

Forty years of experience with liver transplantation

Thomas E. Starzl

Thomas E. Starzl Transplantation Institute, University of Pittsburgh Medical Center, Pittsburgh

Introduction

In 1963, I published an article in *Surgery, Gynecology, and Obstetrics* describing the first cases of human liver transplantation. The following is a copy of the original summary:

"A number of problems are described which must be surmounted for the clinical use of liver homotransplantation, based upon experience with 3 patients. The first patient died of hemorrhage during conclusion of the operation. The second and third patients lived for 22 and 7-1/2 days, respectively, both ultimately dying from multiple pulmonary emboli. Procurement of a viable and relatively undamaged donor organ [was] accomplished with the use of an extracorporeal circuit which perfuses and cools the [donor] liver immediately after death. It has been found necessary to decompress only the inferior vena cava during [the anhepatic] time with an external bypass from the inferior to the superior vena caval systems. During operation, a bleeding diathesis was regularly detectable. The use of the external bypass and [delayed] hypercoagulability may have contributed to the formation of the [pulmonary] emboli. Hepatic functions were immediately deranged [post-operatively], probably as the result of injury incurred during the transplantation, with progressive improvement thereafter. Biochemical evidence of [irreversible] homograft rejection was not observed, and at autopsy in the last 2 patients there was surprisingly good gross and histologic preservation of graft structure. Therapy with azathioprine, prednisone, and actinomycin C had forestalled the rejection process." (1)

These 3 attempts at human liver replacement followed 7yr of research involving organ preservation, surgical technique, and

the physiologic interrelationship of the liver with the pancreas and other intra-abdominal viscera. There were no means of preventing rejection at the beginning, but finally, the decision to go forward hinged on a strategy of immunosuppression developed in 1962 that ultimately revolutionised transplantation of all organs.

The genesis of the idea

Engraftment of an extra liver

The first recorded mention of liver transplantation in either scientific or lay literature was in 1955, when C. Stuart Welch (Albany, NY) described the transplantation of an auxiliary liver to the right paravertebral gutter of mongrel dogs (2). It was then thought that the volume rather than the source of blood delivered to the liver through its double blood supply was the critical determinant of normal hepatic homeostasis. Welch provided his allografts with a portal venous inflow of re-directed host inferior vena caval blood. When they rapidly atrophied, he incorrectly ascribed this to rejection only.

The relevance of hepatotropic factors

Between 1956-58, at the University of Miami where I was a surgical resident, I developed non-transplant dog models to test the hypothesis that the liver and the pancreas cross-modulated. The first evidence suggesting that this was true came from studying the effect on insulin/carbohydrate metabolism of altering portal venous inflow with classical Eck or reverse Eck fistula in alloxan diabetic dogs (3). One of the other procedures developed for the investigation was total hepatectomy (4), the first stage of

orthotopic liver transplantation.

Circumstances in Miami precluded further development (5). However, I performed orthotopic liver transplantation following host hepatectomy a few days after I moved to the Northwestern University (Chicago) in late June 1958, and repeated the operation once or twice/wk throughout the rest of the summer. I wondered if the poor performance of abnormally vascularised orthotopic livers (6) and the acute atrophy of Welch's auxiliary grafts could be explained by the transplants' lack of access to an unknown factor (suspected to be insulin) present in high concentration in portal venous blood (7).

Proving the insulin hypothesis and convincing sceptics that insulin was a true hepatic growth factor, required nearly 15yr (8, 9). In the end however, a precise explanation could be provided for the previously enigmatic pathophysiology of Eck's fistula (10). Eventually, the identification of a family of factors with insulin-like hepatotropic properties which controlled liver structure, function, and the capacity for regeneration defined the new field of hepatotropic physiology (Table 1, 9-20).

Orthotopic liver transplantation

In 1956, Jack Cannon of the University of California, Los Angeles was the first to report liver replacement, citing Welch's article as the stimulus for his work. Cannon alluded to "several successful operations" "without survival of the patient" [dogs] but with no details (21). Definitive information came from the canine experiments at Northwestern University (6, 22) and independently from the team of Francis D. Moore at the Peter Bent Brigham Hospital ("The Brigham", Boston) (23, 24). In contrast to the metabolic basis of the Chicago initiative, Moore's liver research was an offshoot of an institutional commitment to kidney transplantation that had begun a decade earlier.

