

- Søltøft J, Gudmand-Høyer E, Krag B, Kristensen E & Wulff H R (1976) *Lancet* i, 270
- Southgate D A T (1976) In: *Fiber in Human Nutrition*. Ed. G A Spiller and R J Amen. Plenum Publishing Corporation, New York; p 73
- Southgate D A T & Durnin J V G A (1970) *British Journal of Nutrition* 24, 517
- Tainter M L & Buchanan O H (1954) *Annals of the New York Academy of Sciences* 58, 438
- Van Soest P J & McQueen R W (1973) *Proceedings of the Nutrition Society* 32, 123
- Weinreich J (1976) *Lancet* i, 810
- Williams R D & Olmsted W H (1936) *Journal of Nutrition* 11, 433

Infection in the renal transplant patient

Renal transplantation has now been accepted therapy for chronic renal failure for over a decade (Kincaid-Smith 1971, Hulme 1975) but two outstanding problems remain: rejection of the graft and infection in the recipient. Graft survival is sometimes purchased only at the expense of patient wellbeing, mainly because of the unselective immunosuppressive effects of azathioprine and corticosteroids. Severe infection is in fact the commonest cause of death in transplant recipients (Rifkind *et al.* 1967, Hill *et al.* 1967, Parsons *et al.* 1971, Myerowitz *et al.* 1972, Parsons *et al.* 1975, Gurland *et al.* 1976).

A changing pattern of infection has emerged since the early days of transplantation when, due to a general lack of dialysis support, a transplant was often the only alternative to death in uraemia. In early series, bacterial and fungal infections contributed almost equal numbers of deaths, and mortality from *Pneumocystis carinii* and other protozoal infection was considerable. Hill *et al.* (1967) analysed the cause of death in 60 of 113 patients transplanted between 1962 and 1965. Of the 'late' deaths (after twenty-seven days) 86% were due to sepsis, and in almost half (21 of 46) fungal infection was primarily responsible. Rifkind *et al.* (1967) in a follow-up study of 111 patients over 3–40 months found that 55 had died, and post-mortem examination revealed systemic fungal infection in 23. The predominant fungi were *Candida albicans* and *Aspergillus fumigatus*, often together, and it was stated that 'fungi and parasites have become pre-eminent as infecting agents'. In reporting 51 cadaver transplants performed between 1961 and 1971, Bach *et al.* (1973) found that, in their series, death from *Aspergillus fumigatus* was more common than from bacterial sepsis, but believed this to be contrary to general experience. In more recent reports (Hall *et al.* 1976) bacterial infection, usually with Gram-negative organisms, has greatly

predominated over fungal infection as the main cause of death.

In 54 patients transplanted at the Royal Free Hospital from February 1975 to July 1976, eight died, six due to sepsis. In none did post-mortem reveal a systemic mycosis.

The main factor in the control of fungal infection is probably the shorter duration of high-dose corticosteroid therapy (>40 mg/day prednisone) now used to prevent rejection. Anderson *et al.* (1973) showed that important risk factors in immunosuppressed patients included neutropenia, a moderate to severe degree of graft failure, with creatinine clearance less than 40 ml/min, and most significantly ($P < 0.001$) hyperglycaemia, defined as fasting blood sugar greater than 120 mg/100 ml. Hyperglycaemia is often the result of high-dose steroid therapy, and both predispose to fungal infection. In Rifkind's patients (Rifkind *et al.* 1967), clinical fungal infection occurred on average 67 days after transplantation, when the average dose of prednisone was 60 mg/day, whilst bacterial infection usually occurred in the first sixty days. Bach *et al.* (1973) related their high incidence of fungal infection to the number of treated rejection episodes. During 1969/70 these were managed by increasing prednisone to 320 mg/day for the first week, then halving the dose weekly until maintenance levels were reached. They thus employed high-dose steroid therapy for four weeks. During 1971 rejection episodes were treated with seven daily 1 gram doses of intravenous methylprednisolone, with no increase in oral prednisone dosage. The patients treated by short-term increase of oral prednisone had significantly more fungal and nocardial infections, which were further increased if treated rejection episodes were multiple or occurred more than 30 days after transplantation. 60% of the systemic fungal infections developed within 42 days of rejection although, as the authors pointed out, fungal infections may occur long after this period.

Pneumocystis carinii infection is also associated with high-dose steroid therapy (Rifkind *et al.* 1967). At post-mortem, 10 of 51 patients had developed pneumocystis pneumonia 69–599 days after transplantation. These patients had received high-dose steroid therapy for a mean of 113 days as compared to 49 days for all fatal cases. In contrast, no pneumocystis infection occurred in the 54 Royal Free patients, and in only 1 of 40 deaths in another series (Hall *et al.* 1976). Three conclusions may therefore be drawn: (1) Fungal/parasitic infections tend not to occur until several weeks after a transplant. (2) Prolonged or frequent intermittent high-dose steroid therapy predisposes to

them. (3) The greater the number of treated rejection crises the greater the risk of morbidity and mortality from fungal infection.

