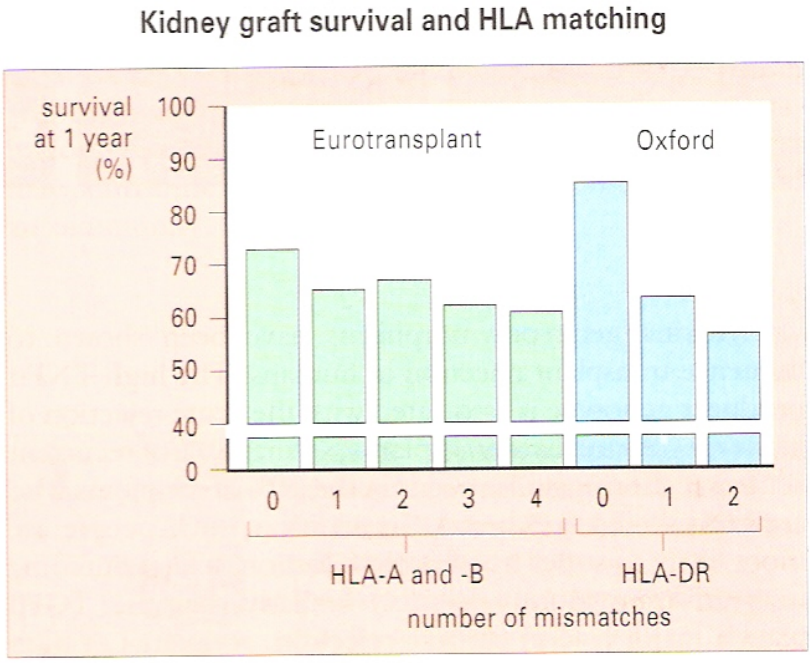

Figure-21 The bar chart shows the percentage survival of cadaver kidney grafts at 1 year in humans in two separate studies. These studies were done before the use of cyclosporine: current outcomes of such engraftment are much improved. In the first study (Eurotransplant), donors were matched for HLA-A and B (class I). In the second study (Oxford) donors were matched for HLA-DR (class II).