Because effective immune suppression was not yet available in either laboratory, it was only possible to do little more than develop the operation and study the events of unaltered rejection. Between 1958 and early

Table 1. Growth factors revealed by studies in eck fistula models (1994)

	reference no.
Stimulatory	
Hormones:	
Insulin	9, 10
Growth factors:	
Cytosol substrate and ALR	11, 12, 13, 14
IGF II	15
TGF- α [▲]	15
HGF	15
Immunosuppressants:	
Cyclosporine	16
FK506	17
Immunophilins	
FKBP ₁₂	18
Inhibitory	
Growth factors:	
TGF β [■]	19
Immunosuppression:	
Rapamycin	20

▲ Mitogenic in tissue culture; ■ inhibitory in tissue culture

1960, 31 of these orthotopic procedures in dogs were performed in Boston and 80 in Chicago. All animals with ≥ 4 dy survival had histopathologic evidence of allograft rejection. The technical principles that emerged from this collective experience were:

- i. the need for splanchnic venous blood for optimal portal re-vascularisation (6);
- ii. core-cooling of the allograft by infusion of chilled solutions into the portal vein (6) as is practised clinically today, and
- iii. decompression of the occluded splanchnic and systemic venous pools into the upper vena caval system through external venous bypasses during the anhepatic stage (6, 24).

In addition to liver transplantation alone, modifications had been added by the end of 1959, including the multivisceral engraftment procedures (25, 26) that would be used clinically with essentially no change 3 decades later (27).

Movement to the clinic

The advent of immunosuppression

Total body irradiation (TBI) (28), adrenal cortical steroids (29), and the myelotoxic drug 6-mercaptopurine (6-MP) (30, 31) were shown to modestly prolong skin allograft survival in several animal species, between 1953-1959. Using TBI, successful kidney transplantation from fraternal (dizygotic) twin donors was accomplished in pts at the Brigham in January, 1959 and again 5mo later in Paris. Although the genetic barrier to transplantation had finally been breached in humans, liver transplant operations still had no conceivable application. Pre-operative conditioning of hepatic canine recipients with TBI appeared to preclude even peri-operative, much less extended, survival (32).

The pre-clinical kidney transplant studies of 6-mercaptopurine (6-MP) and its analogue, azathioprine, by the Englishman, Roy Calne (33, 34) with Joseph Murray at the Brigham (35, 36) and by Zukoski, Lee and Hume in Richmond (37) were viewed in a different light. Whereas kidney transplantation with long survival had never been possible in mongrel dogs previously, about 5% of animals given one or the other of the new drugs lived >100d. The objective of exploiting hepatic replacement to treat human liver disease was settled upon as a high priority during discussions in June, 1961, with William R. Waddell, who left the Massachusetts General Hospital to assume the chairmanship of surgery at the University of Colorado 5mo before I joined him from Chicago. This would require establishing a track record in renal transplantation, a procedure under formal clinical development in the United States only at the Brigham (Joseph Murray), the Medical College of Virginia (David Hume), and the University of California, Los Angeles (UCLA) where Willard Goodwin had put his program on hold.

Our clinical plans for both organs were shelved in January 1962. We had been following the tracks laid by the American kidney transplant pioneers and those in Paris (Rene Kuss and Jean Hamburger), only to realise eventually that we had joined them

in a therapeutic *cul-de-sac*. As late as March 1, 1963, the date of our first liver transplantation, only 6 recipients of kidney allografts in the world had survived ≥ 1 yr (one in Boston and 5 in Paris), all treated with TBI. The clinical results with azathioprine-based immunosuppression were little better (38, 39). Although the longest surviving kidney recipient treated solely with azathioprine or 6-MP based therapy from April 1960 to April 1962, was now 11mo post-operative, we knew from contact with Murray that the patient had deteriorating renal function.

An empirical treatment strategy

The experimental results in the Denver VA canine laboratory resembled those in Boston and Richmond until the summer of 1962 when a significant reproducible observation was made (40, 41). Delayed high doses of prednisone were shown to reliably reverse kidney (and, in pilot studies, liver) rejection that usually developed under primary azathioprine therapy. Most of the dogs died of complications of steroid-induced peptic ulceration, but several lived for years after discontinuation of prednisone and even when azathioprine was also stopped. Using the "double-drug cocktail", the Colorado clinical kidney transplant program was finally opened in November, 1962.

