaken and reported. At least three fetuses have had valves successfully placed at open operation which shunted obstructed cerebrospinal fluid into the amniotic space; all went on to term delivery, and after neonatal ventriculoperitoneal shunts were placed, they were declared neurologically better than they probably would have been without the antenatal intervention.24 Many painstaking operations were undertaken on hydrocephalic monkeys prior to this human experimentation,25 work which is now shifting to the antenatal correction of myelomeningoceles.

A number of fetuses with obstructive uropathy have had urine aspirated and/or diverted into the amniotic space by catheters or open operations.26 Success has been spotty and mixed in these efforts but better patient selection, more experience, and improved catheter designs promise better future results. No fetus with congenital diaphragmatic hernia has yet been operated to my knowledge, partly because we cannot yet predict which ones are at risk of dying from lung hypoplasia.

The future of antenatal diagnosis and treatment is bright. Undoubtedly, more and different disease states will become detectable that can be treated by drugs, hormones, enzymes, and surgical manipulation. Improved fetal monitoring and new tocolytic agents will make fetal surgery safer for mother and baby, and bring into the treatment arena many new diseases such as congenital heart defects, major neural tube defects, and congenital neoplasms. Development of an artificial placenta would remove the threat of the operation triggering premature delivery.27

The ultimate goal, of course, is to discover and remove the noxious stimuli or agents that cause the congenital anomalies to develop, thus putting ourselves completely out of business. The genetic engineer could then take over, correcting defective cells or replacing
them with normal cells, transferring DNA to correct defective genes, and using fetal stem cells to treat children or adults with myelofibrosis. Then, truly this Pandora’s lid will be completely ajar: May the blessings that emanate therefrom be more positive and good than negative and bad.

REFERENCES