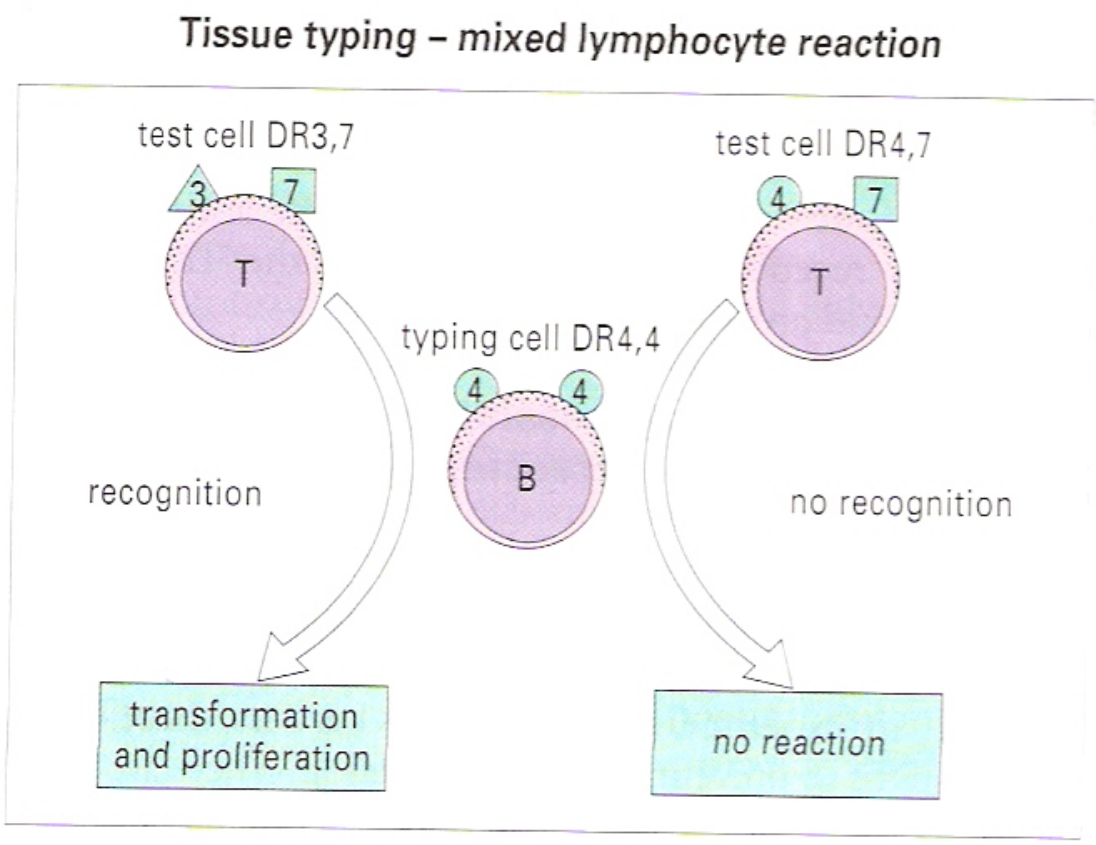

Figure-22 In the mixed lymphocyte rejection, the cells being tested are incubated with 'typing cells of known HLA specificity (DR4,4 in this case). The DR3,7 cells recognize the typing cell as foreign, this is revealed by the test cells transforming and proliferating (the typing cells are treated to stop them dividing in response to test cells). Conversely, DR4,7, which carries the typing cell's specificity (DR4), does not recognize the typing cell and so does not react to it.