The first 10 cases were compiled rapidly and reported in the October 1963 issue of *Surgery, Gynecology, and Obstetrics* (42), preceding the article on liver transplantation in the same journal by 2mo (1). Four of the 10 renal recipients survived ≥ 25 yr including 2 who still bear the longest continuously-functioning kidney allografts in the world after a third of a century (43). It was obvious that these pts could return to an unrestricted environment on reduced-maintenance immunosuppression, suggesting that a state of relative host/graft non-reactivity had been accidentally but regularly induced by the renal allografts. The controversial, but as it turned out apposite, term "tolerance" (see later) was used to describe the change. This was the signal that triggered the liver trials.

The first 3 pts entered were: a moribund child with biliary atresia, a 48yr-old man with Laennec's cirrhosis and an unresectable

hepatoma, and a 62yr-old man with a completely obstructing bile duct carcinoma who had previously undergone bilateral above-knee amputations for peripheral vascular disease. Their high risk factors would preclude candidacy today. Although 2 survived the operation, none of them left the hospital alive.

The aftermath

The Colorado kidney center “mushroomed” overnight while the spark that had ignited it, liver transplantation, was consigned to a self-imposed 3.5yr worldwide moratorium by the end of 1963, following 4 more failures: 2 in Denver (7) and one each in Boston (44) and Paris (45). Three advances applicable to all organs were made during this period:

- i. the purification and clinical introduction in 1966 of antilymphocyte globulin (ALG) for use with azathioprine and prednisone in a triple-drug regimen (46);
- ii. preservation techniques that allowed livers to be stored *ex vivo* for one to 2d (47); and;
- iii. the demonstration (with Paul Terasaki of UCLA) that the quality of donor/recipient HLA-matching had little association with kidney transplant outcome (48). When the liver program was reopened in July, 1967, during the 2yr fellowship of Carl Groth (Stockholm), multiple examples of prolonged liver recipient survival were produced (49, 50).

A second liver transplant program was founded in 1968 by Roy Calne of Cambridge University and fostered by a long lasting inter-university collaboration with the hepatologist Roger Williams at King’s College Hospital, London. The American and English teams sustained each other for the next dozen years, joined in the early 1970’s by Rudolph Pichlmayr in Hannover and by Henri Bismuth in Paris, always tantalisingly close to making liver transplantation, a service. In Denver, 170 pts underwent the operation between 1963 and 1979. Although only 56 survived for 1yr, 25 were alive after 13 to 22yr at the end of 1992 (51), and 19 remain alive today with follow-ups of 17 to 27 years. The immuno-

suppressive regimens used in this period and subsequently are summarised in Table 2 (38, 42, 46, 52-61).

Although the feasibility of liver transplantation was established, the results remained unacceptable until Sir Roy Calne introduced cyclosporine in a clinical series that included 2 liver recipients (58). In a return to the past, the full potential of the new drug was realised for transplantation of the kidney (59), liver (60), and eventually all organs when it was combined with prednisone or used in triple-drug cocktails. The stampede to develop extra-renal transplant centres began. Nine years later, expectations moved up another notch with the substitution of tacrolimus for cyclosporine (61) (Table 2).

In retrospect

Most failed trials are doomed to be footnotes, if as much, in the pages of history. The 1963 liver transplant article escaped obscurity because it was based on principles which were enduring. Aside from the manifold details of the difficult operation, including the role of and complications from veno-venous bypass, there was already accurate insight into the importance of hepatotrophic physiology, and into the cause and treatment of metabolic acidosis. The only non-surgeon author, Kurt von Kaulla, anticipated the intra-operative coagulation disorders, monitored them with serial thromboelastograms, and provided treatment with blood components and epsilon amino caproic acid (an analogue of the currently used aprotinine). Lessons from the research preceding the clinical trial had already cross-fertilised to the kidney and were eventually exploited for all kinds of allografts: core-cooling by infusion of chilled intravascular fluids, *in situ* procurement procedures that presaged the standard flexible procedures of today (62), and the intravascular techniques required for close-quarter anastomoses.