At the Royal Free Hospital, prednisone dosage is reduced to maintenance levels (20 mg/day) by the 42nd postoperative day. Rejection crises are managed by giving no more than 3 g intravenous methylprednisolone, over three days, with no elevation of 'background' steroid dosage. At other centres (personal communications), similar low-dose steroid regimes are used.

Broad-spectrum antibiotics, by suppressing the patient's own bacterial flora, predispose to fungal infection, and the time scale of early bacterial and late fungal infection leads one to suggest that the greater the efficiency and specificity with which early bacterial infections (for example of the urinary tract) are dealt with, the less likely is fungal infection to supervene. Certainly antibiotics such as gentamicin are superior in this respect to antimicrobials of twelve years ago (Noone *et al.* 1974, Hricko *et al.* 1973, Hill *et al.* 1967).

As the prophylactic use of high-dose steroid therapy is further shortened or perhaps abandoned altogether, the incidence of bacterial infection may also decline. In 100 transplants carried out between 1968 and 1976 (McGeown *et al.* 1977), there were no deaths from sepsis in the first 60 days after transplantation. Oral prednisone was begun at a dose of 20 mg/day, and only increased during rejection episodes. Graft survival was not adversely affected.

Once serious infection has occurred in immunosuppressed patients it may be impossible to eradicate. Thus the emphasis must be on prophylaxis, which begins upon acceptance for transplantation. Care is taken over asepsis, particularly around blood access sites and peritoneal dialysis catheters. The particular importance of infection in the urinary tract has been stressed by Myerowitz *et al.* (1972). In 53 episodes of bacteraemia in 140 patients, the primary focus was in the urinary tract in 60%, and in over half this was associated with urinary leakage or obstruction. Among 15 Royal Free patients in whom sepsis developed after a transplantation, there were 19 separate urinary tract infections within the first six weeks. In six of these the organism was also isolated from the blood, and one patient died. Hence, the pre-transplant removal of infective reservoirs such as hydronephrotic or pyelonephrotic kidneys, particularly when vesicoureteric reflux is demonstrated, and the prompt detection and treatment of urinary tract complications following transplantation (Hricko *et al.* 1973, Williams *et al.* 1970) are essential.

During and following the transplant operation, the patient faces unique hazards: the graft itself can be a source of infection, either by bacterial contamination during removal from the donor (Fernando *et al.* 1976) or by pre-existing cytomegalovirus infection in the donor kidney (Andersen & Spencer 1969). Postoperative acute renal failure enhances the effects of azathioprine, and severe hypogammaglobulinaemia (Ku *et al.* 1973) or granulocytopenia (Starzl 1964) may occur rapidly. Pyrexia of infection is often misinterpreted as being due to rejection, and treatment with methylprednisolone will augment immunosuppression and promote infection. Many bacterial infections follow a treated rejection crisis, when renal function is worst and immunosuppression heaviest. Clinically, acute rejection and bacteraemia may be initially indistinguishable. Rigors and hypotension point to the latter, although fever, malaise and oliguria may occur also with rejection. Tenderness and swelling over the graft may result from a ureteric leak, and does not automatically signify rejection. Pyrexia occurring in the presence of neutropenia strongly suggests an infective cause.

Bacterial infections often persist despite drainage and appropriate antibiotics. Of 8 patients who died after transplant, 5 had Gram-negative infections. The average period from transplant to death was 155 days (range 80–190 days) although septicaemia had first occurred within 30 days of operation. All had repeated courses of antibiotics with often very high blood levels, and three had wound abscesses which were adequately drained. Nevertheless, two patients died 184 and 190 days after transplant, due to bacterial invasion of the iliac vessels with aneurysm formation and fatal haemorrhage.

Rapid isolation of the infection agent(s) is thus essential, and aggressive diagnostic techniques to isolate the organism may be required. Pulmonary infections, for example, are often mixed, and mere sputum cultures may be inadequate. Bronchial washings, pleural aspiration/biopsy and lung biopsy (for e.g. *Pneumocystis carinii*) yield a far higher percentage of positive diagnoses (Vereerstraeten *et al.* 1975). Blood cultures are the centrepiece of investigation, and should be done repeatedly. Treatment should be instituted as soon as bacteraemia is suspected, without waiting for bacteriological confirmation. Many anti-infective agents are potentially noxious and unsatisfactory (for example, pentamidine for *Pneumocystis carinii* (Western *et al.* 1970) and amphotericin B for aspergillosis and candidiasis (Ultz 1963)), and should be accompanied by a reduction in immunosuppressive therapy. The correct interpretation of

pyrexia is the transplant surgeon or physician's most vexing problem, and will often determine the fate of both patient and graft.

During the past ten years, improved tissue-matching, integrated dialysis/transplantation programmes, and the introduction of more potent antimicrobial agents, have led to improved survival of patients (Matthew *et al.* 1975). The need for prolonged intensive immunosuppression has been reduced, and grafts in infected patients have more readily been removed. Nevertheless, the overall figure of 30–40% of mortality due to infection has not changed (Parsons *et al.* 1975, Gurland *et al.* 1976). Infection in the transplant patient is an unconquered problem. The balance between treatment and infection is precarious, and until the ideal immunosuppressive agent or technique is found, it will remain so.

