NEW LAMPS FOR OLD: TRANSPLANTATION

Bernard Lytton

I was born between the two great wars. My father had trained as a physician but instead went into business for financial reasons after World War I. Both my parents were very supportive of all the things that I did. The first clear memory I have as a schoolboy, at about the age of eight, was the Silver Jubilee of King George V and Queen Mary, who was formerly the Duchess of Tek. We were issued little pink books containing the history of the king and queen and a map of the world in which the British possessions were colored in pink. The great British Empire comprised a fifth of the world, and how proud we were to wave the flag. Twenty-six years later, when I completed my residency, England had been divested of its empire and had become a small constitutional monarchy applying for admission to the European Economic Community.

That twenty-six-year period was certainly a tumultuous time. At the age of eleven, I went to what was called an English public school, which in this country you would call a private school. The public schools in England were so called because many were founded by and named after public companies or guilds, such as Haberdashers and Merchant Tailors. Their purpose was to provide an education for the sons of the members of the guild. Several of these schools were more socially prominent, such as Eton and Harrow, where many of the aristocracy are educated. Our school was located in Hampstead in north London. Two years after I entered, war was declared; I remember quite distinctly listening to Prime Minister Neville Chamberlain telling us on the radio how Herr Hitler had failed him and we were at war. A year later the school was partially destroyed by a bomb during the first London Blitz in late 1940, so we were moved to our athletic facility in Mill Hill. Due to lack of accommodation

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Bernard Lytton was born in 1926 in London, where he received his undergraduate and graduate education. Much of his high school education was during World War II, and in 1943 he was admitted to the London Hospital Medical College, a school of the University of London, where he took his medical degree. While there he was awarded the Haking Prize in Obstetrics and Gynecology. In 1955 he became a fellow of the Royal College of Surgeons, having completed the two-part examination for this higher degree in surgery. He was then conscripted into the Royal Air Force for two years. He was a surgical resident at the London Hospital, where he subsequently became chief resident. As a British Empire Cancer Fellow at King's College Hospital, he studied the immunology of cancer, which led to an interest in renal transplantation. He immigrated to the United States in 1962 and became an assistant professor in the Urology Department at Yale. In 1967, together with Dr. Howard Levitin, a nephrologist, he began a program of kidney dialysis and later that year did the first kidney transplant in Connecticut. In 1967 he became chief of urology, a position he held for twenty years. During that time he was president of the New England section of the American Urological Association and received the association's Hugh Hampton Young Award. He also received the Francis Gillman Blake Award at Yale for teaching and was a member of a National Institutes of Health study section for four years. In 1987 he was appointed master of Jonathan Edwards College, a position he held for ten years, after which he became emeritus.

for students, we only attended classes three times a week. I had to cycle ten or twelve miles each way to and from home, carrying my books and extensive homework.

I always had an inclination to pursue the sciences, so when I entered the sixth form, where you spent two years after matriculating, I took biology, chemistry, and physics. Mr. Smith, the biology teacher, was a very enthusiastic and charismatic chap. Fortunately for us, he was a conscientious objector and had therefore been left to teach. He gave me a great feeling for biology and what it meant. I dissected a great many fish, frogs, and mice, which I enjoyed doing, and I suppose that was the beginning of my surgical bent.

I had planned to go on to medical school after reading history at Cambridge, but the exigencies of the war prevented it. In 1943, when I finished high school, things looked bad, as it seemed we were losing the war. At the age of seventeen, I couldn't yet join the Army, so I was advised by the draft board to go to medical school and get qualified as a doctor. I was accepted at the London Hospital Medical College as a freshman student. The next two years were a difficult time as we were subjected to the bombing by the new German V1s and V2s. The V1s were pilotless planes that had a ton of explosive in the nose, with a rocket-propelled motor in the back aimed at London. The motor would cut out at a prearranged time so that they crashed into the city. You could hear when the motor cut out and count to ten before you heard the explosion. The Royal Air Force became quite adept at shooting the V1s down or tipping their wings with their own planes so as to put them off course.

The V2s came later. They were large rockets, designed by Werner von Braun, and forerunners of the intercontinental ballistic missiles. They were more terrifying as there was no warning and you only heard the explosion when they landed after being fired from the Netherlands. The only defense was to bomb the launch sites. Fortunately, the Netherlands was retaken fairly soon after the Normandy invasion. The East End of London sustained a lot of casualties and as medical students we were recruited to assist in their care. On one occasion there were several hundred casualties when a V2 fell in the market in Petticoat Lane and all the corridors and basement of the hospital were filled with the wounded.

