### *Primary Immunodeficiency*

These are rare often life-threatening diseases which nevertheless have contributed greatly to our understanding of the immune system. X-linked agammaglobulinaemia is the most common of these disorders and is caused by a failure of cell signalling and maturation of B cells with failure of the light chain gene rearrangement which normally allows the formation of immunoglobulin molecules. Circulating B cells are markedly reduced or absent, there is a failure to make antibody and once maternal antibody has declined the children become susceptible to recurrent episodes of bacterial infection.

Di George's syndrome occurs when there is failure of development of the thymus from the branchial arches, usually as a consequence of a deletion affecting chromosome 22q11, so there is no suitable microenvironment for the maturation of T cells. The patients are vulnerable to infection by viruses, fungi and parasites. There is also a marked propensity to infection by mycobacteria. Severe combined immune deficiency is the situation where both the T cell and B cell components of the immune system are defective. The affected individuals are susceptible to a whole range of microorganisms and frequently succumb to infection as infants. Several different genetic abnormalities have been demonstrated in these patients and different patterns of inheritance.

### *Secondary Immunodeficiency*

Human immunodeficiency virus infection and acquired immune deficiency syndrome (AIDS) are a common worldwide cause of secondary immunodeficiency. The pathogenesis of this infection is dealt with in detail in Chapter 19. Briefly, HIV transmitted by blood or during sexual intercourse is capable of infecting the helper T cells of CD4 class. There is progressive and eventually profound loss of these helper T cells. This has detrimental effects on the capacity of the affected patients to mount an effective immune response. Helper T cells drive both cell-mediated and humoral responses. People with AIDS acquire a progressive susceptibility to a range of infections with various clinical consequences. They may develop intractable viral infections such as cytomegalovirus infections, but they are also often infected with tumour-promoting viruses – papilloma virus causing squamous carcinomas, Epstein–Barr virus (EBV) causing lymphomas and human herpes virus 8 causing Kaposi's sarcoma. They may develop overwhelming tuberculosis, which often lacks the formation of typical granulomas. They acquire protozoal infestation by organisms such as *Pneumocystis jirovecii* (*carinii*) or *Toxoplasma* species. Infective complications, including viral-induced malignancy, are the most common causes of death in the HIV/AIDS population.

Immunosuppression may result from specific therapy or may occur as a complication of therapy. To maintain the survival of transplanted organs, drugs and other therapies are administered to suppress the immune response. The main immunosuppressive drugs are designed to suppress specifically the afferent arm of the immune response, blocking the activation of immune cells reactive to the allogeneic

## 2.1 SPECIAL STUDY TOPIC

## PATHOGENESIS AND RATIONALE FOR THE MANAGEMENT OF POST-TRANSPLANT LYMPHOPROLIFERATIVE DISORDER

A 32-year-old man received a renal transplant for end-stage renal failure because of glomerulonephritis. He was immunosuppressed with tacrolimus and oral steroids. His clinical course was complicated by two acute rejection episodes. For these he was treated with high-dose steroids that on both occasions successfully suppressed the rejection. However, because of these episodes mycophenolate mofetil was added to his immunosuppression treatment in an attempt to prevent further rejection. Mycophenolate mofetil suppresses the proliferation of both B and T lymphocytes by the reversible inhibition of inosine monophosphate dehydrogenase, a key enzyme in the *de novo* synthetic pathway of guanine (Sievens *et al.* 1997).

Several months later the patient presented with enlarged lymph nodes in his groin. A biopsy was done on one of these. It showed a florid lymphoproliferative disorder, which was demonstrated to be of B-lymphocyte origin, to be monoclonal and the cells expressed Epstein–Barr virus (EBV) antigen. A diagnosis of post-transplant lymphoproliferative disorder (PTLD) in the monoclonal phase was made. This is an EBV-driven proliferation of B cells which progresses to a type of lymphoma (see Chapter 8). EBV survived in the infected B cells because the T cells that clear the body of the virus in a healthy individual were being suppressed by his transplant immunosuppression drugs.

Although PTLD is regarded as a neoplasm, chemotherapy is not usually the first choice of treatment as this would further immunosuppress the patient; instead the patient's transplant immunosuppression drug doses should be reduced. This was done with close monitoring of the lymph nodes, peripheral blood cells and transplant function. After 6 months he had no rejection episodes, his lymphadenopathy had regressed and his peripheral blood was free of EBV positive B cells. This is an instance of a viral-induced tumour in the context of immunosuppression being treated by allowing the host defence to clear the relevant virus.

### Reference

Sievens TM, Rossie SJ, Ghobrial RM, *et al.* Mycophenolate mofetil. *Pharmacotherapy* 1997; **17**: 1178–1197.