I am honored to be invited to give this address. It is always a pleasure to be in Mississippi. There is a mystical kinship among Mississippians. It is something akin to an unspoken understanding and brotherhood. I wonder if it comes from a shared and unique history; perhaps from the nature of the land which has sustained us; perhaps it is from our gene pool. Nevertheless, it is real, and we all know it and feel it. I never visit Mississippi without feeling the comfort one feels among old friends and relatives.

Few movements in science have captured the imagination of the public as has the transplantation of organs. It has a resurrective quality and to this day, after 30 years of experience, it seems miraculous to see a person in coma from liver failure or gasping for air from heart failure restored to health. There are now hundreds of thousands of people living, breathing, and going about their daily lives who would absolutely, unequivocally be dead had they been born just a few years earlier, and it has all taken place in about 30 years.

The oldest myths of man dreamed of mixed creatures. The Centaur, half man and half horse, or Minotaur, half man and half bull, reflected the desire to have more speed or more strength. There were many such creatures: the Satyr, the Chimera. All of these seem to represent mankind's desire for characteristics which would enable the species to cope better in a hostile world. We have learned that most myths contain great truths, thus, it is strange that all of these mythical mixed creatures were flawed in either conduct or intellect. They were instinctively known to be

forbidden and fated to be a curse rather than a blessing. It is still the same. There is still fear and suspicion concerning where the actual mixed creatures of today will take us. Today's mixed creatures are not equipped with forbidden strengths or skills, but their "biblically" allotted time is extended by replenishing their dead organs from their fallen brothers and sisters.

St. Cosmos and St. Damion

The first known depiction of a human transplant is shown in this famous medievel painting showing the transplant of the leg of a moor to a nobleman. The doctors were St. Cosmos and St. Damion, the patron saints of healing. The inspiration for this painting is lost in history.

Time Line

To gain some perspective, examine this slide. From the infinity of the past to about 500 B.C. there was only mythology, yet that mythology still affects our thinking. From 500 B.C. to about 1800 A.D. is what I have labeled pre-scientific. Medical scholars will recognize this as being from the time of Hippocrates to that of John Hunter. During this 2,300 years, essentially no progress was made in all of medicine. For the next 150 years a few isolated facts pertinent to transplantation were recorded. Although they were ultimately incorporated into current thought, they were not understood at the time. Not until 1943 did the scientific theory of transplantation begin; and only 20 years later the first successful organ transplant was performed between unrelated individuals.

Time Line #2

The scientific basis of transplantation began in the 40's - clinical transplantation among unrelated individuals began in 1962.

In 1962 I was a senior surgical resident.

Dr. Stewart

John Stewart was my teacher and chief. He was a great teacher and surgeon. He was patriarchal, strict, and autocratic. I think some of the characteristics show in this picture taken about 1950. In the fall of 1962 at the dawn of the age of human transplantation I sought Dr. Stewart's help. I had decided after six years of post medical school training that I wanted an academic career. This required an appointment in a medical school with research opportunities. In plain talk, I wanted him to give me a job, and I asked him for one. He listened quietly and then asked me what I proposed to study?

Since I had already spent a year in his own laboratory studying liver function and had some ideas relative to liver function and nutrition, I suggested that topic.

He said, "I have someone studying that problem, John". The prospects for a job did not seem too bright at that moment. Like any good Mississippian, I had learned from our history that when you back's against the wall it's time to be flexible. So, I said, "Dr. Stewart, What would <u>you</u> suggest that I study?" He responded by saying, "Transplantation is likely to be important for the next several decades, and if you would be willing to go to the immunology department for a couple of years, perhaps we could start

a transplantation program.", I suddenly developed a remarkable interest in transplantation. It was wonderful advice and has given me great pleasure for over 30 years, as well as the opportunity to make a few contributions. I relate this episode to demonstrate the principle that, when some older and experienced person gives you advice, it is sometimes worth following.