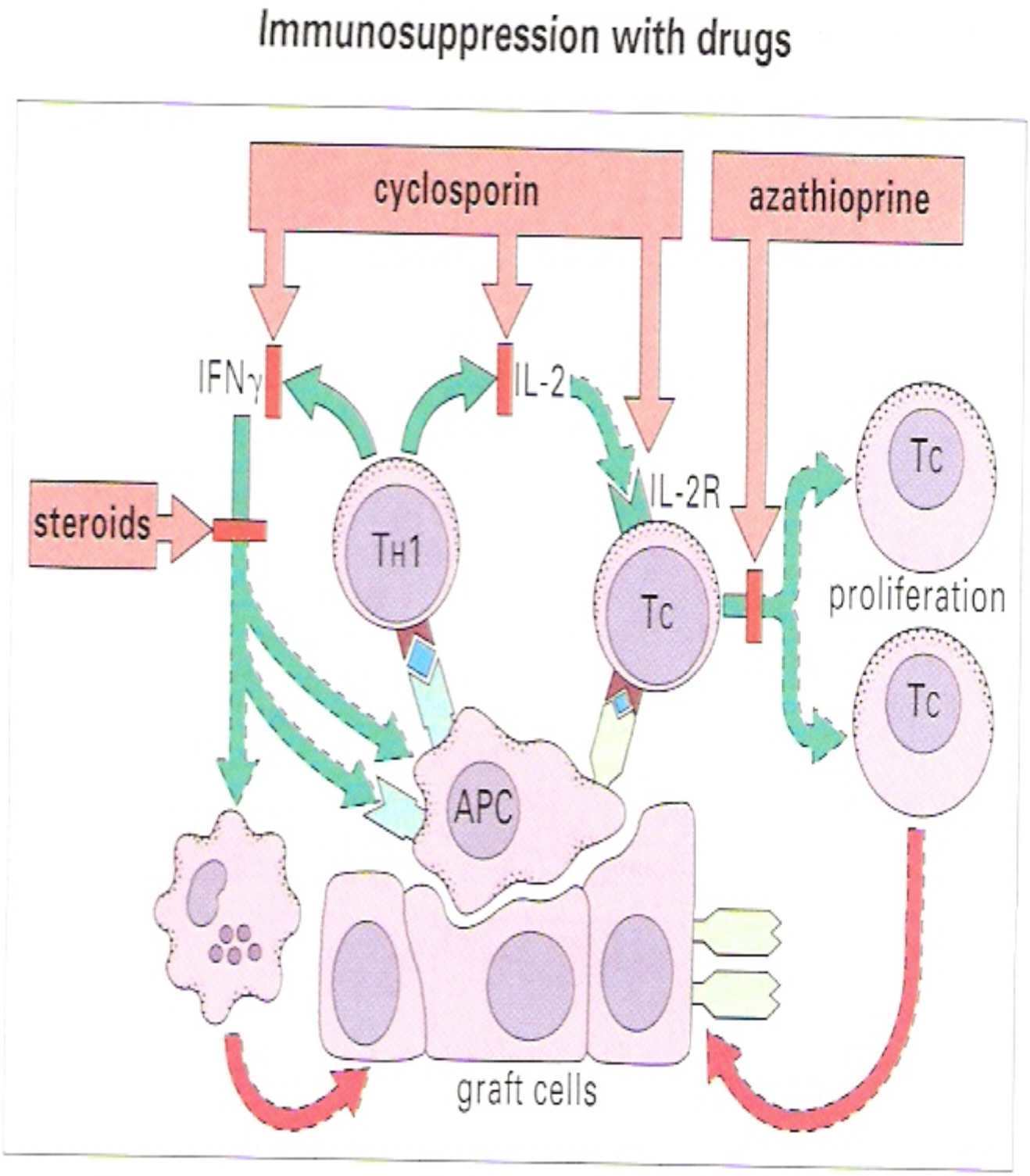

Figure-23 The agents in common clinical use steroids, cyclosporine and azathioprine, suppress the rejection responses at different points. Steroids are anti-inflammatory and suppress activated macrophages, decrease APC function, and reduce MHC expression. Cyclosporine interferes with lymphokine production. Azathioprine prevents the proliferation of activated cells.

