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Simonsen M. Graft versus host reactions. Their natural history, and applicability as tools of research. *Prog. Allergy* 6:349-467, 1962.
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Graft versus host (GVH) reactions are transplant reactions in the reverse: the grafted cells (T lymphocytes) react against their new host with often dramatic and even fatal results. In clinical practice, this is a dreaded complication to bone marrow transplantation. In experimental immunology, it has been a useful model for studies of large fields of cellular immunology, e.g., lymphocyte reactivity, histocompatibility reactions, and immunopathology. [The SCI® indicates that this paper has been cited in over 800 publications.]

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This paper was no breakthrough in scientific discovery but evidently was in scientific popularity. It reviewed the field of graft versus host (GVH) reactions, which I had done much to open up in previous years. It attempted, and almost succeeded, in giving an exhaustive review of the literature from my first description of GVH reactions in 1957[1] up to the beginning of 1962. The literature at the time was growing fast and either focused on GVH reactions as such or on their use as tools for studies of lymphocyte reactivity. Hence, the need for a review was probably real enough. I was approached by the editor of *Progress in Allergy* and undertook to write the review, a task that took me more than three months of uninterrupted work.

Why did the article become so popular, asks *Current Contents®*? Perhaps I wrote it well; at least I tried to. In fact, I also tried to illuminate the big and basic issues of contemporary immunology, such as clonal selection theory, immunological tolerance, and immunocompetent cells, from the new angle provided by GVH technology. Two quantitative assay systems based on GVH reaction were particularly useful in this context: the spleen weight assay introduced by me and the chorioallantoic membrane (CAM) assay introduced by McFarlane Burnet. There have been several later reviews of GVH reactions published.[2,3]

The development leading to the discovery of GVH reactions was quite interesting but also more tortuous than can be dealt with in this limited space. Moreover, I have recently presented my personal views and reminiscences on the subject in a paper entitled "Graft-versus-host-reactions: the history that never was, and the way things happened to happen."[4] With hindsight, I think that the most significant impact that the discovery of GVH reactions had on immunology was indirect: by assisting the discovery that small lymphocytes were the carriers of immunological specificity[5] and by helping to establish that lymphocytes were of two major kinds[6] (later designated T and B cells).

My main personal research efforts around the time I wrote that paper were centered on studies of antigenic strength in histocompatibility. I made the paradoxical finding that the donor spleens used for the production of GVH reactions in mice were not made more potent per unit cell number by specific immunization of the donor mouse in the very strong strain combinations. In fact, there was a reverse ranking order for antigenic strength and the potency ratio between normal and immune cells, for which I introduced the term "factor of immunization." I found these facts hard to reconcile with the clonal selection hypothesis, and so, actually, did Burnet's group,[7] who ran into similar difficulties in their own work with the CAM methods in chickens. The low factor of immunization to a strong major histocompatibility complex stimulus *in vivo* is still a real, albeit half-forgotten, puzzle.

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2. **Elkins W L.** Cellular immunology and the pathogenesis of graft versus host reactions. *Prog. Allergy* 15:78-187, 1971. (Cited 260 times.)
3. **Grebe S C & Streilein J W.** Graft-versus-host reactions: a review. *Adv. Immunol.* 22:120-221, 1976. (Cited 175 times.)
4. **Simonsen M.** Graft-versus-host-reactions: the history that never was, and the way things happened to happen. *Immunol. Rev.* 88:5-23, 1985.
5. **Gowans J L.** The fate of parental strain small lymphocytes in F1 hybrid rats. *Ann. NY Acad. Sci.* 99:432-55, 1962. (Cited 365 times.)
6. **Szenberg A & Warner N L.** Dissociation of immunological responsiveness in fowls with a hormonally arrested development of lymphoid tissues. *Nature* 194:146, 1962. (Cited 120 times.)
7. **Szenberg A, Warner N L, Burnet F M & Lind P E.** Quantitative aspects of the Simonsen phenomenon. II. Circumstances influencing the focal counts obtained on the chorioallantoic membrane. *Brit. J. Exp. Pathol.* 43:129-36, 1962.

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