FINAL

Transplantation as a Model of Medical Progress

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I thank you for inviting me to be visiting professor in this great institution. I am honored to be here. Initially I thought it an appropriate time to reflect upon lessons I have learned that might be helpful to more junior members of the audience, which is almost everyone here. I attempted to write such a talk for several weeks without success. Finally it came to me that the reason I could not write it was that I have learned very little in the last 40 years about conduct, wisdom, virtue, etc., that I did not know at 30. In every culture and every religion courage is preferred to cowardliness, honesty to dishonesty, diligence and discipline to laziness and sloth, but you have already learned that, and if you haven't you probably never will. The problem is not in the knowing it is in the doing. Falkner made it clear in his great novel, Light in August how complex and confusing life appears when looking forward and how predestined and simple it appears looking backward. So, as Forrest Gump said, that's all I have to say about that. What I will talk about is medical progress.

Title slide

I have always had an interest in how medical progress occurs. Why in occurs when in occurs, and why it occurs where it occurs. There is a pair of books written byThorwald in the fifties on surgical progress.

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These are entitled The Century of the Surgeon and The Triumph of Surgery. They are written in novel form. The Protagonist in a Dr. Hartmann, who is a medical doctor who does not practice; however, he contrives to be present at great medical advances. He was in Boston at the first demonstration of anesthesia. He was in Edinburg for a demonstration of antisepsis, etc. They are fun to read and a particularly painless way to learn a little History.. Thorwald clearly was intrigued about how such events come about. He used the metaphor of a white bird to symbolize medical leadership, and envisioned the bird as flying around aimlessly, alighting at random wherever it chose. This is the Great Man theory of History. Progress occurs wherever and whenever a great man appears. This may have resembled the truth when the World of medical science was younger and smaller. Until well into the 20th century the number of Surgeons performing scientific work in the world could be numbered in the dozens. As late as the 1960's I heard it said that the term Surgical Scientist was an oxymoron. In the latter half of the 20th century the number of scientist working on subjects pertinent to Surgery includes many thousands of individuals.

The idea that progress in health care is the product of a single genius certainly is not true today if it were ever true, which I doubt. In fact many people make small contributions which are lost in the literature and remain unappreciated, sometimes for decades. These contributions accumulate until it is possible for some one or some group to synthesize the information,

which lead to a benchmark event. Subsequently many other people make contributions to improve or expand the value of the benchmark event.

It has been said that research is like stumbling about in a darkened room describing what you can feel as best you can. This continues awhile, sometimes for centuries, until someone comes into the room and turns on the light. Thereafter it becomes relatively simple to go around the room and put all the furniture back in order. Once the light is on it is easy to correct the errors, which came from working in the dark. Most of us spend our lives in research either stumbling about in the dark or putting things back in order. Few of us are accorded the privilege of turning on the lights. Nevertheless these other duties are honorable, necessary, and fun. Let us see how transplantation fits this model.

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The Phase of Stumbling about in the Dark:

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Many reports of skin transplantation can be found in antiquity, but Billingham attributed the first documented experimental free full thickness skin autographs to Baronio in 1804. The sheep was the experimental animal. This Milanese physiologist also observed that separation of the tissue from the host for an hour before re-application did not effect its survival. Thus,

autografts of skin were shown to survive. Unfortunately throughout the 19th century the difference between autografts and allografts was unclear.

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Almost a century later (1902) Ullman of Vienna performed a series of dog kidney autografts into the neck. His techniques were very primitive but he was able to establish that blood would flow through such grafts, and urine would be produced at least temporarily. Alexis Carrel between 1904-06 performed similar experiments. These we somewhat less primitive because Carrel devised sutures, needles, and vascular techniques that are still used, but the results were essentially the same.

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Two more decades passed before Williamson, of the Mayo Clinic, performed further experiments with kidney transplantation. Williamson clearly recognized that autotransplants could survive indefinitely, while allografts functioned only temporarily. In 1926 he published photomicrographs of rejecting allografts which documented the anatomic pathology of renal rejection.