As a medical student I was attracted to surgery and to obstetrics and gynecology, and was awarded the class prize in the latter. During my years in medical school, I was a member of the university officer training corps and the admiralty ferry crews. The latter comprised a pool of thirty to forty students who provided the able-bodied crew members, as most of the others were retired senior officers and former yachtsmen. We ferried small auxiliary naval vessels from remote shipyards on rivers throughout England, where they were built, to major naval stations.

After graduation, I was appointed to an internship at the hospital where I had trained and served in various positions for two years. I then fulfilled my two-year military obligation in the RAF, where I learned to fly and later went to Korea. Having completed my service, I wanted to pursue my surgical career but felt out of touch and

needed to find some mode of reentry. I applied and was accepted as an assistant professor in the Department of Anatomy at University College London. The chairman of the department was J.Z. Young, who was well known for his work in neuroanatomy and physiology based on his studies of the axon of the squid. I have always remembered the good advice he gave me: "I know you're going to be a surgeon, but don't pursue degrees. It is what you do that is the most important thing, not the degrees you obtain. It's the research and the work that you do that will make your mark and give you satisfaction."

At University College, I studied the mechanism of peripheral nerve regeneration with Dr. Greg Murray, who later became professor of surgery at King's College Hospital. While I was at University College, Rupert Billingham, Leslie Brent, and Peter Medawar, who were in the Zoology Department, gave a seminar on their classical work on immunological tolerance, for which they subsequently received the Nobel Prize. Tolerance is the ability of the body to reject a foreign protein expressed on a bacterium or graft. A skin graft from another individual is normally rejected because of the body's immune reaction. Billingham, Brent, and Medawar discovered how this system matures. They took cells from mouse A and injected them into mouse B embryos. After birth, these B mice became tolerant to mouse A's skin grafts because they had been injected with mouse A's protein before they were born, before the immune system matured. As a result, they recognized mouse A's skin grafts as "self" and did not reject them. This was an exciting scientific event and caused a great stir in the medical community, as well as arousing my interest in immunology.

I then took the Fellowship of the Royal College of Surgeons examination, which was in two parts, a basic science and a clinical section, and began my practical training as a surgeon. In Britain you usually get the degree before you work as a clinical surgeon. I was fortunate that I was able to go and train with two individuals who had been chief surgical residents after returning from service as military surgeons in World War II, when I was an intern. They had subsequently been appointed as consultants to local hospitals in the East End, and I went there to work with them. The various surgical procedures they taught me gave me important technical skills and confidence early in my career.

During my training in London, I had an opportunity to visit McGill University on an exchange with a resident in Montreal. I was able to experience the American medical system and travel to other medical centers. I first went to Columbus, Ohio, where I met Dr. Robert Zollinger, a well-known surgeon who had a large and respected surgical service and was doing pioneering work on the treatment of peptic ulcers. I then spent a week with Dr. Francis Moore, chief of surgery at Harvard Medical School and at the Peter Bent Brigham Hospital in Boston. He developed the science of fluid and electrolyte replacement for patients who had undergone surgery or were dehydrated. He was also very interested in transplantation and promoted this at the Brigham Hos-

pital, where the first kidney transplant was performed between identical twins in 1955 by Drs. Joseph Murray, Hartwell Harrison, and John Merrill.

I then returned to England and completed my senior residency at the London Hospital during the next two years. I had very good mentors, one of whom, Mr. Hermon Taylor, was both an excellent surgeon and an innovator. He was one of the first to advocate local excision of breast cancers followed by radiation therapy as an alternative to radical removal of the breast, which at that time was the standard treatment. He also developed a technique for the nonoperative treatment of perforated peptic ulcers by carefully monitored gastric suction and administration of antibiotics. He found that in over half of these patients the ulcer healed without an operation, which was a major step forward. The involvement in the development of novel methods of treatment, even though they were sometimes more difficult to carry out than the standard methods, I found very rewarding.

After completing my training at the teaching hospital, I was appointed resident surgeon at one of London's busy outlying hospitals, where I did most of the surgery. After three months I decided that I was performing a service, at only a resident's remuneration, without furthering my education. I contacted the person with whom I had worked at University College and who was now professor of surgery at King's College Hospital. He offered me a position as a British Empire cancer research fellow, and I began a research program on the immunology of cancer. I was interested in whether patients in the late stages of cancer were still capable of evoking an immune response and whether this response disappeared as the disease became more advanced. There was a large population of patients with terminal cancer at St. Joseph's Hospice in the East End of London, to which I had referred patients when I was a resident. I arranged with the hospice to test these patients against tetanus toxoid, used to immunize people against tetanus, to which they had not previously been exposed. Patients with advanced cancer did in fact have a significant impairment in their ability to make antibodies to a new antigen or foreign protein.