However, none of the generically applicable advances, or all together, remotely approached in importance the realisation in the summer of 1962 that rejection could be engineered into prolonged allograft and

LECTURE

Table 2. Principal immunosuppressive drug regimens and adjuncts[▲] used clinically

Agents	Year described and reported (ref.)	Place	Deficiencies	Used for GI organs
Total body irradiation	1960 (52)	Boston	Ineffective, dangerous	No
Azathioprine	1962 (38)	Boston	Ineffective, dangerous	No
Azathioprine-steroids	1963 (42)	Denver	Suboptimal	Yes, liver
Thoracic duct drainage as adjunct	1963 (53)	Stockholm	Nuisance: requires 20 to 30 days pretreatment	Yes [■] , liver
Thymectomy as adjunct	1963 (54)	Denver	Unproven value	Yes, rarely in 1963
Splenectomy as adjunct	1963 (54)	Denver	No longer necessary	Yes, once commonly for liver
ALG as adjunct	1966 (46)	Denver	Suboptimal	Yes
CY substitute for azathioprine	1970 (55)	Denver	No advantage, except for patients with azathioprine toxicity	Yes [▼] , liver
Total lymphoid irradiation	1979 (56, 57)	Palo Alto, Minneapolis	Dangerous, extensive preparation, not quickly reversible	Yes [◆] , for liver
Cyclosporine	1978-1979 (58)	Cambridge	Suboptimal	Yes
Cyclosporine-steroids	1980 (59, 60)	Denver	Nephrotoxicity, rejection not always controlled	Yes
FK506-steroids	1989 (61)	Pittsburgh	Nephrotoxicity, rejection not always controlled	Yes

▲ Until 1966, these were developed with kidney transplantation and applied for livers. From 1966 onward, the liver increasingly became the dominant test organ.

■ It was not realised until much later that pre-treatment for 3 to 4 wk before transplantation was a necessary condition for effective use of TDD.

▼ These trials were summarised many years later with at least 10yr follow-up for surviving pts.

◆ By Professor J.A. Myburgh of Johannesburg

recipient survival by the strategic use of existing agents. The cyclic pattern of convalescence and the consequent achievement of

allograft acceptance remained enigmatic until it was discovered in 1992 that long-surviving organ recipients had donor

leucocyte chimerism in their blood, skin, lymph nodes, and other sites as distant as 3 decades post-transplantation (51, 63).

Then, it could be seen that the prototypic post-operative events following transplantation of all organs were the product of a double immune reaction; host-versus-graft (rejection) and graft-versus-host. Potentially tolerant "passenger leucocytes" of BM origin including pluripotent stem cells had migrated from organs and engrafted peripherally. This was the seminal mechanism of organ allograft acceptance which opened the door to the future. The epiphany (64) provided the missing link to the demonstration 40yr earlier by Billingham, Brent, Medawar (65) that it was possible to induce acquired immunologic tolerance.