The structure of immunosuppressive fungal macrolides

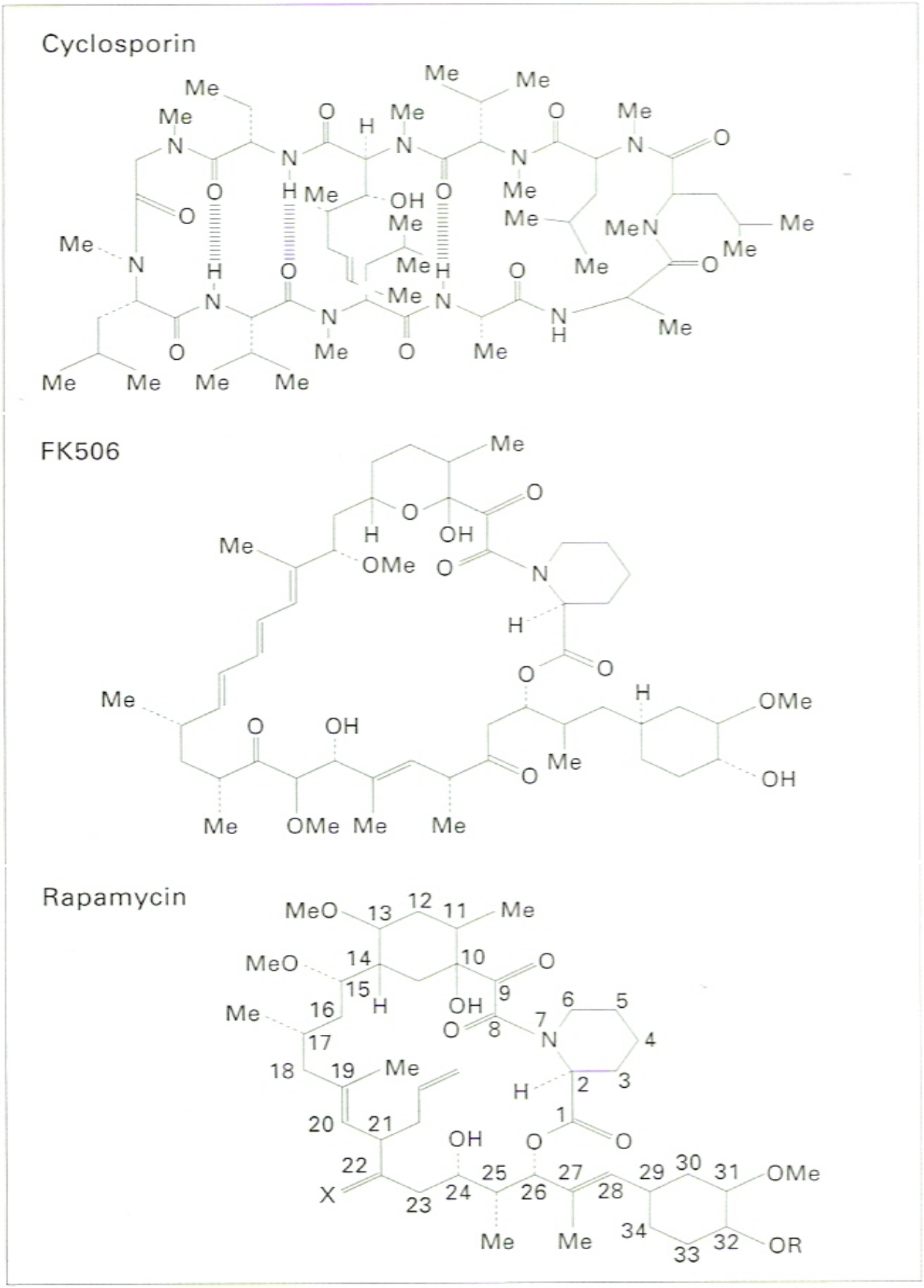

Figure-24 The immunosuppressive fungal macrolides, cyclosporine, FK506 and rapamycin, have quite different structures. They act on lymphocytes in different ways, cyclosporine and FK506 affecting cytokine production and rapamycin interfering with signaling through the IL-2 receptor (IL-2R).

Selective approaches to immunosuppression

agent		target
heterologous antisera/ antibodies	anti-lymphocyte serum (ALS) anti-thymocyte globulin (ATG)	all lymphocytes selective for T cells
monoclonal antibodies	anti-CD3 anti-CD4 anti-CD25 (IL-2R)	mature T cells T_H cells activated T cells
antibody–toxin conjugates	anti-CD5 coupled to the A chain of ricin toxin	activated ($CD5^+$) T cells
cytokine–toxin conjugates	IL-2 coupled to diphtheria toxin	activated T cells (which express IL-2R)
complement inactivating molecules	DAF/MCP CD59 transfected into donor cells (especially of xenografts)	complement-mediated damage via the classical and alternative pathways

Figure-25 Antibodies and cytokines can be targeted to cells of the immune system. By contrast, drugs can have adverse effects on non-lymphoid tissue, e.g. nephrotoxicity and hepatotoxicity. The efficacy of biological agents can be increased by coupling drugs or toxins to them.