At St. Joseph's, I was fortunate to meet Dr. Cicely Saunders, who was interested in the care of the dying. She was recording their feelings and fears during interviews and in this way helped them to talk freely about their illness and dying—a practice that is now part of the hospice concept. Her primary interest, however, was in pharmacology, in which she was doing research for an M.D. degree. She was studying how to administer a combination of medications to relieve pain and anxiety while maintaining consciousness and avoiding dependency. I think the greatest testament to her success was from the sister in charge of the hospice, a Catholic nun, who said that the greatest change since Dr. Saunder's arrival three months earlier was that they no longer required a night staff, as patients were comfortable and slept through the night without medication. She felt the whole aspect of the institution had changed.

A year later, I came to New Haven, a move I had planned several months in advance due to a paucity of consultant positions in the United Kingdom at that time,

and was warmly received by Dr. Paul Beeson, who was professor of medicine at Yale. He was caring for the president of the university, Whitney Griswold, who was suffering from terminal cancer. Beeson mentioned that he had had little experience in caring for a dying patient. I told him of my experience at St. Joseph's and the work that Cicely Saunders was doing. He was most interested and suggested that we invite her to come to Yale and give a talk. I called Cicely, who said she would love to come, and a few weeks later she gave a wonderful talk. Sadly, only about forty people came, but one of them was Florence Wald, then dean of Yale's School of Nursing. She was inspired to start a home hospice care service in New Haven and insisted that I invite Cicely back the following year. This time, more than two hundred people attended the lecture, which generated a lot of interest. Yale subsequently awarded Cicely an honorary degree for her great contributions. She campaigned for and organized the building of St. Christopher's Hospice in south London. Her inspiration also led to the founding of the first hospice in the United States, which opened in Branford, Connecticut, in 1968. It was funded in part by the U.S. Department of Health, Education, and Welfare, which at that time was under the directorship of Dr. Wilbur Cohen, who attended the opening ceremonies. I think Dr. Beeson was able to keep President Griswold comfortable.

While completing my research at King's College, I went to a meeting of the Surgical Research Society and heard Roy Calne describe the work he had been doing with Dr. Joseph Murray in Boston. They had worked out a method for successfully transplanting kidneys in dogs from unrelated donors using 6-mercaptopurine to suppress the immune response. This drug and its successor, imuran, were developed at the Wellcome laboratories by Drs. George Hitchings and Gertrude Elion, for which they received the Nobel Prize. Dr. Elion visited Yale as a Tetelman fellow in 1995. My own work on cancer immunology, the ability to suppress the immune response, and the discovery of tolerance provided a great stimulus for a lasting interest in clinical transplantation.

After completing my appointment at King's, I decided to return to the United States rather than waiting around for a consultant's position to become vacant in London. Fortunately, a position at Yale had just been vacated by Dr. James Glenn, who had gone to Duke as chief of urology. Dr. Marvin Harvard, who was then Yale's chief of urology, needed an assistant and offered me a two-year appointment. I arrived in New Haven on St. Patrick's Day 1962. It was snowing lightly, a rather dismal sight after the blossoms I had left behind in London. It turned out that if I stayed for four years I would be eligible to take the urology boards without having to repeat any of the residency requirements, so my appointment was extended for four years. I first established a practice in infertility in collaboration with Dr. Lee Buxton, who was chief of obstetrics and gynecology and had a special interest in reproduction. Dr. Beeson offered me a position in his laboratory, where I worked with Dr. Vincent Andriole on the effects of increased intraluminal pressure on the promotion of infections in the

bladder. I enjoyed teaching the medical students on ward rounds and they honored me with the teaching prize, dubbing me "Lytton from Britain, the Lord of the Flies."

After I had been at Yale about four years, I was appointed chief of urology after a national search. Dr. Harvard had decided to go into private practice when the new chief of surgery, Dr. Jack Cole, insisted that every faculty member become full-time. Dr. Cole decided on three things that he wanted to develop in the department, one of which was transplantation. I told him that I had some experience in this area and that I was keen to start a transplant program. He was very supportive and backed me by providing the necessary resources and assisting personally with the first kidney transplant. In order to start a transplant program, you need to have a group of patients with renal failure maintained on dialysis. I collaborated with Dr. Howard Levitin, an experienced nephrologist, to develop a dialysis program for patients with kidney failure. We took over two small rooms on the second floor of the old hospital building, in the nephrology section, and acquired two of the early dialysis machines. We were fortunate to have the services of a very dedicated nurse who ran the machines.

