Transplantation

The first successful human corneal transplant was around 1900 by Zirm, corneal xenografting having been tried as early as 1837 but without notable success. From the early 1950s, Calne envisaged kidney transplantation as practicable therapy; and surgical, immunological, and immunosuppressive advances made it so by the mid-1980s. By 1970, Barnard had pioneered heart transplantation; and liver transplantation was also under way. Xenografting from transgenic pigs is the challenge of the next decade, together with improvements in unrelated donor bone marrow transplantation.

By 1990, transplantation had achieved one-year graft survival rates of 80% or more for most solid organs, and has done so through surgical innovation, advances in immunosuppression, beneficial matching of kidney donor to recipient, better preservation solutions, and by studying center variation in donor rates as well as in transplant outcome. Epidemiological studies monitor malignancies secondary to immunosuppression. **Quality of life** as well as length of life (*see* **Life Expectancy**) is improved by transplantation.

Statistical science has underpinned most of this progress. Well-conducted randomized controlled trials (*see* **Clinical Trials, Overview**) of new immunosuppression therapies and preservation fluids have been published [23]; there has been occasional but critical early stopping of trials, because of overimmunosuppression, on the basis of **surrogate endpoints** of rejection episodes and major infections [14]. Proposals for the design and analysis of randomized trials with recurrent events [3] have had application in kidney transplantation. Two small trials in bone marrow transplantation were used to illustrate a new statistical measure to aid in the interpretation of published trials [1].

Beneficial matching [7, 10]; that is, the rules by which cadaveric donor kidneys have been exchanged in the UK, had a statistical basis and has persisted for 10 years up to 1997 when extended, also on statistical grounds, to favorable matching. Similar work on matching and matchability (see below) has been done independently by Mickey and colleagues [12, 22]. **Validation studies** have featured, whether in independent data sets (matching effects in distinct epochs of follow-up [9, 26, 28]) or by **meta-analysis** (DR mismatching in corneal transplantation [17]). Matchability score, dependent upon human leukocyte antigen (HLA) phenotype and exchange rules, for patients on the kidney transplant waiting list was introduced by Gilks [6, 8, 10] to summarize a patient's chance of getting a well-matched donor kidney in two or five years, and hence to aid individual decision-making on whether to accept or reject an offered kidney.

Special studies such as Corneal Transplant Follow-up Study (CTFS) and International Marrow Unrelated Search and Transplant (I MUST) Study have been set up to establish the core data that national registries (*see* **Disease Registers**) should seek to collect because they determine either waiting times [18], tissue allocation or prognosis [19] or quality of outcome, for which visual acuity is a natural measure [27]. In the I MUST Study, minimization, as in randomized trials, was adapted to select prospectively a **control** cohort of twice as many HLA-identical sibling transplants to correspond to the unrelated donor transplants in terms of marginal frequency for age group, diagnosis, risk, and transplant center. A second aspect of the design of the I MUST Study is noteworthy: in unrelated bone marrow donor searches, the patients for whom the search procedure finds an unrelated HLA-identical donor are effectively selected by "genetic randomization". A **time-dependent covariate** indicator (or several to account fully for nonproportionality of hazards (*see* **Proportional Hazards**) post transplant) can be switched on at that time and, by following all patients for whom an unrelated donor search was initiated, the effect of unrelated HLA-identical bone marrow transplantation against alternative management can be estimated in an **unbiased** manner. Effective **randomization** makes the proposed analysis even more powerful than the use of a time-dependent indicator to switch patients from "awaiting cardiac transplantation" to "recipient status" [21], leading to appropriate analyses of the cost-effectiveness of heart transplantation (*see* **Health Economics**).

Cardiothoracic transplantation has posed other important statistical problems, including analysis of repeated biopsies after cardiac transplantation [25], informative **censoring** of quality-of-life measurements [4], and individualization of cyclosporine dose by monitoring the variability of cyclosporine blood levels and also the patient's kidney and liver function [2]. **Kalman filter** techniques [20], applied to weight-adjusted reciprocal creatinine for detection of

2 Transplantation

kidney rejection episodes, were pioneering but did not become routine, perhaps because they were developed before cyclosporine. Sharples [11, 24] used a Gibbs sampling approach (*see* **Markov Chain Monte Carlo**) to modeling the longer-term risk of developing coronary occlusive disease after heart transplantation and thereby showed that there were particularly high transition intensities from mild to severe disease and from severe disease to death; thus, once mild disease developed, a patient's deterioration was rapid and research should focus on reducing progression from mild to severe disease.

