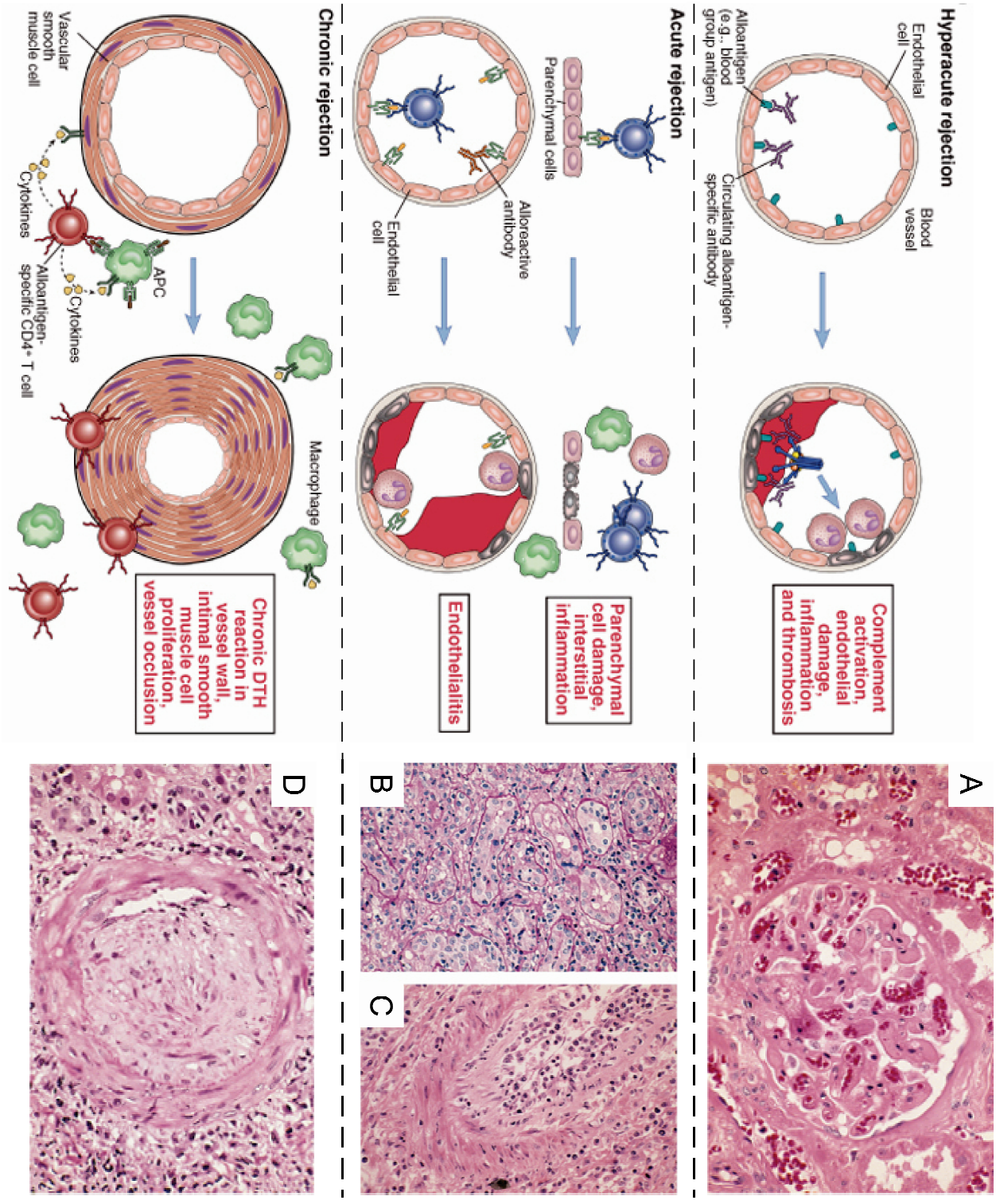

Figure 6. Immune mechanisms and histopathology of different forms of graft rejection (adapted from Abbas *et al.* 2007, [1]). In **hyperacute rejection**, preformed antibodies reactive with vascular endothelium activate complement and trigger rapid intravascular thrombosis and necrosis of the vessel wall. In acute rejection, $CD8^+$ T lymphocytes reactive with alloantigens on endothelial cells and parenchymal cells mediate damage to these cell types. (continued)

occlusion. This kind of rejection occurs right after anastomosis of host and donor vessels and is termed hyperacute rejection phase (**Figure 6A**). However, due to low levels of alloreactive antibody, hyperacute rejection may progress slowly over several years [1].

Acute rejection begins a few days after transplantation and is mediated by effector T cells and antibodies reactive to donor antigens present on endothelial and vascular cells (**Figure 6B+C**). T cells initiate direct killing of graft cells and produce cytokines that recruit and activate inflammatory cells thereby increasing graft damage (**Figure 6B** and **6C**). Antibodies against vessel wall antigens contribute to acute rejection by activating complement inducing vessel wall necrosis and acute inflammation; a histologic pattern different from hyperacute rejection [1].

Graft vasculopathy is characterized by proliferation of intimal smooth muscle cells, arterial occlusion and finally ischemic damage (**Figure 6D**). Graft vasculopathy is the consequence of a combination of processes, including damage by perioperative ischemia, acute rejection episodes and chronic DTH-like reactions. Proliferation of arterial smooth muscle cells is a result of growth factors and chemokines secreted by endothelial cells, smooth muscle cells and macrophages in response to cytokines produced by alloreactive T cells. Graft vasculopathy finally leads to chronic rejection due to the slow replacement of parenchymal cells by non-functioning fibrous tissue in response to the progress of arterial lesions and acute rejection episodes [1].

(**Figure 6** continued) Alloreactive antibodies formed after engraftment may also contribute to vascular injury. In chronic rejection with graft arteriosclerosis, injury to the vessel wall leads to intimal smooth muscle cell proliferation and luminal occlusion. This lesion may be caused by a chronic DTH reaction to alloantigens in the vessel wall. Photomicrographs on the right side of figure 6 show the **histopathology of rejecting renal allografts: 6A. Hyperacute rejection** of a kidney allograft with endothelial damage, platelet and thrombin thrombi and early neutrophil infiltration in a glomerulus. **6B. Acute rejection** of a kidney with inflammatory cells in the connective tissue around the tubules and between epithelial cells of the tubules. **6C. Acute rejection** of a kidney allograft with destructive inflammatory reaction destroying the endothelial layer of an artery. **6D. Chronic rejection** in a kidney allograft with graft arteriosclerosis. The vascular lumen is replaced by an accumulation of smooth muscle cells and connective tissue in the vessel intima.