References

1. Starzl TE et al. Homotransplantation of the liver in humans. *Surg. Gynecol. Obstet.* 1963; **117**: 659-676.
2. Welch CS. A note on transplantation of the whole liver in dogs. *Transplant. Bull.* 1955; **2**: 54.
3. Meyer WH Jr et al. The effect of Eck and reverse Eck fistula in dogs with experimental diabetes mellitus. *Surgery* 1959; **45**: 760-764.
4. Starzl TE et al. A new method for one-stage hepatectomy in dogs. *Surgery* 1959; **46**: 880-886.
5. Starzl TE. A Trip South. In: *The Puzzle People: Memoirs of a Transplant Surgeon*. Pittsburgh, Pennsylvania: University of Pittsburgh Press, 1992; 47-58.
6. Starzl TE et al. Reconstructive problems in canine liver homotransplantation with special reference to the postoperative role of hepatic venous flow. *Surg. Gynecol. Obstet.* 1960; **111**: 733-743.
7. Starzl TE et al. Immunosuppression after experimental and clinical homotransplantation of the liver. *Ann. Surg.* 1964; **160**: 411-439.
8. Starzl TE et al. The origin, hormonal nature, and action of hepatotrophic substances in portal venous blood. *Surg. Gynecol. Obstet.* 1973; **137**: 179-199.
9. Starzl TE et al. Intraportal insulin protects from the liver injury of portacaval shunt in dogs. *Lancet* 1975; **2**: 1241-1246.
10. Starzl TE et al. Effects of insulin, glucagon, and insulin/glucagon infusions on liver morphology and cell division after complete portacaval shunt in dogs. *Lancet* 1976; **1**: 821-825.
11. Francavilla A et al. Augmenter of liver regeneration (ALR): its place in the universe of hepatic growth factors. *Hepatology* 1994; **20**: 747-757.
12. Starzl TE et al. Growth-stimulating factor in regenerating canine liver. *Lancet* 1979; **1**: 127-130.
13. Francavilla A et al. Extraction and partial purification of a hepatic stimulatory substance in rats, mice and dogs. *Cancer Res.* 1987; **47**: 5600-5605.
14. Hagiya M et al. Cloning and sequence analysis of the rat augmenter of liver regeneration (ALR) gene: Expression of biology active recombinant ALR and demonstration of tissue distribution. *Proc. Natl. Acad. Sci.* 1994; **91**: 8142-8146.
15. Francavilla A et al. Screening for candidate hepatic growth factors by selective portal infusion after canine Eck's fistula. *Hepatology* 1991; **14**: 665-670.
16. Mazzaferro V et al. The hepatotrophic influence of cyclosporine. *Surgery* 1990; **107**: 533-539.
17. Starzl TE et al. Hepatotrophic effects of FK 506 in dogs. *Transplantation* 1991; **51**: 67-70.
18. Starzl TE et al. Hepatotrophic properties in dogs of human FKBP, the binding protein for FK506 and rapamycin. *Transplantation* 1991; **52**: 751-753.
19. Francavilla A et al. Effect on the canine eck fistula liver of intraportal TGF- β alone or with hepatic growth factors. *Hepatology* 1992; **16**: 1267-1270.
20. Francavilla A et al. Inhibition of liver, kidney, and intestine regeneration by rapamycin. *Transplantation* 1992; **53**: 496-498.
21. Cannon JA. Brief Report. *Transplant. Bull.* 1956; **3**: p. 7
22. Starzl TE et al. Studies on the rejection of the transplanted homologous dog liver. *Surg. Gynecol. Obstet.* 1961; **112**: 135-144.
23. Moore FD et al. One-stage homotransplantation of the liver following total hepatectomy in dogs. *Transplant. Bull.* 1959; **6**: 103-110.
24. Moore FD et al. Experimental whole-organ transplantation of the liver and of the spleen. *Ann. Surg.* 1960; **152**: 374-387.
25. Starzl TE and Kaupp HA Jr. Mass homotransplantation of abdominal organs in dogs. *Surg. Forum* 1960; **11**: 28-30.
26. Starzl TE et al. Homotransplantation of multiple visceral organs. *Am. J. Surg.* 1962; **103**: 219-229.
27. Starzl TE et al. The many faces of multi-visceral transplantation. *Surg. Gynecol. Obstet.* 1991; **172**: 335-344.
28. Dempster WJ et al. Prolongation of survival of skin homotransplants in the rabbit by irradiation of the host. *Br. J. Exp. Pathol.* 1950; **31**: 670-679.

