It’s my job to talk today about the care of the infant with irreversible renal failure. And so I want to begin with a description or at least an explanation for why it is that in your medical center and at Stanford the cardiac surgeons control a lot of what goes on there. End stage renal disease is an uncommon condition with irreversible renal failure occurring in only 11 per million children, with congenital heart disease substantially more common then that.
And what I want to talk about is the end stage renal disease that occurs in these smallest patients.
Now if you look in 1977 at the incidence of end stage renal disease and of course this is not a true incidence, it's the incidence of referral for treatment of end stage renal disease, it seemed to be quite low in these youngest patients. And then as you look ahead there's even been an epidemic of end stage renal disease in infants or we figured something out. And I want to show you a little bit about that.

### Table 1. ESRD incidence in the United States in 1977, 1987 and 1996 by age at start of ESRD therapy

<table>
<thead>
<tr>
<th>Age group (years)</th>
<th>New pts 1977</th>
<th>PMP/year 1977</th>
<th>PMP/year 1987</th>
<th>PMP/year 1996</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-4</td>
<td>2</td>
<td>6</td>
<td>10</td>
<td></td>
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<tr>
<td>5-9</td>
<td>4</td>
<td>5</td>
<td>7</td>
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<tr>
<td>10-14</td>
<td>11</td>
<td>12</td>
<td>13</td>
<td></td>
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<tr>
<td>15-19</td>
<td>21</td>
<td>23</td>
<td>30</td>
<td></td>
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<tr>
<td>20-44</td>
<td>-</td>
<td>76</td>
<td>125</td>
<td></td>
</tr>
<tr>
<td>45-64</td>
<td>-</td>
<td>272</td>
<td>473</td>
<td></td>
</tr>
<tr>
<td>65-74</td>
<td>-</td>
<td>520</td>
<td>1042</td>
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</tr>
</tbody>
</table>

PMP=Per million population, age-adjusted.

Data from USRDS 1987 and 1996 reference [41, 45].
But first to go back to what the situation was like in the 1970's. Children less than five years of age were rarely referred for chronic dialysis or kidney transplantation and in fact, the available dialysis modalities then were poorly suited for infants and small children. We had hemodialysis and intermittent peritoneal dialysis. Survival for those who actually did get referred for treatment was very poor; less than forty percent of these babies survived. Those who did survive suffered from serious neurologic dysfunction and growth failure.
I looked for a photograph of a baby or a small child being hemodialyzed in the late seventies and early eighties and I couldn't find one. It was really very primitive and of course the major problem had to do with vascular access with these babies. But also the dialysis procedure itself was extremely risky and uncomfortable. The only way we could do it was to place the baby on a scale and then measure weight loss, ultrafiltration, fluid removal by the change in the actual weight of the baby over time during the dialysis procedure. So obviously hemodialysis for babies in the late seventies and early eighties was not a good therapy.
Transplantation was also a poor therapy. In 1984, I had the opportunity to look at all of the published cases of infants less than 2 years of age who had received a kidney transplant and you can see of these 46 babies, 19 had died and 11 had graft failure, who very soon thereafter died. Clearly, transplantation wasn't the answer.
Dr. Kohaut has already described to you the problems these babies had with growth failure. As you can see, this is when most of the failure occurred in children with renal insufficiency was during their infancy.
And then something I think that was even more disturbing and that was the recognition of a chronic brain disorder that occurred in babies with chronic renal insufficiency that had onset early in life. And this study from the University of Minnesota was the best summary of this condition - The Progressive Encephalopathy in Children with Chronic Renal Failure in Infancy. The study was of 23 babies whose renal failure was diagnosed at less than one year of age and of these 20 developed serious neurologic dysfunction. These babies had seizures, dyskinesias, hypotonia and developmental delay. Now these were babies who were screened, who did not have congenital CNS abnormalities and had not had perinatal insults. And just to note something Dr. Kohaut pointed out to you, decreased head growth was seen in all of these babies.
And so it was not surprising that as we completed our training and launched our careers in pediatric nephrology this group of patients were considered not really suitable for referral for chronic dialysis and transplantation and this quotation, from 1978, is well known among pediatric nephrologists: "Although it is technically possible to perform hemodialysis and transplantation in these children, the myriad of well-known problems should contraindicate such therapy except under the most unusual circumstances."