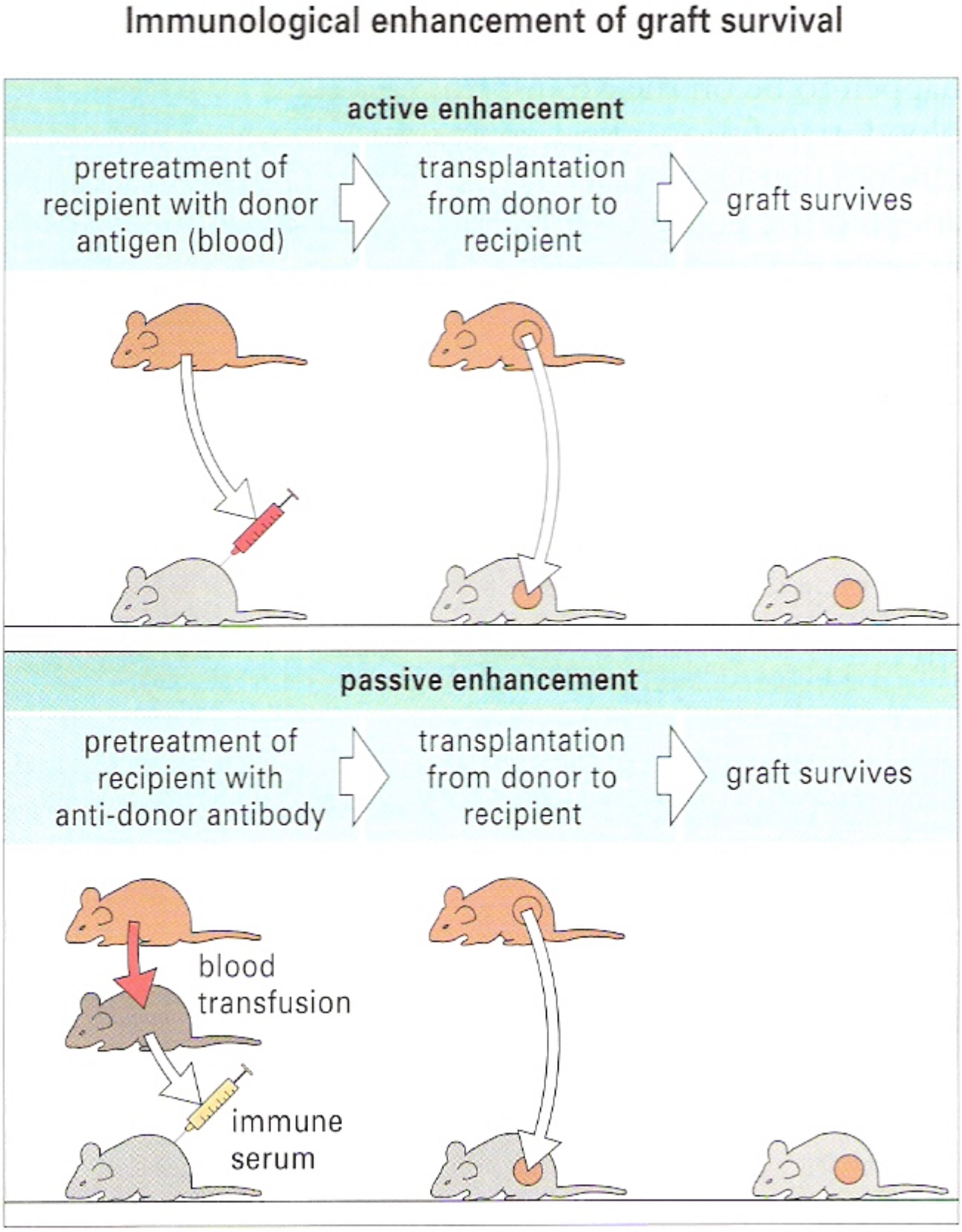

Figure-26 Pretreatment of recipients with donor antigen given intravenously can prolong the survival of a subsequent allograft. This is known as active enhancement of graft survival because the effect requires an active response on the part of the recipient. (Note that the same blood, given by a different route, can result in rapid rejection.) Alternatively, anti-donor antibody given to the recipient at the time of transplantation can cause passive enhancement of graft survival. Both active and passive enhancement are immunologically specific, as only the response to the particular donor is suppressed and the survival of 'third-party' unrelated grafts is not enhanced.