Peter Medawar

This is a picture of Sir Peter Medawar taken in the 1950's. I have dated the beginning of transplantation science with him. What did he do? Very simply, he defined the problem and discovered the ground rules.

Medawar was a young zoologist during the Battle of Britain, when Hitler was trying to bomb England out of the war. From the bombings many people were severely burned. The Research Council asked him to examine ways of covering these burns. He wondered if skin grafts could be taken from relatives to transplant onto the burn wounds. This proved unsuccessful, but he wondered why, and continued his studies in animals after the war.

Although his experiments were a model of simplicity, I will not go through them, but they led to the realization that the barrier to transplantation was a process of immunity and was based on the fact

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that the body can detect self from non-self. It has been said that mankind owes its dominance over this planet to its oversized brain, but the quality of its ability to distinguish self from non-self is

comparably important. This sounds simple, but it is incredibly complex. In simplest terms, the human body may be considered a bag of proteins suspended in water. We burn carbohydrates for ready fuel and store excess fuel as fat. Proteins are commonly very complex and large molecules. For example, if a protein molecule as big as this room were identical to one of your own protein molecules except for a spot the size of a pencil, your body can tell that it is foreign and will take steps to destroy it.

This function is performed by a group of highly specialized cells circulating in body fluids with reserve forces in various staging areas such as lymph nodes, the spleen, and the bone marrow. For however many years mankind has existed, these cells have correctly assumed that any foreign protein or non-self which gains entrance into the body is harmful and should be eliminated, thus ridding us of bacteria, viruses, cancer cells, and many other noxious agents.

After millions of years of experienct, this defense system has become exceedingly sophisticated and efficient. For the past 30 years we have been trying to convince them that they should accept whole organs of foreign protein in 1-3 pound quantities. It should not be surprising that this is hard to do. These host defense cells are very suspicious, disciplined, and ruthless.

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Transplantation has arrived at the current state by several lines of investigation as shown simplistically here.

The biologic division has concentrated on learning how this

remarkable capacity to recognize self from non-self works. What cells do it and how they do it - I have labeled this the physiologic approach. This approach has produced many volumes of fundamental information, which has opened up whole new worlds of study, but its impact on clinical transplantation has yet to be profound.

The idea of tissue types has occupied hundreds of scientists. This idea arose from successful blood typing. It seemed logical to expect that tissues could be typed in a similar way. It turned out that tissue types were actually markers of self identity used by the hose defense system, and everyone except identical twins is different. So, although the study of tissue types has provided new concepts of how the system works, but with a few singular exceptions, has also not yet had great impact upon clinical transplantation.

The production of tolerance; that is, finding a way to convince the recipient that the foreign protein transplanted is actually self, has been, and continues to be, the Holy Grail. It can be done some time, in some members of some species, but not reliably. Thus, it is possible to do, but as yet it, too, has eluded our grasp.

I have spent my career studying these biologic processes. This may have been a bad choice, since commonly I feel like Omar Khayyam who wrote,

Myself when young did eagerly frequent

Doctor and Saint and heard great argument about it and about:

but evermore

came out by the same door where in I went.

Nevertheless, the solution lies here.

Real progress, however, came from the clinical line. That progress has been driven by pharmacology. An ever-increasing number of drugs has been developed which can cripple or kill the cells producing rejection. These drugs are becoming increasingly precise and there are now some which can selectively kill certain cells while allowing others to survive to protect the recipient from dying of other foreign proteins. Yet, most recipients who die following transplantation still die as a consequence of drugs.

A practical step forward was made when methods were developed that could preserve the organs taken from a donor for 1-3 days. Although it would be better to preserve them for weeks or months, there is enough time to perform the transplants.

Finally, a nationwide organization has evolved to allow the efficient delivery of the service of transplantation, and I was privileged to have some role in this process.

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By 1966 there were a few dozen people surviving with kidney transplants, probably 10 or 12 surviving on liver transplants and no one from other organs. In 1991, 7,737 kidney transplants, almost 3,000 liver transplants, somewhat over 2,000 heart transplants, etc. were done. Pancreas and lung are on the horizon and more recently successful bowel transplants have been reported.

