The human fetus has always been very mysterious because we could not look inside the uterus and can not see that the fetus had the problem just like you and I have problems. This morning I like to review the past 10 years in the development of fetal diagnosis and treatment.

We, surgeons, could see the babies after birth who had problems that was already too advanced to face. We did over the last 10 years to take the long way round. We went to the laboratory doing research on which problems make sense to fix before birth, and then we studied human fetuses with these problems to find out what happened to them without intervention. Then a few cases with whom all works were done were possible to arrive at fetal surgery.

Here are some of the problems that appear to make sense to fix before births. We are talking about some lesions such as urinary tract obstruction, congenital diaphragmatic hernia, cystic adenomatoid malformation of the lungs, sacrococcygeal teratoma, and some heart problems.

**URINARY TRACT OBSTRUCTION**

I like to state how the system developed over the last 10 years by looking at the problem of urinary tract obstruction in fetus.

Male babies have posterior urethral valve. It is a very simple problem to fix after birth. But many times the babies were not survived because this simple problem of obstruction leads to the consequences like renal dysplasia and pulmonary hypoplasia. We ensure those problems by studying in experimental animal. We chose the fetal lamb in this case. We could obstruct the urinary tract and show the kidneys ruined. And then we could unobstruct the urinary tract by making two openings in the bladder and show that the kidneys worked better. At the same time we had documented the natural history of the human fetus with urinary tract obstruction.

Here are three examples of babies, to whom we followed with serial sonogram before birth. We knew that there were babies, who could not survive if their obstruction persisted. The next question was "Could we find those babies who are going to die? Which one had enough renal function left if we fix the obstruction?" For this, we had asked another question. We need a marker to see the renal function before birth. Through a long series of studies of human fetuses, we found by sampling the fetal urine and measuring number of things that we could in fact detect in those fetuses who had adequate renal function. Once we know which fetus to treat, then watch and detect out what we needed to do.

We have developed several techniques for correcting the obstruction before birth. One simple
CONTROL OF BLEEDING

One of the thing that we learned early is that we needed the control of bleeding from the edge of the gravid uterus, which is extremely blurring. One technique is the development of an absor-balbe steplong device, which has proven to be very helpful. Here we tested them on a monkey. Recently we have developed a particular type of clamps. These simple but important clamps are placed around the edges of the uterus. We use them for adequate exposure and hemostasis.

MONITORING OF THE FETUS

How well the fetus doing during and after operation was checked. It has proven more difficult than we thought. We tried many ways but none of them was good enough. We recently developed the technology, that solved the problem, the technology having a miniaturized radiotelemetry device, which monitors fetal EKG, temperature, and activity. We placed it subcutaneously in the fetus and left it there and the baby born with it. We can monitor continuously with the device. Fetal surgery can be done with using this technique. Once we have developed the technique, we could go on to do what we intended to do. In the earlier cases of urinary tract obstruction, by making an incision to the mother’s abdomen, by making an incision on the uterus to take the fetal part out, to do the monitoring which we developed, and we did the proper relief of obstruction. We had the bladder marsupialized to the abdominal wall in this case, a very simple procedure, which took only 10 minutes. I think the first fetus being exposed for that procedure. It is now the 1st successful operation for urinary tract obstruction. All babies have survived and have done well. We can do these operation very early and have done it as early as 18 weeks of gestational age. So it is the best example of fetal surgery.

DIAPHRAGMATIC HERNIA

Now I am discussing with another great prob-
lem of the fetus, i.e. DIAPHRAGMATIC HERNIA. The babies with congenital diaphragmatic hernia died because their lungs are too hypoplastic to support extraterine life.

We took the same approach for diaphragmatic hernia as urinary tract obstruction but it has taken much longer and has been much more difficult. We developed a fetal lamb model, where we got diaphragmatic hernia and showed that fetal lungs had grown by correcting diaphragmatic hernia. The pathophysiology was quite simple. No doubt that the right thing to do is to make the lungs grow.

It is very difficult to achieve a correction of this problem technically. We developed those techniques first in the lamb. We did it on premature and lambs after birth. By giving subcostal incision we reached the viscera of the chest. We filled up that side by sliding stabilizing the mediastinum and then we learned that we had enlarged the abdominal cavity with a little patch in order to accommodate the viscera. We did not appreciate this procedure at first but it is absolutely necessary because unlike the baby after birth, the fetus cannot tolerate the increased intraabdominal pressure because the intraabdominal course of the portal vein and the umbilical vein are compressed.

We have experience with a significant amount of fetuses with diaphragmatic hernia because we can find them by ultrasound of seeing the stomach bubble inside the chest. Here is the shadowing of the waves on the sonogram of the human fetus with diaphragmatic hernia and you see the bubbles in the chest.