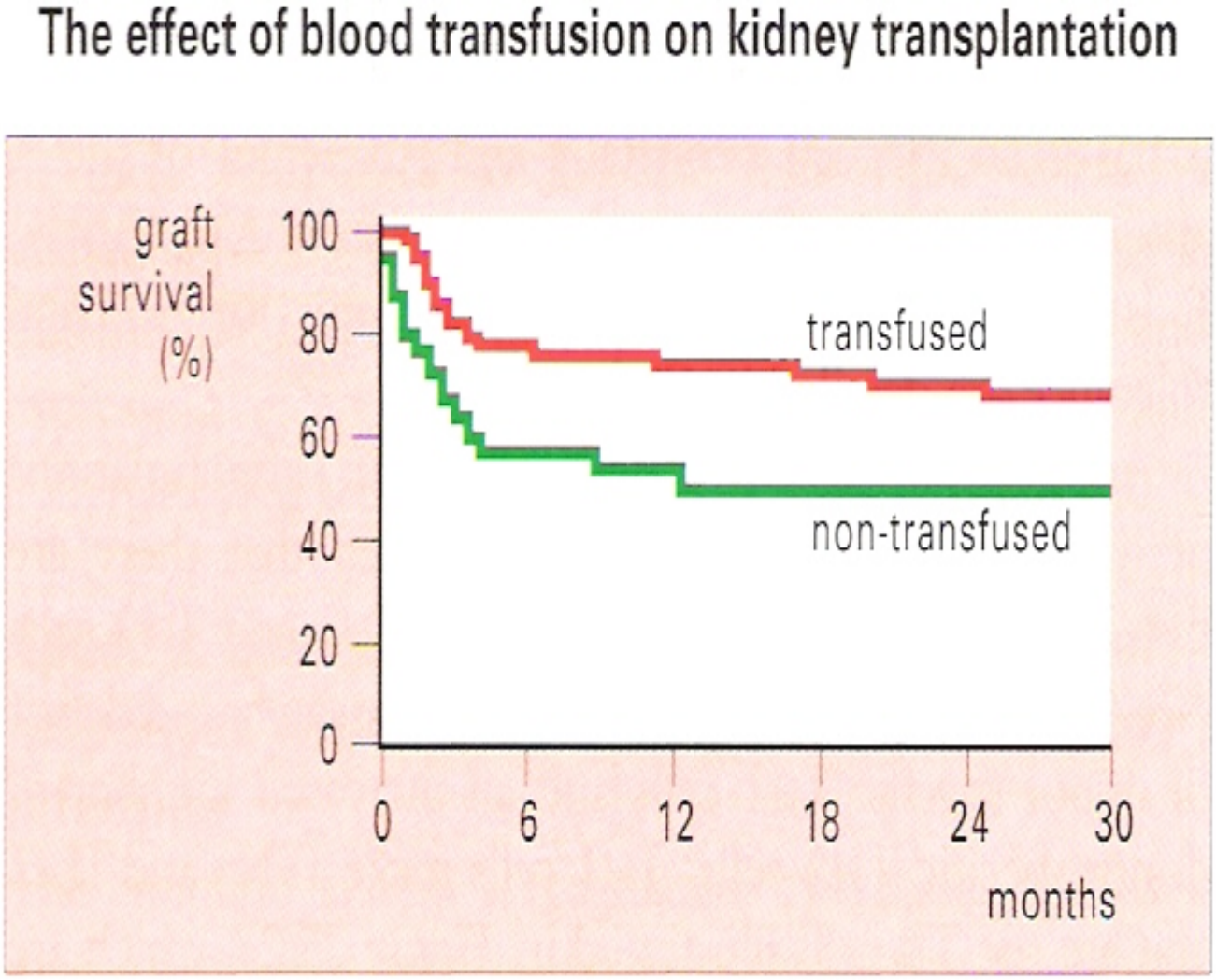

Figure-27 Survival of kidney grafts is higher in transfused patients (102 patients) than in non-transfused patients (71 patients).

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