I am greatly honored to participate in this forum as a representative of the Tulane Class of '55 (Reputed to be one of Tulane's finest). Members of the class believed that by the summer of '52, and I think their self-evaluation has stood the test of time.

Further, I take pride in the fact that three of the five previous speakers are in one way or another students of mine.

Dr. Bollinger (Class of '70) spent a good part of his 3rd and 4th years at Tulane in my laboratory and we published some papers together on transplantation in gnotobiotic animals, which are still landmarks in that area. On my advice he went to Duke for training with Sabiston and Amos and has become one of this countries leading surgical scientists with his studies of the immunobiology of tolerance and now xenografts.

Dr. Busuttil (Class of '71) I taught as a student. He was obviously brilliant and committed. I admired his investigations while a student in collaboration with Dr. Elmo Cerise relating to bacterial contamination of abdominal drains. After his training at UCLA he has become one of the premier liver transplant surgeons and scholars in this nation. Certainly he would rank second only to Tom Starzl, the father of the field who was his teacher.

Dr. Van Meter (Class of '81) I did not know until he returned to New Orleans after his surgical training at the University of Virginia. He became a student of John Ochsner (Class of '52), and together they made the heart transplant program at Ochsner Foundation a national resource. I have worked with him on the

Board of the Louisiana Organ Procurement Foundation for several years, and I have been pleased to observe his growth and maturation.

These three alone make a pretty good crop, but there are others. Dr. Mike Rohr, class of '67, directs transplantation at Bowman Gray and Mike McFadden (Class of 1974) is nationally known for his work in lung transplantation at Oschner. Undoubtedly there are others unknown to me.

Almost exactly 40 years ago while the class of '55 were seniors, Joseph Murray and

SLIDE (1-A & 2-A)

associates performed the first renal transplant between identical twins. This demonstrated that the obstacle to success was not biochemical, nor neurologic. Some 10 such isografts were performed by the end of 1958. In 1959 the 11th identical twin transplant in the world was done at Charity Hospital. The patient was from Houma and was a patient of Dr. John Menville. The principal surgeon was Dr. Oscar Creech, then Chairman of Surgery at Tulane. In addition to Drs. Creech and Menville, other members of the operative team included Dr. Miles Pratt and Dr. Robert Schramel.

Some 6 years passed after the first identical twin transplant while several groups investigated transplants between non-twins and unrelated individuals without substantive success until Azathioprine was discovered in 1960. This was the first good immunosuppressive agent and led to the first successful renal

transplant between unrelated individuals in 1962 by the Harvard group. Only one year later in

SLIDE (1-B & 2-B)

1963 the first successful cadaver donor renal transplant in Louisiana was performed by Tulane Surgery.

These years, 1955-63, were years of military service and residency training for the class of '55. So, just about the time the class of '55 "hit the streets" allogeneic organ transplantation experience began in earnest.

SLIDE (1-C & 2-C)

1963, the year I began 2 year fellowship in fundamental immunology, was a banner year in transplantation. Goodwin introduced the use of steroids for immunosuppression. Tom Starzl attempted the first human liver transplant and began his heroic 20-year journey toward successful liver transplantation. Starzl made the journey essentially alone in this country and his only companion in the world was Calne of England. Little by little he made progress and when the appropriate immunosuppressive drug became available he finally succeeded. Also, in 1963 Reemtsma began a series of 13 chimpanzee to human xenografts at Tulane. These experiments attracted worldwide attention, but ultimately failed. In retrospect, they were doomed from the beginning because of our lack of knowledge about immune responses, but they did lay the foundation for today's rebirth of interest. Reemtsma ultimately became Chairman of Surgery at Columbia and his laboratories have been among the most respected in the country for

over three decades. The current Tulane transplant program led by Etheredge is a direct, uninterrupted descendant of that started by Creech and Reemtsma. Essentially all transplantation in Louisiana originated either at Tulane or by Tulane graduates.

Thereafter there was a continued expansion of clinical renal

SLIDE (I-D & 2-D)

transplantation. Bernard's first heart transplant in '67 caught the imagination of the world, but again success was rare and was not really successful with regularity until Cyclosporin became available in 1983.

Periodic clinical attempts at extra renal transplants were made in many places. Drapanas and I did a liver transplant at Tulane in '68 which failed after a few days, and John Ochsner did Louisiana's first heart transplant in '69 at Ochsner's Foundation.

In 1963 most of us in the field hypnotized by early success, thought the problem would soon be solved, but in fact, we were entering a 20 year period of scientific stagnation. Although the technology spread, management improved, mortality decreased, and results gradually improved in renal transplantation. Although great strides were made in fundamental immunobiology, no major scientific discovery modified the field for those two long decades.

Throughout this long period of relative scientific stagnation in clinical transplantation the frontier subtly changed from science to mechanics. The need for multi-institutional organ procurement programs became apparent, and several such groups developed. The Midwest Organ Bank and New England Organ Bank are

examples. The largest of these was the Southeastern Organ Procurement Foundation (SEOPF) which

SLIDE 3

eventually included some 44 or 45 centers. SEOPF developed regional recipient lists, computerized matching, and regional cross matching trays. They established standards for recognizing donors, organ retrieval techniques,

SLIDE 3-B

preservation and transportation. Public education was patronized. These were the nuts and bolts issues, perhaps mundane, but essential matters and served as the foundation for a system which could deliver the service of transplantation to patients as treatment. Several Louisianians were in leadershiip roles in SEOPF during this time.

