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## Graft-versus-host disease following liver transplantation

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Graft-versus-host disease (GVHD) is a well recognized complication of allogeneic bone marrow transplantation[1,2], but has also been described after small bowel[3], pancreatico-splenic[4], heart-lung transplantation[5] and transfusion of non-irradiated blood products to immunocompromised patients[6,7]. Minor manifestations of immunological reactivity of the transplanted liver towards the recipient have also been recognized for some time. Transient haemolytic anaemia occurring 2-3 weeks after ABO compatible, but different ABO type is the commonest form[8-10] although IgG production by hilar lymph nodes has also been described[11]. Graft versus host reactions of major clinical significance after orthotopic liver transplantation (OLT) were initially considered rare, but are now being reported with increasing frequency[12-16].

Billingham[17] proposed that for GVHD to occur there have to be histocompatibility differences between donor and recipient, the transplanted graft must contain immunologically competent cells and the recipient must be immunocompromised and incapable of mounting an effective response to destroy transplanted lymphocytes.

Acute GVHD occurs within 2 months of organ transplantation and targets the epithelium of the skin and hair follicles, intestine and the immune system which show increased expression of class I and II antigens in association with an infiltrate of donor CD4+ and CD8+ lymphocytes[18]. The liver itself is not involved in GVHD after liver transplantation as it is recognized as 'self' by the transplanted lymphoid tissue[19]. The initial signs of acute GVHD are fever and the development of a pruritic maculo-papular rash which is most marked on the palms, soles and ears. The rash progresses in severe cases to erythroderma and the formation of bullae with desquamation. Nausea and diarrhoea develop as a result of the mucosal injury to the intestinal crypts. Pancytopenia secondary to bone marrow hypo- or aplasia results from the destruction of haemopoietic stem cells.

Acute GVHD delays the patient's immunological recovery and increases the risk of supervening infection. Immunocompetence is further reduced by the immunosuppressant drugs used to treat GVHD. There is an association with cytomegalovirus (CMV) infection, but whether this reflects the severity of immunosuppression or facilitates the development of GVHD by further depressing patient immunocompetence is not clear. Herpes simplex virus positive serology has also been associated with an increased risk of GVHD after bone marrow transplantation, possibly by acting as a minor transplant antigen and enhancing the initial alloreactivity of the graft[20]. It has not been reported after liver transplantation. A link has been suggested between GVHD and therapy (which included alpha-interferon) to prevent recurrent hepatitis B infection after liver transplantation[16].

Immunocompromised patients, for example, presenting with fulminant hepatic failure[13], with lymphopenia secondary to alcoholic liver disease[11] or who are receiving steroid therapy appear to be predisposed to GVHD. Donor lymphocytes appear to survive for at least 38 days[15].

The diagnosis of GVHD should be suspected in any patient developing a rash and fever following OLT. Examination of a skin biopsy and bone marrow aspirate may support the diagnosis, but will not exclude viral infections, particularly CMV, or drug reactions. The diagnosis may be confirmed by the demonstration of chimerism of donor and recipient HLA by typing peripheral lymphocytes[12-16].

GVHD has been treated with methylprednisolone and anti-lymphocyte immunoglobulin in addition to cyclosporin A, but with limited success. FK506 is a

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relatively new macrolide immunosuppressive agent which has been used successfully in the management of severe GVHD following human[21] and rat bone marrow transplantation and small bowel transplantation[22-24]. However, little has been published regarding its use in treating GVHD after liver transplantation. FK506 works by inhibiting lymphokine release and proliferation of lymphocytes in response to alloantigens at much lower concentrations than cyclosporin A. Other treatments which have been tried include thalidomide and monoclonal antibodies against T-cell lymphokines, interleukin-2 and tumour necrosis factor.

Early recognition of GVHD may improve survival of patients; however, the majority have been recognized late and have died from overwhelming sepsis. Recognition and treatment of coexistent CMV infection is important and prophylactic administration of Ganciclovir should be given. The precise role of FK506 in the prevention or treatment of established GVHD needs to be determined. The recognition of an increasing number of cases of GVHD following liver transplantation suggests that it may occur more commonly than previously thought and with greater clinical awareness milder forms of GVHD may be recognized.

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## The portrayal of the physician in non-medical literature - the physician and his family

The fictional physician is rarely a happily married man helping the children with their homework or sharing the day's experiences with his wife. Even before the current epidemic of marital breakdowns, physicians were frequently portrayed as single, divorced or widowed. A few fictional physicians have six or eight children[1,2] but one hears little about these children and from the point of view of the plot they are irrelevant.

Dr Herzenstube, the compassionate country doctor in The Brothers Karamazov was 'a confirmed bachelor all his life'[3]. Doctor Chebutykin in Chekhov's 'Three Sisters'[4] is an ignorant, drunken clown who 'never got round to marrying'. Ravic, the alcoholic refugee

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