Graft-vs.-host disease (GVHD) continues to be a major complication after allogeneic bone marrow transplantation, especially with the increasing use of unrelated and mismatched donors. To understand how best to prevent GVHD and to treat GVHD should prophylaxis fail, it is necessary to have a good understanding of the underlying immunology of GVHD. There has been recent progress in understanding two basic aspects of the immune response in GVHD — the immunologic target and the effector mechanisms. First, the target of the immune response in GVHD has been identified as histocompatibility antigens possessed by the host but not the donor. Recognition of self antigens in GVHD has been documented, showing that GVHD is more than simple alloreactivity. Second, the effector mechanism in GVHD was initially thought to be direct cytotoxicity by alloreactive T cells. Cytokines are now known to play a central role in mediating many of the clinical and experimental manifestations of GVHD.

Immunologic background

Graft-vs.-host disease was originally called ‘secondary disease’ to differentiate it from the radiation sickness and aplasia occurring after total body irradiation [1]. Mice receiving syngeneic transplants recovered normally. Animals receiving allogeneic transplants developed erythroderma, wasting, diarrhea, and jaundice, and ultimately died of ‘secondary disease.’ Skin biopsies of these animals showed vacuolar alteration of the basilar epidermis and dyskeratotic epithelial cells in the epidermis or hair follicle. As the disease advanced, the vacuoles at the basement membrane progressed to cleft and frank subepidermal bulla formation. In the liver, lymphocytic infiltration and necrosis of the small bile ducts were seen. Crypt necrosis leading to eventual mucosal denudation was seen in the intestinal tracts of animals with GVHD [1]. Further experimental work showed that F1 hybrid recipients given parental haploidentical marrow developed secondary disease, but parental strain recipients given F1 hybrid marrow did not [2]. These observations led to the conclusion that secondary disease was due to recognition of host histocompat-
ibility antigens by donor (graft) lymphocytes — hence the name graft-versus-host disease [3]. Billingham summarized these observations by defining the classical requirements for GVHD [3]. These requirements were the following:

1. The graft must contain immunologically competent cells.
2. The host must possess important transplantation alloantigens that are lacking in the donor graft, so that the host appears foreign to the graft and is therefore capable of stimulating it antigenically.
3. The host itself must be incapable of mounting an effective immunological reaction against the graft, at least for sufficient time for the latter to manifest its immunological capabilities: that is, it must have the security of tenure.

The immunologic recognition and response seen in GVHD were felt to be due to histocompatibility differences between the donor and recipient. This classic concept of GVHD as delineated by Billingham accounted for the GVHD seen both after marrow transplantation and in immunoincompetent individuals receiving unirradiated blood products. The manifestations of GVHD in the animals were duplicated in the initial human transplants. This construct also accounted for the therapeutic approaches used for GVHD. The original agents used for prophylaxis and treatment of GVHD were lymphocytotoxic agents (i.e., steroids, methotrexate, cyclophosphamide, and antithymocyte globulin) used to destroy cytotoxic T cells.

There were several cases reported of patients who received syngeneic or autologous transplants and developed clinical GVHD [4–6]. In most cases, the GVHD involved the skin only. In a few cases, multiorgan disease with involvement of the liver and/or gut was observed [5]. These cases were at first attributed to unirradiated blood products or severe infections such as CMV-mimicking GVHD. Over time, however, a more subtle explanation was appreciated. GVHD in these patients arose from recognition of self antigens. The development of an animal model of autologous GVHD allowed new insights into the complexity of GVHD.

**Autologous GVHD**

Glazier et al. initially described an animal model of autologous GVHD [7]. Rats given total body irradiation followed by syngeneic transplants and cyclosporine would develop a syndrome that clinically and histologically resembles allogeneic GVHD. The possibility of strain drift accounting for this observation was discounted by performing autologous transplants in which the animals were allowed to reconstitute from a single shielded limb [8]. In both cases (animals receiving syngeneic marrow or animals undergoing autologous reconstitution), the animals developed autologous GVHD, as shown by erythroderma and histology consistent with GVHD. Further laboratory work has shown that autologous GVHD is directed against an apparent public determinant of the MHC class II [9,10]. Monoclonal antibodies against class II antigens blocked this recognition (in vitro and in vivo), whereas monoclonal