P R Walker
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References

- Andersen H K & Spencer E S
(1969) *Acta Medica Scandinavica* **186**, 7–19
- Anderson R J, Schafer L A, Olin D B & Eickhoff T C
(1973) *American Journal of Medicine* **54**, 453–460
- Bach M C, Sahyoun A, Adler J L, Schlesinger R M, Breman J, Madras P, P'eng F & Monaco A P
(1973) *Lancet* **i**, 180–184
- Fernando O N, Higgins A F & Moorhead J F
(1976) *Lancet* **ii**, 368
- Gurland H J, Brunner F P, Chantler C, Jacobs C, Schärer K, Sellwood N H, Spies G & Wing A J
(1976) *Dialysis, Transplantation, Nephrology* **13**, 3–58
- Hall C L, Sansom J R, Obeid M L, Blainey J D, Robinson B H B, Mackintosh P, Dawson-Edwards P & Barnes A D
(1976) *British Medical Journal* **i**, 547–550
- Hill R B, Dahrling B E, Starzl T E & Rifkind D
(1967) *American Journal of Medicine* **42**, 327–334
- Hricko G M, Birch A G, Bennett A H & Wilson R E
(1973) *Annals of Surgery* **178**, 609–615
- Hulme B
(1975) In: *Recent Advances in Renal Disease*. Ed. N F Jones. Churchill Livingstone, Edinburgh & New York; p 222
- Kincaid-Smith P
(1971) In: *Cecil-Loeb Textbook of Medicine*, 13th edn. Ed. P B Beeson & W McDermott. Saunders, Philadelphia; p 1168
- Ku G, Varghese Z, Fernando O N, Baillod R, Hopewell J P & Moorhead J F
(1973) *British Medical Journal* **iv**, 702–707
- Matthew T H, Marshall V C, Vikraman P, Hill A V L, Johnson W, McOmish D, Morris P J & Kincaid-Smith P
(1975) *Lancet* **ii**, 137–140
- McGeown M G, Kennedy J A, Loughbridge W G G, Douglas J, Alexander J A, Clarke S D, McEvoy J & Hewitt J C
(1977) *Lancet* **ii**, 648–651
- Myerowitz R L, Medeiros A A & O'Brien T F
(1972) *American Journal of Medicine* **53**, 308–314
- Noone P, Pattison J R & Davies D G
(1974) *Postgraduate Medical Journal* **50**, Suppl. 7, 9–16
- Parsons F M, Brunner F P, Burck H C, Gräser W, Gurland H J, Härten H, Schärer K & Spies G W
(1975) *Dialysis, Transplantation, Nephrology* **11**, 3–67
- Parsons F M, Brunner F P, Gurland H J & Härten H
(1971) *Proceedings of the European Dialysis and Transplant Association* **8**, 3–25
- Rifkind D, Marchioro T L, Schneck S A & Hill R B jr
(1967) *American Journal of Medicine* **43**, 28–38
- Starzl T E
(1964) *Experience in Renal Transplantation*. Saunders, Philadelphia & London; p 181
- Ultz J P
(1963) *New England Journal of Medicine* **268**, 938–940
- Vereerstraeten P, De Koster J P, Vereerstraeten J, Kinnaert P, Van Geertruyden J & Toussaint C
(1975) *Dialysis, Transplantation, Nephrology* **11**, 300–307
- Western K, Perera D R & Schultz M G
(1970) *Annals of Internal Medicine* **73**, 695–702
- Williams G, Birch A G, Wilson R E, Harrison J H & Murray J E
(1970) *British Journal of Urology* **42**, 21–27

Tonsillectomy

Anyone venturing into the jungle surrounding tonsillectomy deserves praise. Dr Ingle Wright (p. 112) is treading a well-trodden path, although her destination never becomes absolutely clear. Past workers have been this way before and, for example, Eggston & Wolff (1947) wrote 'After having examined many thousands, it is difficult to establish if tonsils are pathologic. One cannot offer patients any definite diagnosis either bacteriologic or pathologic when the tonsillar structures are diseased'. It would seem that that era is still with us. Dr Wright's findings of age and sex distribution are interesting but available from many sources other than pathology departments.

While it is not a matter central to Dr Wright's paper, the functions of these aggregations of lymphoid tissue and the price one may pay for their loss, have never been far from the minds of otolaryngologists. It has long been apparent that the tonsils and adenoids, by virtue of their position astride the entrance to air and food passages, might comprise a unique fragment of the lymphoid apparatus. By the same token, it is apparent that their loss produces no marked degree of immune crippledom, but sophisticated studies reveal minor losses (Ogra 1971). From time to time the alarm bells ring; a higher than expected incidence of Hodgkin's disease is reported in adenotonsillectomized persons (Vianna *et al.* 1971). A moment's reflection suggests that cause and effect cannot be deduced, since the ailments prompting the surgery also may have had a hand, somewhere along the line, in initiating the development of the lymphoma. The mind boggles at the size of the prospective trial designed to unravel this one – the retrospectroscope offering no solutions!