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Emil Holman was a resident here in 1924. I believe he was the last house surgeon to be trained, or partly trained, by Halsted (I am sure Dr. Cameron can tell me). Holman was treating a 28-month-old child for severe burns of the face and trunk. He had on at least one previous occasion used living donors of pinch allografts to aid in wound coverage. He grafted skin from

two volunteer donors on day 0. In 18 days the original grafts were still alive and spreading, so another group of grafts were placed on the wound from a third donor. 22 days from the beginning he placed a fourth group of allografts was placed, but these were from one of the original donors. At 30 days the original grafts as well as the last grafts (the second set from the original donor) were degenerating, while the grafts from the 3rd donor survived for another 2 weeks before they "melted away".
Holman deduced from the experiment that "the agency" which caused the first allografts to disappear had no effect on the viability of the grafts from the third donor, and that the destroying agency was therefore specific for each set of grafts. " It seems plausible to suppose therefore, that each group of grafts develops its own antibody that is responsible for the subsequent disappearance of the new epidermis".

Moore in his textbook of 1964 describes this experiment in some detail and quotes a letter from Holman written 40 years after the original experiments when he said, somewhat wistfully, " What an opportunity we missed by not pursuing this further."

To summarize thus far, between 1804 and 1924 it was established that autografts of skin and kidneys survive permanently while allografts function temporarily but always fail. The rejection pathology was described and rejection was thought to be a specific immune response.

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It is not surprising that some would wonder about the effect of genetic similarity to graft survival. Padgett of Kansas City reported upon 44 allografts of skin performed between individuals of varying ages and genetic relationships. These included 4 isografts, i.e. grafts exchanged between each twin of 2 pair. These grafts had all survived for a year at the time of publication in 1932. Furthermore grafts between first and second-degree relatives survived longer than those between unrelated individuals. Brown of St Louis added another set of isografts in 1937. These grafts had survived over 3 years at the time of publication. The fact that rejection of transplants between genetically identical individuals does not occur was established. .

Now comes the Second World War. Bombings of the cities of England produced enormous numbers of severe burns. The National Research Council asked two young men to look into what could be used to cover these wounds. They looked into the use of allogeneic skin and found that it was not successful. They noted that a second graft of skin from the same donor survived a shorter period of time than the first. They called this accelerated rejection the second-set reaction a term which came into common usage later. They reported these findings, which, in view of their original purpose, were negative

9. Picture of Medawar-1

One of these young men was Peter Medawar, who was a Zoologist. On his return to Oxford he continued his experiments with skin grafts in rabbits. He determined mean survival time, described the specificity of the reaction by demonstrated that an animal would reject a second graft from the same donor very rapidly, but treated a graft from a third donor as a first-set graft. He realized that the reaction against Allografts was immunologic. In other words, he reproduced Holman's findings.

10. Picture of Medawar-2

This is Medawar 40 years later. Just to remind you of what time does to all of us.

Meanwhile across the North Sea a Dutch internist was presented with many injured soldiers with acute renal failure. A condition associated with crush injuries, myoglobinuria, and dehydration. This was variably called lower nephron nephrosis, or the crush syndrome. Dr. Wilhelm Kolff realized that these young men would recover if they could live until a diuresis occurred. Some did but many didn't. Prior to the war he had conceived of a machine for extracorporal dialysis. The properties of the recently discovered plastic called cellophane had come to his attention, and he had performed some dialysis experiments with urea, which proved that urea would diffuse across this membrane. During the intervening period Heparin had been isolated. So, during the war years Kolff began his attempts to produce an artificial kidney. He pumped heparinized blood through small tubes of cellophane stretched between two circular wheels that were rotated through a bath of saline. He

treated 14 patients between 43' and 45', all of whom died. He experienced many technical difficulties. He had to finance the project himself, as well as personally build, and operate the machines by hand. He finally had a survivor on his 15th try. After the war he brought prototype kidneys to England, Canada, and the United States. He also sent one to Poland, which he said disappeared behind the iron curtain never to be heard from again. When he visited The Brigham Hospital in 1947 all he had left were blueprints. These he left with Dr. Carl Walter who built an improved machine. Dr George Thorn asked John Merrill to undertake the treatment of acute renal failure with the artificial kidney, and soon there was more experience with the instrument at the Brigham than anywhere else in the country. This machine ultimately created a group of patients whose condition compelled physicians to consider renal transplantation.