Hurley, J Ped 93:528, 1978
Now into that situation came Jack Montcrief. Jack is an internist in private practice in Austin, Texas. And what Jack remembered was that there was another form of dialysis that had actually a longer history than hemodialysis but had dropped out of favor. And that is peritoneal dialysis and those of you who may remember that peritoneal dialysis works by placing an indwelling catheter through the anterior abdominal wall and dialysate is then infused into the peritoneal cavity with the peritoneal membrane acting as the dialysis membrane.
Well, peritoneal dialysis is the first form of dialysis, invented in 1923. And the intermittent method of peritoneal dialysis mimicked the intermittent method of doing hemodialysis, that is, you treat for a while and then you stop treatment. The acute renal failure treatments in the 1940s were followed in the 1960s by the development of methods to do long term intermittent peritoneal dialysis. But by the 1970s, which Jack Moncrief was looking at, was the realization that the long term technique and patient survival was poor with intermittent peritoneal dialysis, that less than a third of these patients were still alive three years after starting dialysis. This was in adults, intermittent peritoneal dialysis.
And the complications that these patients had, the problems that they showed, were actually a falling BUN and creatinine. Now you know that might be a sign of doing very good dialysis, but in fact it was a consequence of malnutrition. If you're very poorly dialyzed, your appetite is gone, you stop eating, and your BUN actually falls. Hypoalbuminemia, muscle wasting, poor appetite, fatigue, weakness, all the signs and symptoms of inadequate dialysis, were what the patients on intermittent peritoneal dialysis showed in the late sixties.
And so in 1979, methods to improve intermittent peritoneal dialysis were summarized by Bob Gutman, and increasing dialysate flow, optimizing temperature, optimizing dwell time and volume, increasing ultrafiltration, all of these things to try and change the characteristics of the human peritoneal membrane were proposed. None of them worked. And they weren't likely to work.
And that’s because dialysis is a very simple process. (On this slide the blood is blue and the dialysate is red.) It’s simply the placement of a semipermeable membrane between the blood and a fluid that contains different concentrations of electrolytes, and no cells.
And so what Jack Moncrief realized is that there really are only four things that determine solute clearance, one of which is blood flow rate. So in hemodialysis you just turn up the blood pump. In peritoneal dialysis, that’s not under your control. It’s the cardiac output of the child. The dialysate flow rate had actually been attempted to be turned up in peritoneal dialysis, and some of us were even doing dialysis with two catheters, one for dialysate to flow into the abdomen and another with dialysate to flow out. They were automated machines that pumped dialysate in and out of the belly as fast as it would go. It still did not work. You couldn’t change the permeability of the membrane the way you could with hemodialysis, where you just invented a new membrane. And so you were stuck with the patient’s peritoneal membrane. But what Jack Moncrief realized is that the one element that had not been fully exploited was time.
And so he and a biomedical engineer, Bob Popovich, devised a method to make dialysis continuous because the dialysate volume was maintained within the peritoneal cavity, 24 hours a day, around the clock.
And so their procedure was to have a plastic bag full of dialysate infused into the peritoneal cavity. The empty bag is rolled up and kept in the patient’s pocket. They walk around for three or four hours, do whatever they’re doing, they’re ambulatory. And then at the end of that time, that empty bag is unrolled, the dialysate is allowed to drain out. A new bag is placed on the line. And you repeat the exchange and go on about your business. Twenty-four hours a day, seven days a week.
Well, this was called continuous ambulatory peritoneal dialysis, CAPD, and it did in fact seem miraculous at the time because there were many patients who had lost vascular access, who could not be transplanted, for whom this was lifesaving. But for pediatric nephrologists, it was truly considered a breakthrough. Those of us from those days remember that peritoneal dialysis was used the way Dr. Goldstein uses hemofiltration now. We treated everything with peritoneal dialysis. We treated diseases and conditions like salicylate intoxication, and Rye syndrome. In fact, in the intensive care units, in the late seventies, you didn’t actually have a chance to succumb to whatever critical disorder was causing your illness without having Dr. Hill’s service provide a consultation and do peritoneal dialysis. So, boy, we knew how to do peritoneal dialysis!
And this is where we were able then to take those techniques and apply them to children with chronic renal failure. And this is a bit of a historical photograph. This is the first infant treated, the first child treated with continuous ambulatory peritoneal dialysis in the United States. He went on to receive a kidney transplant. He’s now working in a sawmill in Oregon. And then the stampede was on. And now continuous peritoneal dialysis accounts for over 70% of pediatric dialysis around the world. Of course as card-carrying nephrologists we did our best to make this seem complicated. But it was really a very simple and very basic therapy. It wasn’t too long before it became mechanized.
And buried in here is a baby. But here is the cycling equipment. It was simple enough to be performed at home. And so families learned to do this at home. And here you can see the equipment that goes with this infant’s home peritoneal dialysis.
And we also learned that you needed two tubes for these babies. You needed a dialysate catheter, obviously; but you also needed a feeding tube. And it was in fact the combination of continuous, effective peritoneal dialysis and aggressive nutrition that sort of made the breakthrough for these babies.