Renal graft failure rates have been published in the UK on a center-anonymized basis since the early 1970s. Center variation has reduced considerably in the post-cyclosporine era [5] and further analysis by the confidence ranking methods developed by Goldstein & Spiegelhalter [13] would allow comparison of centers over calendar time, with or without adjustment for **case mix**, but taking account of center **covariates** such as whether a department of transplant immunology or transfusion medicine was responsible for tissue typing and cross-matching. In renal transplantation where centers' policies, let alone practice, on acceptance of older or asystolic donors, adherence to favorable matching, and retransplantation of older or diabetic or highly sensitized recipients may differ greatly, there is merit in no adjustment for case mix on the basis that the case mix is effectively center-determined.

Donor statistics are as important in transplantation as understanding the determinants of graft outcome. Confidential audit of all deaths in intensive care units in England and Wales in 1989–1990 [15, 16] showed that the second reason, after relatives' refusal, for missed suitable organs differed for the different organs–e.g. failure to ask in the case of kidneys but nonprocurement of offered suitable livers. The confidential audit also showed that even if all potential kidney donors in intensive care units became actual donors the need for cadaveric kidneys would not be met. Since then, the problem of nonprocurement of donor livers has been solved by designation of new centers but the shortage of donor kidneys has been exacerbated by the successful introduction of rear seat-belt legislation which saves lives.

References

[1] Begg, C.B. (1985). A measure to aid in the interpretation of published clinical trials, *Statistics in Medicine* **4**, 1–10.

[2] Best, N.G., Trull, A.K., Tan, K.K., Spiegelhalter, D.J., Cary, N. & Wallwork, J. (1996). Pharmacodynamics of cyclosporine in heart and heart-lung transplant recipients I: blood cyclosporine concentrations and other risk factors for cardiac allograft rejection, *Transplantation* **62**, 1429–1435.

[3] Cook, R.J. (1995). The design and analysis of randomized trials with recurrent events, *Statistics in Medicine* **14**, 2081–2098.

[4] Cox, D.R., Fitzpatrick, R., Fletcher, A.E., Gore, S.M., Jones, D.R. & Spiegelhalter, D.J. (1992). Quality of life assessment: can we keep it simple? (with discussion), *Journal of the Royal Statistical Society, Series A* **155**, 353–393.

[5] Gilks, W.R. (1987). Some applications of hierarchical models in kidney transplantation, *Statistician* **36**, 127–136.

[6] Gilks, W.R. (1991). Tissue matching and matchability in kidney transplantation, *Applied Statistics* **40**, 317–336.

[7] Gilks, W.R., Bradley, B.A., Gore, S.M. & Klouda, P.T. (1987). Substantial benefits of tissue matching in renal transplantation, *Transplantation* **43**, 669–674.

[8] Gilks, W.R., Gore, S.M. & Bradley, B.A. (1988). Matchability in kidney transplantation, *Tissue Antigens* **32**, 121–129.

[9] Gilks, W.R., Gore, S.M. & Bradley, B.A. (1990). Renal transplant rejection–transient immunodominance of HLA mismatches, *Transplantation* **50**, 141–146.

[10] Gilks, W.R., Gore, S.M. & Bradley, B.A. (1991). Predicting match grade and waiting time to kidney transplantation, *Transplantation* **51**, 618–624.

[11] Gilks, W.R., Clayton, D.G., Spiegelhalter, D.J., Best, N.G., McNeil, A.J., Sharples, L.D. & Kirby, A.J. (1993). Modelling complexity: applications of Gibbs sampling in medicine, *Journal of the Royal Statistical Society, Series B* **55**, 39–52.