11. Picture of Kolff

At a lecture at Tulane in the early 70's Kolff reflected upon the political situation surrounding his work. Dr. Kolff was a Jew. ~~Some of you may remember that the Nazis had more difficulty with their final solution in Holland than in many of the occupied countries. Shortly after the occupation they promulgated an order that all Jews should wear the Star of David prominently displayed. The following day all Dutch citizens appeared with such a star pinned to their clothes. There were also substantial underground efforts to protect all their citizens.~~ Still, it was hazardous being a Jew in nazi occupied Europe. Kolff survived because he was a physician and provided

care to injured nazi soldiers as well as others. He felt that the authorities never quite understood what he was doing, but they did recognize it as a potential advantage to their cause. He always emphasized to them that the machine had many defects and needed further work for fear that in the end they would lose patience and he would be killed. It is hard to imagine how relieved he was when that war was over and he was able to proceed with his work in freedom.

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At the war's end events began to accelerate. Owen of Wisconsin noted in 1948 that when cattle twins were born with two fused placentas they each could be shown to have more than one blood type throughout their lives. Later a pair of human fraternal twins was found by Dunsford, each twin had both blood types A as well as O cells. That loop was finally closed in 1959 when Woodruff (the wartime prototype for Col. Bogey) and Lennox observed another pair of twins each with two blood types. Skin grafts between the two survived permanently. Thus human chimeras do occasionally occur naturally produced by intrauterine exposure to foreign cells.

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Owen's work led Billingham, Brent, and Medawar to inject six intrauterine CBA fetuses with cells from A-strain adult mice. Five healthy mice were born and after eight weeks skin grafts from A-strain mice were placed. Grafts on two mice failed in the usual time. Grafts on the other three survived. Two survived indefinitely and the third failed in about 75 days. Ultimately cells of

normal CBA mice were injected into the two tolerant mice and produced graft rejection. Of course, later this experiment was reproduced many times, but it is interesting that the concept of acquired immunologic tolerance derived from this experiment with 5 mice.

This was a very influential experiment and set the world to thinking about actively acquired tolerance. Acquired tolerance in the Adult has been the Holy Grail of transplantation since this 1953 report. It still has not been accomplished 47 years later, although recent experiments suggest we are coming ever closer. This experiment was also had great influence on the thoughts of Burnet in his clonal selection theory of immunity.

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Meanwhile due to the moral imperative produced by patients dying in renal heroic efforts at renal transplantation had already begun. In 1947 Hufnagel, Hume (Dr. Mel Williams' teacher) and Landsteiner were presented with a young woman in uremic coma produced by acute renal failure secondary to sepsis acquired in pregnancy. They acquired a fresh kidney from a cadaver and placed it in the antecubital fossa. The kidney produced urine immediately and functioned for some 48 hours when functioned declined and it was removed. However the patient was greatly improved and was clear mentally. She survived until diuresis began and recovered fully. This operation was done at the patient's bedside with a "goose-necked" lamp, since for

administrative reasons they were not allowed to perform it in the operating suite. Sound familiar?

(lights)

By 1951 work with dialysis produced a number of patients who were initially thought to have acute renal failure, but for one reason or another did not recover. At that time dialysis was performed by repeatedly cannulating large vessels, that is, before dialysis access procedures had been worked out. Thus, the length of time patients could be kept alive with chronic renal failure was quite limited. Thus, David Hume encouraged by Merrill and Thorn began a series of cadaver donor renal transplants into the femoral triangle, without immunosuppression. Hume did nine such transplants. Most functioned initially but failed after a few days, but one functioned and supported life for 175 days before it failed in association with severe hypertension and infection. Joe Murray, who continued this work, performed 6 additional transplants with no prolonged survival. During this time period Murray devised the extraperitoneal kidney transplant in the dog which was suitable for human use and is still used today.

The stage was now set. It was known that skin grafts between genetically identical individuals would survive permanently. That acquired immunologic tolerance was possible. An artificial organ was available to prolong life for people in renal failure, at least temporarily. A population of such patients was available. An appropriate operation to transplant a kidney in the human

had been developed, and transplanted kidneys were known to support life until rejection occurred.