And so it became rather routine, as it is today, to have an infant born with end stage renal disease - this is Molly; she was the second child, infant, to be treated with CAPD - and have her then go through a period of infancy and young childhood on continuous peritoneal dialysis. Come to kidney transplantation, and move on to lead a relatively normal life.
And so the major advances that made this possible for these babies were continuous ambulatory peritoneal dialysis, controlled enteral nutrition or tube feeding, the development of growth hormone and erythropoietin in the last ten years have completed the package. So now we do feel that we have for these patients a complete package.
And in fact in 2002, the situation for infants with end stage renal disease is substantially different. Now patient survival is certainly improved. It’s much better than the less than 40% that it was twenty years ago. But it’s still less than that of older age groups on dialysis. Graft survival in these children has tremendously improved, and now we are able to offer kidney transplantation to infants with the probability of success 75 to 95% of the time. I think a critical element in this development has been the recognition that neurodevelopment in these children is normal over 80% of the time.
In a paper recently published by Dr. Kohaut and Dr. Warrity from their two centers, just to show you where this therapy now stands, they had 34 infants who started long-term dialysis at less than three months. 82% survived one year. And of those, 79% had completely normal mental development scores. And 24 of the 28 were successfully transplanted at about two years of age.
The keys to the successful management of infants with irreversible renal failure are adequate dialysis, and that means peritoneal dialysis most of the time, aggressive nutrition, no aluminum-containing medications, and successful transplantation.
Now I have just a few minutes left to talk about transplantation for these babies. One of the key elements to the success of transplantation in these babies was the recognition that age and size matched kidneys were not successful. Prior to about ten years ago, babies who received kidney transplants frequently received a transplant from an infant or pediatric cadaver donor. About the same size. Maybe a little larger. Those did very poorly and have been completely abandoned. And in fact the best kidney transplant for this baby comes from of his parents. When you put the adult size kidney into the abdomen of these babies, it pretty much occupies the entire right side of the abdomen. And that's what I've spent the last four years, it seems like, doing at Stanford, is trying to learn how to do this properly. We now are transplanting about six to ten of these babies under four years of age, every year.
Now I don't really have time to go into all of the methods that are used now to make this work. This is just to show that our results at all ages, including these infants at two years, are now approaching 100% success.
But if you look at all of the North American results, this is from UNOS, what you can see is that while there still is some greater initial graft loss around the country - and this is the youngest age group under two, and this is the group from two to five. So they start out lower. But after that, their graft survival probability out to seven years is better than those of the older children. And as just an aside here, I’d have to say that after spending twenty years working on how to make things better for infants, it’s time that we turned around and started making things better for adolescents. Because it is, in fact, the adolescent group who now have the worst results with kidney transplantation, which we think has a psychological basis with the poor compliance with the transplant regimen. But that’s just an aside.
In fact, if you look at babies now who receive a parent donor kidney under the age of five years, their predicted half-life - this is the point at which it’s predicted 50% of those transplants will be lost - is 31 years. This means that the projected outcome with these children, these youngest children who 20 years ago weren’t even offered therapy, is better than the best outcomes predicted for the best group of adults.
The life expectancy of the infant who has end stage renal disease, who survives that first year of dialysis to receive a successful kidney transplant, is now greater than 40 years.
But we have a long way still to go. And in fact if you look at - this is transplant survival in infants, and this is dialysis survival in infants - clearly long-term dialysis is a poor solution for these babies. You need to get them transplanted somewhere between one and two years of age.
Now it may be that the problem has to do with patient selection. And it's one thing to offer transplantation to a baby. It's another to offer dialysis. And so one of the unanswered questions and controversies in nephrology now is, when do we withhold treatment? When do we offer, when should we not offer, chronic dialysis to babies?
Because you know you’re going to have to dialyze these babies for a year or so to get them to be large enough to receive the parent’s kidney. So how do you decide which babies should receive this therapy and which shouldn’t? And I’d have to say that the jury is still out on that one, but we do have more and more information that will help make this decision. And this is a study by Eileen Ellis and Ellen Wood which showed that if a baby - these were 21 babies who began continuous peritoneal dialysis during the first year of life - if all that baby had was isolated renal failure, no other dysfunctional organ systems, they all survived. If that baby had even one additional organ system, just a little less than half survived. If the baby had an adequate urine output - and you know many of these babies are polyuric - only two of them, 20% of them died. But if the baby was anuric, more of them did not survive.
• Presence of non-renal co-morbid conditions increases risk of death on dialysis (Ellis, 1995; Ledermann, 2000; Wood, 2001)
• Pulmonary/pulmonary hypoplasia, cardiac and neurologic dysfunction associated with increased mortality
• Anuric infants at greater risk than polyuric
• Risks are additive

