SUMMARY

Nowadays, orthotopic liver transplatation is an accepted therapeutic possibility for non-curable end-stage liver diseases. Despite the impressive improvements achieved within thirty years of liver transplantation the procedure is still accompanied by serious complications. One of the complications is graft rejection. Similar to other organ grafts the liver graft is also subject to the host's alloresponse although the liver tends to be less vividly rejected as compared with the kidney graft. Hyperacute rejection is either non-existent or extremely rare although the liver is regularly transplanted between HLA mismatched individuals. Acute rejection is a regularly present especially in the first months after transplantation. In most cases this complication responds well to treatment. The prognosis of chronic rejection is less favourable because sofar anti rejection treatment does not seem to influence the course leaving retransplantation as the only therapeutic possibility.

This thesis is focussed upon graft rejection, based on studies on serial graft biopsies. Biopsy monitoring of the transplanted liver has proven to be a safe and accurate diagnostic aid.

In chapter I the morphology of acute rejection in biopsies of liver allografts obtained in the first two weeks after transplantation (Tx) was analyzed. Material from patients maintained on conventional immunosuppressive therapy consisting of azathioprine and prednisone (AZA, Groningen) was compared to that of patients receiving cyclosporine A and prednisone (with or without azathioprine) in low doses (CSA, Minneapolis). Follow up biopsies ranged from 3 weeks to one year after Tx. Time zero biopsies and/or pretransplant biopsies served as baseline histology. Our data revealed an identical morphologic picture during acute rejection early after Tx in both patient groups except for a more marked degree of venous endothelialitis and hepatocyte ballooning in the Minnesota material. The follow up biopsies suggested a spontaneous resolution of these early rejection episodes without anti rejection treatment in 6 of the 10 AZA patients. No differences in the long term survival rate between the CSA and AZA treated patients were observed.

The study in chapter II documents MHC Class I and II expression during early acute rejection of human liver grafts. Serial graft biopsies were studied. 10 patients received azathioprine (AZA) and prednisone; 6 patients were treated with quadruple therapy (azathioprine, cyclosporine A, prednisone and cyclophosphamide). To study the specificity of changes in MHC antigen-expression, biopsies of 6 patients with minor or no morphological abnormalities served as controls. In addition, phenotypes of inflammatory cells present during rejection were analyzed using a panel of monoclonal antibodies.

Our results show that during acute rejection expression of MHC Class I and II antigens increased significantly in both the AZA treated patients and those treated with quadruple therapy, in a similar pattern. There was enhanced MHC

Class I expression on hepatocytes, bile duct epithelium and sinusoidal endothelium, and Class II antigen on Kupffer cells and sinusoidal endothelium. Bile duct epithelium was consistently positive for Class II antigen; no significant difference with the non-rejection group was observed. T cells are the predominant inflammatory cells during rejection with equal quantities of CD4+ and CD8+ cells. A majority of the infiltrating T cells shows expression of Class II antigen but does not react with anti Interleukin-2 receptor antibody. This may be the result of immunosuppressive therapy or a simple reflection of the temporary expression of Interleukin-2 receptors during lymphocyte activation.We hypothesized that the induction of MHC antigens on bile duct epithelium preludes to rejection whereas the expression on hepatocytes represents an epiphenomenon.

The disappearance of certain cell populations of donor origin and their replacement by recipient-specific cells constitutes a possible explanation for the relatively mild course of acute rejection despite lack of MHC compatibility in human orthotopic liver transplantations. In chapter III, graft biopsies of 12 OLT patients from a total of 42 patients were studied for expression of MHC antigens after transplantation using monoclonal antibodies to HLA-ABC and HLA-DR. The patients were selected based upon donor-recipient mismatching for HLA-A2, B7, Drw52, or DQw1. Monoclonal antibodies to these 4 polymorphic HLA antigens and monoclonal antibodies to HLA-ABC and -DR were applied to frozen tissue sections and visualized using an immunoperoxidase technique. Expression of HLA-ABC and -DR on, respectively, hepatocytes and bile duct epithelium were observed in posttransplant graft conditions such as viral infections, cholangitis, and acute rejection. However, no specific pattern of MHC antigen distribution was observed for these various pathological graft conditions.

Disappearance of DR-positive Kupffer cells of donor origin and immigration of recipient ones was encountered in the early posttransplant biopsies. This Kupffer cell replacement coincided with a reversible episode of acute rejection. The disappearance of highly immunogenic cellular components as HLA-DR positive Kupffer cells of graft origin may be one of the mechanisms contributing to the mild rejection response observed in human liver transplantation.

In chapter IV four cases of chronic rejection were selected from a total of 48 patients who underwent orthoptic liver transplantation in Groningen from 1979 to 1985. The histopathologic changes in these endstage livers (two removed at ReTx, two at autopsy) consisted of obliterative arterial vasculopathy with intimal fibrosis and subintimal accumulation of lipid-laden macrophages ("foam cells"), sinusoidal foam cells, portal enlargement with fibrosis, severe cholestasis, and a decreased number of portal bile ducts with damage of the remaining and larger ones. Comparison of percutaneous serial graft biopsies from each of these four cases obtained before and 1, 3 to 4, and 6 to 8 weeks following OLT (a total of 16 biopsies) with time-matched biopsies of six cases with SO (22

biopsies) did not reveal morphologic differences between both groups, except for the appearance of sinusoidal foam cells in three of the four cases with ultimate CR. It is concluded that sofar, no predictive histologic features are available for chronic rejection.

The pathogenetic mechanisms of chronic liver allograft rejection is unknown. Recent studies reported the influence of lymphocytotoxic antibodies and HLA mismatching on the development of chronic rejection.

In chapter V the influence of these two factors are investigated in 9 patients with chronic rejection out of 83 orthotopic liver transplantations. The results of this study show that patients with a positive lymphocytotoxic crossmatch due to donor specific antibodies are significantly more likely to develop chronic rejection while HLA-DR mismatch also seem to be a contributary factor. It is hypothesized that host anti-idiotypic antibodies might be an important aid in the defense against the development of chronic rejection.

In the general discussion, finally, the findings in the foregoing chapters are discussed in the context of the 3 phases of alloresponse: alloantigen presentation and recognition, T cell activation and generation of effector cells and graft destruction.