We began in the summer of 1967 by dialyzing four patients a week. It is necessary to create a mode of vascular access in order to run the patient's blood through the semipermeable membrane in the machine to filter off the impurities and excess fluid. To provide access requires arteriolising the veins in the arm by creating a shunt between an artery and a vein so as to make the veins large enough for easy access with a large needle and increase the blood flow in the veins to provide enough volume for the dialysis process. The original dialysis machine was devised by Dr. Wilhelm Kolff, a Dutchman who was an intern in Holland at the time of the German invasion during World War II. He used sausage skins as the dialyzing membrane, but unfortunately many of his patients died of infection and problems with the technology. After the war he visited the Peter Bent Brigham Hospital in Boston and described his experiences. Two physicians at the Brigham designed an improved machine based on Dr. Kolff's idea, and by the mid-1950s dialysis was a relatively safe and readily available procedure. The first method of access we used was one devised by Dr. Belding Scribner in Seattle. An external device that connected an artery to a vein, it had the disadvantage that it constantly clotted and had to be frequently revised. We soon adopted a new method of anastomosing an artery and vein at the wrist to arteriolise the veins, and this became our standard procedure.

I soon realized that dialysis was not the answer for patients with chronic kidney disease, but was only a holding action. Despite the fact that dialysis was required three times a week, many patients did not feel well, were chronically anemic, and had psychological problems. They found working difficult, due to chronic fatigue, and were unable to travel very far. One of our early dialysis patients, a former Polish fighter pilot in the RAF, had difficulty tolerating the fluid and dietary restrictions. We decided that he would be a good candidate for our first kidney transplant patient, as he was not doing well on dialysis.

On December 18, 1967, three Yale undergraduate students were traveling south on I-91 from Hartford, when they ran into a patch of fog just outside New Haven, caused by the smoke from an old incinerator burning refuse. The car crashed and one student sustained a severe head injury. In hospital, he was subsequently found to be brain dead, with no hope of recovery. Permission was obtained from the family to remove his kidneys. The recipient was brought to the operating room to prepare him. As the chief resident and I were about to take out the kidneys in the recovery room of the operating suite, I was called to the phone. It was the chief administrator of the hospital, demanding to know who had given me permission to do a transplant in his hospital. I said something impolite, hung up, went back to the recovery room, and proceeded with the operation. Fortunately, all was forgiven the next day, as the patient was doing well and the newspapers reported it as a first for the hospital. The pilot returned to his native Poland for a visit, but after two years he died of an overwhelming infection following a perforation of the rectum, probably caused by the high doses of prednisone he was receiving to suppress the immune response.

There was one bad moment during the transplant operation: after I had completed the anastomosis of the blood vessels and the kidney began to make urine, I suddenly realized that the kidney was upside down. My heart sank, until I remembered from my physiology classes that it did not matter which way up organs were, since peristalsis overcame gravity. This is exactly what happened. Later it became common practice to put a kidney in upside down if it made the operation easier. We were soon performing two or three kidney transplants every month, which led to an exciting but difficult time. We were using large doses of steroids and imuran to suppress the immune response to get the kidney to survive. Unfortunately, many patients developed severe and unusual infections due to the suppression of their immune system, much as AIDS patients do today. It took a year or two to realize how serious the problem was and how to deal with it. We began to understand, using a variety of tests, when the rejection of a kidney became inevitable and not to persist with the immunosuppressive medications. We also learned that smaller doses were effective, thereby decreasing the morbidity and improving patient survival. Initially, 50 percent of kidney recipients survived for two years, but by restricting the use of the immunosuppressive drugs we soon had a 90 percent survival rate. So we were able to give a patient a second transplant.

We next recruited an immunologist to the team, as we needed to test for compatibility between donors and recipients, similar to typing for a blood transfusion. Two immunologists and I went down to Duke to see Dr. Bernard Amos, who was a pioneer in the field of tissue typing, to solicit his advice and obtain some sera to start our own laboratory. We recruited a young immunologist, Dr. Nancy Ruddle, who is now a distinguished professor of immunology, to perform the tissue typing and crossmatching. As we became more sophisticated, we achieved better results. I and three

colleagues in urology, together with several nephrologists, developed the program over the next fifteen years, which proved to be a very good team approach.