SLIDE 4

In 1983 a new immunosuppressive agent brought real progress. Cyclosporin which is not marrow toxic and does not affect immunologic memory was introduced. It improved renal transplantation, but it revolutionized extra renal transplantation. Survival of liver and heart transplants doubled and tripled. Pancreatic and lung transplants became feasible.

SLIDE 5

Monoclonal technology produced OKT3, a pure antithymocyte globulin, which made the treatment of rejection more reliable.

These discoveries increased the demand for transplants immeasurably and experimental procedures became demanded as therapy.

The country seemed shocked to learn that a national system designed to deliver this service was nonexistent. A public outcry arose, and the congress passed a law in response.

This law, the National Transplant Act of 1984, required a National Organ Procurement and Transplantation Network and was an effort to establish a national health care policy in transplantation.

The implementation of this act was ultimately carried out by the United Network of Organ Sharing or UNOS, which was patterned in large part from SEOPF. Again, several Louisianians and Tulane graduates played leadership roles in developing this national

SLIDE 6

system. There is no other medical system in the country comparable to UNOS. Every potential recipient in the nation is on its computerized list. All donors are registered. Where the organs go, to whom, and why is recorded, as is the outcome of every transplant, through its Scientific Registry. UNOS also certifies all transplant centers by established standards.

The following series of slides from the UNOS scientific registry illustrates the current status of clinical whole organ transplantation in the United States.

SLIDE 7

This slide shows the number of transplant centers in the US and associated organizations which are members of UNOS. Note that these are no longer strictly professional groups, but includes patients, patient advocacy groups, and various public organizations.

SLIDE 8

There are now 278 transplant centers approved by UNOS to transplant the following organs.

SLIDE 9

In the calendar year of 1993 the following transplants were performed: approximately 11,000 kidneys, 3,442 livers, 2,300 hearts. This does not seem too bad for a whole new discipline which came to experimental reality only 33 years ago, but --

SLIDE 10

This is a list of the patients waiting for organs on 1 February 1995. A total of 34,008 patients. More than 1/3 of these patients will die waiting for an organ.

What is needed?

SLIDE 11

More organs and longer survival. Insofar as survival is concerned, look at this slide.

SLIDE 12

These are from the UCLA national registry for kidneys. Note the enormous numbers and the log scale. A similar graph can be

drawn for the results of liver, heart, or any other organ transplant.

The fact is that almost all progress in long-term survival has been produced by improved survival within the first year. The rate of graft loss after the first year has continued unchanged over the last 30 years.

SLIDE 13

This slide simply confirms that statement by showing 1, 2, and 3 year survival of several different organ allografts.

What does this mean? I think it is a testimony to the strength of the human immune system. Since the origin of man, foreign protein within the body has been bad and commonly led to death, so we have developed an extraordinary system of isolating and destroying such material. A thirty-year effort to subvert this mechanism after several million years of evolution might be expected to be difficult. The body does not forget. As long as an organ of foreign protein in present, the body unceasingly attacks, and although the attack is blunted by drugs or the organ adapts in some way, the relentless attack continues until eventually the immune system wins and the organ is destroyed.

SLIDE 14

What is needed is a way to convince the body that the new tissue is autogenous so that it will be tolerated as an intrinsic component of that body.

This process is called acquired immunologic tolerance. It can be produced in lower animals by various manipulations. This was

shown in the '50's, but a practical way of producing it in the human has not been developed. I do believe that will be accomplished if not during my career, then during the next few decades.

Such an innovation would stretch the organ supply since one graft would last indefinitely and repeat grafts would not be required. It would obviously greatly decrease morbidity. Nevertheless, the supply will never satisfy the demand.

SLIDE 15

Another avenue of research is the use of organs from other animals. There is great interest in this subject at present as discussed by Dr. Bollinger. The pig seems to be the most promising donor if it can be humanized by transgenic technology; however, I wonder if it will not be easier to produce animalized humans than humanized animals.

This 40 year odyssey has led to many changes and new disciplines.

SLIDE 16

The transplant immunobiologist has developed a much clearer understanding of the fundamental function of the immune system. Antigen processing, multiphasic immune responses, self-identification, immune surveillance, etc. are but a few of the new concepts generated by this field.

SLIDE 17

The transplant surgeon, internist, and coordinator are completely new professionals.

SLIDE 18 (Blank)

General surgery of the liver, kidney, pancreas and other organs has benefitted. Autografts and ex-vivo surgical repairs have become common. So, although the journey is not complete, a great distance has been traveled.

Transplantation has already had a great impact upon the human race and will have even greater impact as time passes. It has modified our ethical behavior considerably. We now operate on healthy people to benefit other sick people, a step unprecedented in human history. We diagnose death on neurologic grounds rather than cardiac directly as a consequence of the need for organs. Society will almost certainly soon reassert its ownership of the cadaver, making it illegal to waste useable organs.

Genetically engineering a sub-human species to supply organs is probably feasible. Transplantation will likely greatly alter how we think of ourselves and our place in the universe. Possibly more than any other event since Copernicus discovered that the Earth was not the center of the universe.

I hope that tolerance and xenografting will become realities before the class of '55 leaves the stage. But, whatever happens, it has been a great game to play and a great privilege to play in it. Thank you for the honor of making these comments.