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This Week's Citation Classic

Allison A C, Denman A M & Barnes R D. Cooperating and controlling functions of thymus-derived lymphocytes in relation to autoimmunity. *Lancet* **2**:135-40, 1971.
[Clinical Research Centre, Harrow, Middlesex, England]

It is suggested that thymus-derived lymphocytes play two roles in preventing autoimmunity. T-lymphocytes, but not B-lymphocytes, are unresponsive to autoantigens. Ways in which the requirement for autoreactive T-lymphocytes can be bypassed are discussed. These result in stimulation of B-lymphocytes to secrete autoantibodies. Suppressor T-lymphocytes can also inhibit autoimmune reactions. [The *SCI*® indicates that this paper has been cited over 410 times since 1971.]

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"This article was an attempt to resolve a long-standing difficulty in immunology. Since animals do not as a rule make antibodies against their own body constituents, it had been thought that lymphocytes with capacity to produce such autoantibodies are eliminated or inactivated in embryonic or early postnatal life. Yet certain manipulations (e.g., injection of autologous tissues in adjuvants or of heterologous cross-reactive proteins) lead to autoantibody formation. We offered two explanations for this apparent paradox, one reinforcing the other. The first proposal was that tolerance to self-antigens is selective, involving only T-lymphocytes, and leaving B-lymphocytes with the capacity to make autoantibodies when suitably stimulated. The requirements for autoantigen-specific helper T-lymphocytes could be bypassed in different ways, for example by adjuvants, graft-versus-host reactions, virus infections, or immunization with heterologous cross-reactive proteins. In the article several predictions were made on the basis of this hypothesis, and during the years that followed publication these were confirmed experimentally in our laboratory and others.

"The second proposal was that suppressor T-lymphocytes normally prevent autoimmune reactions. Before the article was published, I attended a meeting on immune regulation at Brook Lodge, Michigan. I suggested that T-lymphocytes must have suppressor as well as helper functions, quoting observations on autoimmunity that had been made by my colleagues Denman and Barnes. Remarkably, three other participants at the meeting (Gershon, Herzenberg, and Tada) had independently reached the same conclusion from different experimental observations. Thus the concept of suppressor T-lymphocytes was launched. It is now known that these represent a distinct subpopulation of cells, investigation of which has led to major advances in cellular immunology in the last eight years.

"What is so gratifying about our paper is not only that it is widely cited, but that the predictions in the article generated a great deal of experimental work. Traveling in Britain, Europe, North and South America, and Australia, I have met many young investigators who tell me how they were stimulated by the article and began their experiments to test the hypotheses presented. Several of these research workers have already made well known contributions to the field, some as visiting scientists in my laboratory. Thus the article was timely and had a substantial impact. Much experimental evidence in support of both hypotheses in this paper has accumulated, as subsequently reviewed.[1]

"My own researches on immunological tolerance have continued with several colleagues, leading to the use of the drug Cyclosporin A to elicit specific tolerance to allografts.[2,3] Selective inhibition by the drug of helper and cytotoxic-T-lymphocytes, while allowing the generation of specific suppressor cells, is evidently involved. Since this is what transplantation immunologists have been attempting to do for decades, we believe these articles should also become Citation Classics, and it will be interesting to see what happens."

1. **Allison A C.** Autoimmune diseases: concepts of pathogenesis and control. (Talal N. ed.) Autoimmunity: genetic. immunologic. virotogic. and clinical aspects. New York: Academic Press, 1977. p. 91-139.
2. **Green C I, Allison A C & Precious S.** Induction of specific tolerance in rabbits by kidney allografting and short periods of Cyclosporin A treatment. *Lancet* **2**:123-5, 1979.
3. **Tutschka P, Beschorner W E, Allison A C, Burns W H & Santos G W.** Use of Cyclosporin A in allogeneic bone marrow transplantation in the rat. Nature **280**:148-51, 1979.