What we needed to know is how badly the fetuses do when they are diagnosed as diaphragmatic hernia, in other words how we fix it before birth. The answer is quite interesting. Fetuses diagnosed before 24 weeks of gestation usually died. In a multicenter survey that documented the natural history and clinical outcome of fetal diaphragmatic hernia in 94 cases, which we gathered from various places, the mortality rate was high (80%). It is quite interesting because our experience as pediatric surgeons is not enough to prevent the death of these fetuses. We did not see the worse baby in the pediatric surgical unit. They did not make it to us. The next reason is that the ECMO, which we do, has no significant role in surviving the bad babies with diaphragmatic hernia.

What determines whether a baby having diaphragmatic hernia is going to live or going to die, is the lungs and the volume of hernia. If the viscera does not go up into the chest until near birth, these babies are granted to survive. In other babies whose viscera goes up very early and the stomach become dilated, those babies are granted to die. We have nothing to do. What I chose those babies of diaphragmatic hernia is to offer the family to end the pregnancy. If they choose or we can do the delivery of that fetus in usual manner, we do the best we can do for the baby including the ECMO, high frequency ventilation, delayed surgery, all those things help a little but no one can save the bad baby.

Let me show you what factors are involved in the baby and how we tried to fix the problem before birth. In this case the placenta situated in front. That is a big factor because you can not destroy the placenta when you make an uterine incision. We keep the uterus high up in the abdomen and make the incision in the uterus even in the back, which are now doing in a number of cases. But in this case we used a low anterior oblique uterine incision that paralleled the edge of the placenta. We took baby's left arm out and put on the monitoring device. Now we are using the telemetry device and place it subcutaneously. Then we made a subcostal incision, pull the viscera out of the chest including the stomach to repair the diaphragmatic defect. Then we closed the diaphragm and we almost always required Goretex because there is no diaphragm in severe cases. We had to enlarge the abdomen with the patch.

The problem is primarily technical. It is not a physiologic problem. If we can correct them, the baby can survive.
We did not understand why the procedure would not work until we studied the blood flow in the umbilical vein. The incarcerated intra-thoracic liver presented a problem that went beyond the technical problem of bleeding; tipping the liver down into the abdomen kinks the umbilical vein and compromises umbilical blood flow because the umbilical vein carries the entire cardiac output and the babies die. It is a terrible problem. We tried many ways to get around the problem including by constructing a little prosthetic diaphragm around and leaving the liver within the chest. But none of them were successful. We think that the only way to solve the problem is to resect the left lobe of the liver. We did not think that we could do that technically until we went to the laboratory and developed the technique to resect the liver and now we can do it rather easily. It involves some laser works to control bleeding. Here is the baby having the left lobe herniated into the chest and died. We tried to apply the technique after death by resecting the left lobe of the liver. I think that it is doable thing.

We tried to salvage 8 highly selected fetuses with severe congenital diaphragmatic hernia by open fetal surgery. The experience with these very severe cases initially was discouraging, but each of these cases contributed to invaluable knowledge and experience, that eventually led to the first clinical success. The last 4 fetuses were repaired successfully and the technical problem with mildly herniated liver proved to be surmountable. All had good lung function after birth. Although two subsequently died of nonpulmonary problems, the last 2 babies have done well.

That is the story of the diaphragmatic hernia where we stand and fetal diaphragmatic hernia repair remains a formidable technical challenge.

**CONGENITAL CYSTIC ADENOMATOID MALFORMATION**

Perhaps we can now tell a better histroy, i.e. congenital cystic adenomatoid malformation of the lung. You all know that many of these babies present as very simple problem, which can be treated after birth and babies become fine. But there are some babies for whom we can not do anything because they die in the uterus because their malformation is too big. We can now recognize that babies who have cystic disease of the lung were seen in fair number. The invariably fatal outcome seen with large CCAM lesions is related to several factors, including development of hydrops, hypoplasia of normal lung tissue secondary to prolonged compression in utero, and lack of early diagnosis and immediate postnatal surgery. In utero surgical decompression or removal of CCAM will reverse hydrops and allow sufficient lung growth to permit survival in these severe cases. We have treated 5 fetuses who had cystic adenomatoid malformation of the lung in the last 2 months.

Here we did pulmonary resection in fetal lambs. We did the operation as we described before. In these cases we simply did pulmonary resection and took out a huge mass. The baby’s physiologic problem decreased, the cyst resolved, and hydrops resolved. The lung expanded and filled up the space. This baby is perfectly normal today. So that maneuver is a happy story for us. Here I show you 4 babies, who were having hydrops, 3 out of them are now alive.