In 1983, two things happened. First, the field of transplantation expanded as other organs such as liver, pancreas, lung, and heart began to be transplanted. Second, a new immunosuppressant called cyclosporine became available and proved to be more effective in preventing rejection with fewer side effects. This led to an increased number of kidney transplants. At this juncture, one of my associates who had been primarily involved in the transplant program decided to leave for personal reasons. The chief of surgery at that time, Dr. Arthur Baue, decided to establish a separate transplant service and recruited a transplant surgeon to head it. Furthermore, with the increasing volume of urology, it became progressively more difficult for me to do both.

I should backtrack a little to the time when the federal Medicare program made dialysis available to everyone with renal failure. This resulted in a proliferation of dialysis units throughout the United States. It became the golden age for the nephrologists, as dialysis units proved to be very profitable. Unfortunately, enthusiasm overcame reason, and it became the conventional wisdom that dialysis was better and safer than transplantation, which was a retrograde step. In fact, an analysis of our patients showed that those on dialysis had the same mortality as those who underwent transplantation, but that the morbidity on dialysis was much greater: 50 percent of patients on dialysis died within five years from accelerated cardiovascular disease. These deaths were attributed to "natural causes," however, whereas a death following transplantation was due to the surgery. It was a difference of perception that often arises between internists and surgeons. Our patients after receiving a kidney transplant felt better and less fatigued, were physically independent, were not anemic, and had an improved sexual function. With the introduction of cyclosporine, the results of transplantation improved dramatically, about 85 percent surviving for five years.

This was also a time of major changes in the field of urology. Prior to 1980, 30 percent of the operations performed by urologists were for stone disease. In the early 1980s percutaneous puncture of the kidneys was developed, whereby the kidney was entered with a small tube passed through the skin. This tube carried a light and a lens so that the inside of the kidney could be visualized and stones could be located. These nephroscopes had an additional channel through which a probe could be passed to transmit either ultrasound or electrohydraulic energy to break up the stones into very small fragments so that they could be aspirated through the instrument or allowed to pass naturally, thus obviating the need for a big open procedure on the kidney.

Subsequently, a ureteroscope was designed. This was a very small instrument that could be passed through the patient's urethra into the bladder and then up into the ureters or kidney tubes, right up into the kidney. Stones stuck in the ureter or lodged in the kidney could be seen directly and disintegrated with an electrohydraulically energized probe or a laser, leaving fragments small enough to be passed naturally. At the same time, the extracorporeal shock-wave lithotripter, or stone-crushing machine,

was invented by engineers at the Dornier airplane company in Munich, Germany. In this procedure, stones in the kidney are broken up by a shock wave generated outside the body and focused on the stone in the kidney under X ray control, thus creating sufficient energy to break the stone into small pieces that the patient can pass. This has proved to be a major advance in the noninvasive treatment of renal stones.

In 1964, I became interested in replacing the bladder with an intestinal pouch joined to the urethra, so as to obviate the use of an external opening with an appliance. I constructed a neobladder in three patients at the Veterans Hospital in West Haven, making an artificial bladder out of intestine. One bladder succeeded and the patient lived for twenty-five years, urinating through his urethra. Unfortunately, the other two bladders failed and the patients had to be given external devices. We were unable to pursue this because at that time it became standard practice to irradiate the bladder prior to surgery for bladder cancer. The radiation precluded the use of intestine for reconstructive procedures due to impairment of the blood supply.

After twenty years it was determined that radiation did not improve the survival of patients with bladder cancer undergoing cystectomy. So in the early 1980s there was a renewed interest in bladder substitutes, stimulated by the work of Dr. Nils Kock from Sweden, who first described an operation to form a reservoir for patients who had lost their colons and subsequently modified this for use as a urinary reservoir. He was describing this rather complex operation, which didn't work very well, at the Urological Association. I was sitting next to a young surgeon from Ulm in Germany, whom I had known as a resident and who had worked out a technique for making a bladder substitute out of small intestine. He said that he had done three or four such operations and that the results were very good. I had already made five or six new bladders out of pouches created from large intestine, but while they functioned well, there was a problem with continence, especially at night. When I went home, I adopted the procedure my friend had described and it proved to have excellent results. Since then we have performed this operation on about two hundred patients following removal of the bladder, and this has been a significant advance in the surgical treatment of bladder cancer.

In 1986, I was offered the position of acting master of Branford College by Bart Giamatti. After that year, Benno Schmidt asked if I would like to continue as master of Jonathan Edwards College, where I served for ten years, until 1997. I continued my work in the Medical School but stepped down as chief of the urology section when I was appointed master. I became emeritus in 1997.