And in fact, looking at studies from England as well as North America, the presence of nonrenal co-morbid conditions increases the risk of death on dialysis. And these are sort of clustered in pulmonary, pulmonary hypoplasia, cardiac, and neurologic dysfunction. Anuric infants are at a greater risk than polyuric, and these risks are sort of additive. Now I want to make it clear that we’re talking about uncorrectable chronic problems. And so your cardiac surgeons will quickly say, “Oh, Tetralogy of Fallot, not a problem. We’ll fix that.” And I think that we still don’t know how to best blend renal replacement therapy and major cardiac surgery. But certainly pulmonary hypoplasia and severe brain damage is a predictor of a poor outcome in a baby who needs chronic dialysis.
And so when to refer the infant with end stage disease for dialysis and eventual transplantation, I think it’s very clear now that the babies who should be referred are any baby who has only renal failure. Where renal failure is the only system that’s in failure. Especially if they are still making any urine at all. Now it’s reasonable to think a while before referring the baby who has major damage to at least one additional system, especially pulmonary, cardiac, or brain damage. Now I want to echo something that you heard from Ed Kohaut earlier. And the key to all of this is early referral. And so this is not a situation to sit around and think about. It’s important that you are aware, and make the diagnosis, that you get the nephrologist involved early, and that you make the decision to go for therapy as soon as you can.
Now I want to conclude with just a few general comments. What do we really want for these children who have, after all, a terminal disease, or a terminal disorder? End stage renal disease is a lethal condition. We want them to survive. We want them to have a life free from pain and discomfort as much as possible. We want them to live at home with their family, have friends their own age, go to school, develop intellectual capacity, maintain gainful employment, and maintain adult relationships. This is what we want for these children. And I think that with the developments that have occurred over the last 20 years, and for me a process that began here at Baylor, working with Leighton Hill, we now have the tools we need to offer this kind of outcome to the majority of these babies.

Thank you very much.