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One day in 1954 Merrill received a call referring a young man in renal failure for evaluation and treatment. At the conclusion of the call the referring physician said," by the way, this patient has an identical twin". That turned on a light for Dr. Merrill. After evaluation of both twins, an exchange of skin grafts to prove identity, a kidney transplant was performed Dec. 23, 1954. Dr. Hartwell Harrison removed the kidney and Dr. Joseph Murray implanted it. This patient survived for 9 years and died of recurrent glomerulonephritis; however the recipient of the second such transplant is still alive some 45 years later. Over the next 18 years 49 transplants between identical twins were performed with a 5-year graft survival rate of 86%. From this experience it was learned that transplanted kidneys could maintain the recipient in perfect health, that the technique of the operation was quite satisfactory, and that nephrectomy in the healthy donor was safe.

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The light comes on:

Between 1958-62 there was some effort to use total body irradiation and bone marrow transplantation to condition recipients for renal transplantation, but although there were occasional successes this effort was abandoned as too toxic. In 1959 Schwartz and Dameshek found that 6-mercaptopurine could produce acquired immunologic tolerance to soluble antigen in adult

rabbits. This led almost immediately to trials of this agent in dog renal transplant models by Calne, Zukowski, and Pierce, and their associates. Graft survivals were obtained but still the difference between lethal doses and immunosuppression was too close. The Boroughs Wellcome Company carried out a crash research program that shortly provided an analog of 6-mercaptopurine named azathioprin. This agent along with steroids proved suitable for human use and provided the backbone for renal transplantation for the next 20years. Antithymocyte globulin was used as an ancillary drug through this period.

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The first successful renal transplant between unrelated individuals was performed in Jan. 1962. The effort spread like wildfire.

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By April of '63 Murray had performed 13 transplants at The Brigham. Starzl had performed 46 at Colorado, 13 by Goodwin at UCLA, Hume had started at MCV, Calne in England, and Woodruff in Scotland. With these protocols about 50% of unrelated kidneys functioned for a year but only about 30% for 5 years.

Of course, the pioneers of histocompatibility were busily at work and the ideal results obtained with HLA identical siblings was soon apparent.

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Putting the furniture back in Order:

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I should pay homage at this time to the original pioneers from whom I learned the most: Murray, Starzl, Hume, Najarian, Russel, Hardy, and Rheemsma. All of whom, save Hume, I can call friends and councilors, but I want to spend sometime talking about a group which I would like to call " **the boys of summer.**

I finished my residency in 1963 and then spent two years in immunology fellowship, which was completed in the summer of 65. The first kidney transplant performed by me was in 1964. At that time there was a group of young people at the beginning of their careers who were attracted into transplantation. We became colleagues and friends and have remained so for almost 40 years. We have been straightening out the room,

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The Boys of Summer.

Some of you know that I have wasted a fair amount of my time as a baseball aficionado <u>The Boys of Summer</u> , by Roger Kahn is said by many to be the greatest book ever written about baseball. It is about the Brooklyn Dodgers of the fifties. It is about a fabled team in a fabled time, a Camelot that lasted only a few years and disappeared. Even the place where the team played was destroyed, It occurred to me that this group of surgeons might be thought of as The Boys of

Summer. I would like to use this team as a metaphor for them. So, I am going to present to you my transplantation team which has put the furniture back in place for the last 38 years.

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This slide juxtaposes The Dodger team with the transplant team. Here is the infield.

23.Picture of Monaco

Catcher: Anthony Monaco. He is catcher because he like Campanello has the dogged determination to focus on a problem and never let go. He has pursued the study of tolerance for his entire career, taught many students, and like Roy Campanella has overcome serious handicaps with grace and courage.

24.Picture of Belzer

First Base: Fred Belzer, the father of organ preservation, master of organ procurement, creator of two world class transplant centers, chief surgeon at the U of Wisconsin, and like Hodges a great player in the clutch.

25.Picture of Kountz

Second Base: Samuel Kountz. Born in a small Arkansas town, an african-american who made an epic journey to ultimately become Chairman of Surgery at SUNY Downstate. He contributed to organ

preservation, organized transplant systems, and was the first to use high dose steroids to reverse rejection. Like Jackie Robinson he was a great American, broke many barriers, and died prematurely.

26.Picture of Diethelm

Short Stop: Gil Diethelm, The great chairman of Surgery at the U. of Alabama, who built the highest volume kidney transplant program in the country, as well as a model organ procurement agency. Gil grew up in the northeast and had his medical education there. After 30 years in Alabama he fumed at me many times about how long it took to be considered a Southerner. So it is fitting that he stand in for Peewee Reese, the archetypal southerner of the Dodgers. Further as Peewee never let a ground ball by him, Gil never let a transplant in Alabama get by him.