LECTURE

29. Billingham RE et al. Effect of cortisone on survival of skin homografts in rabbits. *Br. Med. J.* 1951; **1**: 1157-1163.
30. Schwartz R and Dameshek W. The effects of 6-mercaptopurine on homograft reactions. *J. Clin. Invest.* 1960; **39**: 952-958.
31. Meeker WR et al. Prolongation of skin homograft survival in rabbits by 6-mercaptopurine. *Proc. Soc. Exp. Biol.* 1959; **102**: 459-461.
32. Starzl TE et al. Canine liver homotransplants: The effect of host and graft irradiation. *Arch. Surg.* 1962; **85**: 460-464.
33. Calne RY. The rejection of renal homografts: inhibition in dogs by 6-mercaptopurine. *Lancet* 1960; **1**: 417-418.
34. Calne RY. Inhibition of the rejection of renal homografts in dogs with purine analogues. *Transplant. Bull.* 1961; **28**: 445-461.
35. Calne RY and Murray JE. Inhibition of the rejection of renal homografts in dogs by Burroughs Wellcome 57-322. *Surg. Forum* 1961; **12**: 118-120.
36. Calne RY et al. A study of the effects of drugs in prolonging survival of homologous renal transplants in dogs. *Ann. NY. Acad. Sci.* 1962; **99**: 743-761.
37. Zukoski CF et al. The prolongation of functional survival of canine renal homografts by 6-mercaptopurine. *Surg. Forum* 1960; **11**: 470-472.
38. Murray JE et al. Kidney transplantation in modified recipients. *Ann. Surg.* 1962; **156**: 337-355.
39. Murray JE et al. Prolonged survival of human-kidney homografts by immunosuppressive drug therapy. *N. Engl. J. Med.* 1963; **268**: 1315-1323.
40. Starzl TE. The Rocky Mountains. In: *The Puzzle People: Memoirs of a Transplant Surgeon*. Pittsburgh, Pennsylvania: University of Pittsburgh Press, 1992; 83-95.
41. Marchioro TL et al. The role of adrenocortical steroids in reversing established homograft rejection. *Surgery* 1964; **55**: 412-417.
42. Starzl TE et al. The reversal of rejection in human renal homografts with subsequent development of homograft tolerance. *Surg. Gynecol. Obstet.* 1963; **117**: 385-395.
43. Braun WE. World Transplant Records 1995. Patients who currently have functioning transplants. Kidney (living-related). In: Cecka JM and Terasaki PI eds.; *Clinical Transplants 1995*, UCLA Tissue Typing Laboratory. Los Angeles, CA: 1996; p. 503.
44. Moore FD et al. Immunosuppression and vascular insufficiency in liver transplantation. *Ann. NY. Acad. Sci.* 1964; **102**: 729-738.
45. Demirleau et al. Tentative d'homogreffes hépatique (Attempted hepatic homograft). *Mem. Acad. Chir. (Paris)* 1964; **90**: 177-179.
46. Starzl TE et al. The use of heterologous antilymphoid agents in canine renal and liver homotransplantation and in human renal homotransplantation. *Surg. Gynecol. Obstet.* 1967; **124**: 301-318.
47. Brettschneider L et al. The use of combined preservation techniques for extended storage of orthotopic liver homografts. *Surg. Gynecol. Obstet.* 1968; **126**: 263-274.
48. Terasaki PI et al. Serotyping for homotransplantation. VI. Selection of kidney donors for thirty-two recipients. *Ann. NY. Acad. Sci.* 1966; **129**: 500-520.
49. Starzl TE et al. Orthotopic homotransplantation of the human liver. *Ann. Surg.* 1968; **168**: 392-415.
50. Starzl TE. *Experience in Hepatic Transplantation*. WB Saunders Company, Philadelphia, 1969; 1-545.
51. Starzl TE et al. Cell migration and chimerism after whole organ transplantation: The basis of graft acceptance. *Hepatology* 1993; **17**: 1127-1152.
52. Murray JE et al. Study of transplantation immunity after total body irradiation: Clinical and experimental investigation. *Surgery* 1960; **48**: 272-284.
53. Franksson C. Survival of homografts of skin in rats depleted of lymphocytes by chronic drainage from the thoracic duct. *Lancet* 1984; **1**: 1331-1332.
54. Starzl TE et al. Splenectomy and thymectomy in human renal transplantation. *Proc. Soc. Exp. Biol. Med.* 1963; **113**: 929-932.
55. Starzl TE et al. Cyclophosphamide and whole organ transplantation in humans. *Surg. Gynecol. Obstet.* 1971; **133**: 981-991.
56. Strober S et al. Transplantation tolerance after total lymphoid irradiation. *Transplant. Proc.* 1979; **11**: 1032-1038.
57. Najarian JS et al. Fractional total lymphoid irradiation (TL1) as preparative immunosuppression on high risk renal transplantation. *Ann. Surg.* 1982; **196**: 442-452.
58. Calne RY et al. Cyclosporin A initially as the only immunosuppressant in 34 recipients of cadaveric organs: 32 kidneys, 2 pancreases, and 2 livers. *Lancet* 1979; **2**: 1033-1036.
59. Starzl TE et al. The use of cyclosporin A and prednisone in cadaver kidney transplantation. *Surg. Gynecol. Obstet.* 1980; **151**: 17-26.
60. Starzl TE et al. Liver transplantation with use of cyclosporin A and prednisone. *N. Engl. J. Med.* 1981; **305**: 266-269.
61. Starzl TE et al. FK 506 for human liver, kidney and pancreas transplantation. *Lancet* 1989; **2**: 1000-1004.

LECTURE

62. Starzl TE et al. A flexible procedure for multiple cadaveric organ procurement. *Surg. Gynecol. Obstet.* 1984; **158**: 223-230.
63. Starzl TE et al. Cell migration, chimerism, and graft acceptance. *Lancet* 1992; **339**: 1579-1582.
64. Starzl TE et al. The lost chord: Microchimerism. *Immunol. Today* 1996; **17**: 577-584.
65. Billingham RE et al. "Actively acquired tolerance" of foreign cells. *Nature* 1953; **172**: 603-606.