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Here are the one year patient and graft survivals. Heart and kidney are quite respectable and all are more successful than the treatment of most cancers.

It still seems miraculous to me to realize that transplantation has come from science fiction to clinical reality within one professional lifetime. But, it is not a miracle. It is an example of what can be done when enough brainpower is focused on a problem and given the resources to do it. Transplantation science has been almost unique because it has drawn the attention of thousands of the best scientific minds in the world and it drew them from all disciplines: surgeons, internists, biochemists, immunologists, biologists, etc. It is a tribute to modern communication systems and the international free sharing of information. It is also unusual since no great single insight has driven the field, such as the discovery of anesthesia, asepsis, penicillin; rather many small steps provided by many individuals have built the science.

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Some philosophers have said that the study of science is futile, since each answer creates many more questions and problems. Thus, there is no end and transplantation is no exception. I have already shown this, by stating how each line of investigation has led to many other lines.

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These are lists of people in the U.S. awaiting organs for

transplantation. The total today exceeds 30,000. The majority of patients on this list (excluding kidney) will die before they get a transplant. This was not a problem 30 years ago - they would all be dead.

Slide

The donor supply is totally inadequate. The total number of people who unavoidably die each year who have organs that could be transplanted has been estimated as between 10-30 thousand. Today, only 4-5 thousand agree to organ donation. The public must realize that it has become immoral for organs to be buried that would restore others to health, and I expect that it will be against the law before another 30 years has passed.

Scientists must develop better means of preserving organs so that they may be banked for use at the most appropriate time. It should also be possible to improve the health of organs damaged by the agonal phase of death.

Similarly, true tolerance must be produced. The organs we transplant today do not survive beyond 5-10 years on the average (although there are occasional spectacular exceptions). Even though rejection is suppressed, the body rarely stops its effort to destroy it and ultimately it succeeds. Tolerance would prevent this chronic warfare. Thus, organs would be more durable and predictable, and waste would be reduced.

Finally, we will have to face costs. These procedures can be incredibly expensive. Do we have the will to invest in a second chance for people with lethal organ failure?

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Many problems will be ethical or moral - rather than **scientific.** In years to come, it may be hard to die with anything but brain death or widespread cancer, or extensive blood vessel disease. The supply of human organs for transplantation will ultimately never be sufficient, even if every available organ is donated.

What will happen then? Will we simply provide organs on a first come, first serve basis? Will President Clinton not be placed ahead of a murderer? Who will decide, and on what basis. Will it be decided on a social basis? Is a great scientist or mathmatical genius more important to save than the mentally retarded?

You may also ask about donors. With few exceptions all organ **donation comes from the irretrievably dead.** Should organs be taken from people who are about to die, but are not dead? How about prisoners sentenced to death? How about permanently mentally deranged or incapacitated?

Before long it should be possible to genetically arrange the production of human beings with minimal brain function. Should we produce such creatures for organ supply?

Perhaps the most hopeful solution would be to produce certain animals genetically manipulated to produce humanoid organs. Would that be acceptable?

Do we wish to pay the price - in simple economic terms to extend life for everyone? Who will decide and on what criteria.

Transplantation science, genetic engineering, transgenic science are areas which will redefine our ethics - all of which tends ultimately to redefine man in a more animalistic or materialistic way. What is the individual worth? Who survives? Is the individual worth whatever some group defines as its worth to the species? I have always thought, when contemplating these questions, that subsequent generations would have to make these choices. But, it has all happened so quickly. It is now upon us. At this moment, a revolution in health care is being contemplated. So these choices may have to be made by this current generation. Perhaps with a transplant or two, we may see it through.

I have completed my formal remarks. Since I have concluded with some rather heavy matters, I would like to finish on a lighter note. Perhaps the most enjoyable part of this Mississippian's journey into transplantation has been the people I have traveled with. Here are some of them.

(Ad lib remarks - pictures of colleagues and patients)