27.Picture of Simmons

Third Base: Dick Simmons: A renowned surgical scientist who established the research component of the pioneer program at U. of Minn. and was later Chairman of Surgery at U. of Pittsburgh. Billy Cox was known as a great glove man with the artistry of a dancer. Simmons has the same class, with great intellect and smoothness.

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28.Picture of Barker

Right Field: Clyde Barker. Clyde has spent most of his professional life in Philadelphia associated with U. of Pennsylvania. A perennial scholar of tolerance and pancreatic transplantation, he has led that venerable department with distinction and scholarship. He stands in for Furillo who was a heavy hitter and known as the emperor of right field.

29. Picture of Williams

Center Field: For Duke Snider, Mel Williams. Brilliant, talented, and versatile he studied both cellular and humoral immunity. He was one of the first to recognize and prove the cause of hyperacute rejection. He was a guiding force in the foundation of the national transplant network, and the first President of UNOS More recently he has become the master of the mega-aneurysm. Like the Duke perhaps the most talented of them all, also like the Duke he can be a little eccentric at time. He has been a fast and dependable friend, but I do hope he has quit performing his Voodoo dance at the conclusion of each operation.

30.Picture of Hardy

Left Field: Mark Hardy. Mark has spent his life in New York City. For the past 25 years he has been associated with Columbia. He has studied thymic tolerance, pancreatic islet transplants, models of cardiac allografts, and the effect of ultra-violet irradiation on immune events. His intellectual versatility makes him an appropriate stand-in for Andy Pafko.

31.Picture of Corry

Pitcher: Rob Corry. A product of Yale, Johns Hopkins, and The Mass. General he has the confidence and charisma of the pitcher Carl Erskine. Rob had done as much to make pancreatic transplantation a clinical reality as anyone. More than half of his publications is on this subject. Erskine rose to prominence on his mastery of the curve ball, and Rob on his mastery of pancreatic transplantation.

32.Picture of Jonasson

Pitcher: Olga Jonasson. To represent Clem Labine as one to depend upon as a stopper, Olga Jonasson is my nomination. She has always been able to take the heat. Obviously she is not a boy, but she can play with anyone. A student of histocompatibility and pesensitization, she also ran a long-term experiment in primates trying to reproduce

the complications of diabetes. She was chief surgeon at Cook County Hospital for several years and as the chair of Surgery at Ohio State was the first woman to become chairman of Surgery of a major medical school.

33.Picture of Alexander

Utility player: Wes Alexander. Wes, to my knowledge, has no counterpart on the Dodger Club, or anywhere else. Since his residency training he has been associated with U. of Cincinnati. He has studied transplantation, infection, nutrition, and burn therapy, and made substantial contributions in each area.

So, that is my team. How have they played?

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They improved or produced new operative technology, new and more specific immunosuppressive agents. They established extra-renal transplantation. They defined organ donors and educated an entire nation about donation.

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They developed organ preservation, and a national network for transplantation to bring this treatment to the people. They trained a whole generation of transplant surgeons, improved the treatment of infection, and clarified the immune response and mechanisms of tolerance.

I do not imply that they did it alone, but they represent the generation that did.

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This team of 11 published 3910 papers, not including book chapters, books, or abstracts. Seven were or are chair of surgery in University departments. Nine were president of the American society of transplant surgeons, and the group was also president of 10 other national societies. Nine served on national institutes of health study sections.

I have used transplantation as a model of how medical progress occurs. Others could do the same for cardiac surgery, vascular surgery, the genetic code, asepsis, and essentially any other field of study. Perhaps it is only of academic interest, but if you are working in the dark your recognition is likely to be posthumous, if you turn on the

light expect a call from Stockholm, if you are in phase three, your work is likely to be recognized and clearly useful.

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I said at the outset I didn't have any wisdom to share but I will close with a few aphorisms.

Select a field in which there is some light, you invest some time in the dark but not much. You must find a place to work that is supportive. Your best judgement about life comes from your gut rather than your head. Once started don't look back.

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Scientific pleasure comes from the doing. Be honest, work a long time, and don't worry about the money,

Thank you for the opportunity to present these ruminations.