[12] Gjertson, D.W., Terasaki, P.I., Takemoto, S. & Mickey, M.R. (1991). National allocation of cadaveric kidneys by HLA matching. Projected effect on outcome and costs, *New England Journal of Medicine* **324**, 1032–1036.

[13] Goldstein, H. & Spiegelhalter, D.J. (1996). League tables and their limitations: statistical issues in comparisons of institutional performance (with discussion), *Journal of the Royal Statistical Society, Series A* **159**, 385–444.

[14] Gore, S.M. (1995). Statistical thinking and when to stop a clinical trial, in *Logic in Medicine*, 2nd Ed., C.I. Phillips, ed. *British Medical Journal*, London, pp. 116–132.

[15] Gore, S.M., Taylor, R.M.R. & Wallwork, J. (1991). Availability of transplantable organs from brain stem

dead donors in intensive care units, *British Medical Journal* **302**, 149–153.

[16] Gore, S.M., Cable, D.J. & Holland, A.J. (1992). Organ donation from intensive care units in England and Wales: two year confidential audit of deaths in intensive care, *British Medical Journal* **304**, 349–355.

[17] Gore, S.M., Vail, A., Bradley, B.A., Rogers, C.A., Easty, D.L. & Armitage, W.J. (1995). HLA-DR matching in corneal transplantation: systematic review of published evidence, *Transplantation* **60**, 1033–1039.

[18] Howard, M.R., Gore, S.M., Hows, J.M., Downie, T.R. & Bradley, B.A. (1995). A prospective study of factors determining the outcome of unrelated marrow donor searches: report from the International Marrow Unrelated Search and Transplant Study Working Group on behalf of collaborating centers, *Bone Marrow Transplant* **15**, 499–503.

[19] Hows, J., Bradley, B.A., Gore, S., Downie, T., Howard, M. & Gluckman, E. (1993). The International Marrow Unrelated Search and Transplant (I MUST) Study, *Bone Marrow Transplant* **12**, 371–380.

[20] Knapp, M.S., Smith, A.F.M., Trimble, I.M., Pownall, R. & Gordon, K. (1983). Mathematical and statistical aids to evaluate data from renal patients, *Kidney International* **24**, 474–486.

[21] Mantel, N. & Byar, D.P. (1974). Evaluation of response-time data involving transient states: an illustration using heart transplant data, *Journal of the American Statistical Association* **69**, 81–86.

[22] Mickey, M.R. (1985). HLA matching in transplants from cadaver donors, in *Clinical Kidney Transplants*, P.I. Terasaki, ed. UCLA Tissue Typing Laboratory, Los Angeles, pp. 45–56.

[23] Ploeg, R.J., van Bockel, J.H., Langendijk, P.T., Groenewegen, M., van der Woude, F.J., Persijn, G.G., Thorogood, J. & Hermans, J. (1992). Effect of preservation solution on results of cadaveric kidney transplantation. The European Multicentre Study Group, *Lancet* **340**, 129–137.

[24] Sharples, L.D. (1993). Use of Gibbs sampler to estimate transition rates between grades of coronary disease following cardiac transplantation, *Statistics in Medicine* **12**, 1155–1170.

[25] Spiegelhalter, D.J. & Stovin, P.G.I. (1983). An analysis of repeated biopsies following cardiac transplantation, *Statistics in Medicine* **2**, 33–40.

[26] Thorogood, J., Persijn, G.G., Schreuder, G.M., d'Amaro, J., Zantvoort, F.A., van Houwelingen, J.C. & van Rood, J.J. (1991). The effect of HLA matching on kidney graft survival in separate post-transplantation intervals, *Transplantation* **50**, 146–150.

[27] Vail, A., Gore, S.M., Bradley, B.A., Easty, D.L. & Rogers, C.A. on Behalf of Corneal Transplant Follow-up Study Collaborators (1994). Corneal graft survival and visual outcome, *Ophthalmology* **101**, 120–127.

[28] Van Houwelingen, H.C. & Thorogood, J. (1995). Construction, validation and updating of a prognostic model for kidney graft survival, *Statistics in Medicine* **14**, 1999–2008.

S.M. GORE