**SACROCOCCYGEAL TERATOMA**

Now we consider about sacrococcygeal teratoma. When it is like this size, it is fixable after birth by resecting the teratoma without injury to the fetus and that baby is normal today. On the other hand, when diagnosed before of 30 weeks gestation there has been development of massive tumor enlargement, fetal hydrops, and placental-galy. These babies die in utero. Large tumor in severe cases behaves as a large arteriovenous fistula with markedly increased distal aortic blood flow and shunting of blood away from the placenta. I think that it is necessary to ligate the base of the tumor or take it out as we did like in this case.
COMPLETE HEART BLOCK

There are some other problems that we are facing in case of fetus. One is complete heart block. There are babies who have complete heart block. Half of them have no other associated cardiac anomalies. This is due to connective tissue disease of the mother and few of them leads to birth and basically they are normal. This type of babies needs simply a pace maker, which should be placed in the intruterine life until delivery. We developed a model of complete heart block in fetal lambs and have demonstrated the feasibility of epicardial ventricular or atrioventricular pacing to increase cardiac output. We worked on fetal lambs and developed them complete heart block. Here the low pacing device and lamb heart shown after we remove it. We demonstrated that if you pace them the lamb would survive so that it needs to be done in human fetus. They will be done in future not yet. Hypothermia or bypass technique may make open fetal cardiac surgery possible in the future to fix some anatomical problem in the fetal heart. So we work on a technique to get to the fetal heart. Left him cool down until his heart essentially stops or goes slow enough that we can work on it. Fix the heart, warm it up. Put it back in the uterus. That’s all where we stand at the present time.

FETAL SURGERY USING ENDOSCOPE

You can see that there are some limitation on what we can do in terms of operating the fetuses. We have to face the problems of preterm labour, keeping the uterus relax, keeping the fetus warm and expanding the lungs, we can do for the fetus. One solution, which we think is perhaps the most exciting thing for the next decade, is to operate on the fetus without opening the uterus, but to do this thing is beyond what we have done before was a catheter manipulated under sonography. We think that we should apply the technique. Many of our colleague have done laparoscopic technique in case of fetuses. So for the last year we have been working very hard on this technique. This laparoscopic technique, we call it fetoscope, will involve inserting a camera and working on a video-screen, which magnifies the view, so we are looking at the fetus problems easily. We insufflated the uterus with CO2 just like the abdomen and we can introduce various devices to manipulate what you wish. It is very exciting to do. We have to modify the actual technical way that instrument is used inside the uterus in an air space made by CO2. This case where creating a cleft lip, taking the device and reaching inside and going to sweep left through the fetuses lip and palate. Then we can go on to develop a technique to instant repair, repairing the cleft lip and palate that we have done in both fetal sheepes and monkeys.

So far the future I think that endoscopic work inside the uterus is going to be less invasive, far safer, less uterine trauma and going to allow us to work much earlier gestation, may be done on around 14 weeks—18 weeks of gestation, that time we can take advantage of the potential for healing without scar formation.

FETAL WOUND HEALING

I would like to end today’s discussion with a little separated phenomenon. This phenomenon is a fascinating one. Fetal wound healing occurs without scar formation, fibrosis, or contracture.

If we know how the fetus’s wounds heal without scar, we might be able to apply it in the wound having healing problems.

The extracellular matrix and particularly the hyaluronic acid seems to be very important in the phenomenon of scarless healing. The fetal wound is rich in hyaluronic acid, which is a key molecule of the extracellular matrix. The striking difference is the deposition of the hyaluronic acid in the wound of a fetus and that of an adult.

We can do some interesting experiments that pointed it directly how the fetus heals without scar. In case we are going to compare, we put the skin graft from the mother on to the fetus. If we do before 60 day of gestation, there is no immuno-
logical rejection, so the transplant tissue is unimportant. Then we came to the second operation. Once we put the maternal skin graft, we make an incision through the maternal skin graft, the adult skin in the fetal environment and through the fetuses own skin in the fetal environment. The adult skin graft heals in a typical adult way with a scar. The fetal skin, which is right next to the adult skin graft heals without scar.

One of the nice thing about working in the lamb adult is that we can manipulate to answer a number of questions that we can ask. For instance, “Is it related to the gestational age?” The answer is “yes”. About midway through the third trimester, the phenomenon goes away. It behaves like adults. We can manipulate it into the fetal wound in adult environment. What is allowing the fetus to heal without scar? In the adult lamb model what we can do in the very early gestational age of the fetal lamb is that we made an incision and studied them and compared them directly. This incision is in the mother and this in the fetus, who is lying in the mother’s abdomen. At the same time incisions were made in the fetus and now we can see and compare them. What are the difference? We can do a number of manipulation and we can ask whether collagen deposition in fetal wound healing is different from adult wound healing. Collagen is not the problem. The principle difference which we found between adult wound healing and fetal wound healing, is whether the message is in the cell or in the matrix. Scarless healing is not a product of fetal environment but it is intrinsic to the fetal tissue.

The one clinical application of this phenomenon is potential for fixing cleft lip and palate in a human fetus. We feel very strongly that they should not be done at the present time. We think fetal surgery by weighing the risk and benefit of this particular problem. At this time and at this stage of our knowledge, the risk is far away from the benefit. They are not a life threatening condition. I think that we should confine ourself to trying to save the baby’s life. I am still working on that with fetoscopic technique. It is possible that we want to fix cleft lip and palate or myelomeningocele.

どうもありがとうございました

(このテキストは総会事務局において講演テープから一部変更して編集したものです)