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In retrospect, it seems obvious that effective immunity requires the coordinated activities of many cell types. Given their functional specialization and differences in lifespans, it makes sense that different kinds of lymphocytes are initially generated and then replenished in separate sites. There were tantalizing clues to this in the early 1960s, but a remarkable convergence of clinical findings and studies with experimental animals was needed to delineate clearly the origins of what now are known as B and T cells.

Using a chicken model, Max Cooper first showed that the cells that derived from the bursa of Fabricius were responsible for Ab production, whereas the thymus-derived cells were the effectors of delayed-type hypersensitivity and graft vs host reactions (1, 2).

Modifying methods developed by Glick, Warner, and others (3, 4), Cooper combined surgical thymectomy and/or bursectomy of posthatched chickens with sublethal irradiation. This novel strategy effectively eliminated lymphocytes produced before the time of surgery and generated the first definitive evidence for distinct roles for cells derived from the bursa vs those derived from the thymus (1). While footpad injection of diphtheria toxoid into control chickens resulted in an impressive and obvious delayed allergic response, similar injections of thymectomized, irradiated chickens failed to cause demonstrable reactions. An underlying deficit in small lymphocytes was associated with the defective cellular immunity. Conversely, in bursectomized, irradiated chickens, there was no Ab response to immunization with BSA or Brucella abortus, whereas control chickens produced high levels of Abs to both challenges. An absence of germinal centers and plasma cells was the cellular correlate of the agammaglobulinemic state induced by bursectomy and irradiation. Clearly, removal of these two organs resulted in distinguishable and separable phenotypes. Importantly, Ab responses were not normal in thymectomized/irradiated chickens, suggesting functional cooperation between T and B cells, and complementing parallel studies conducted with mice (reviewed in Refs. 5 and 6).

These new observations simultaneously solved and raised important issues. For example, how did the new insight help to explain human immunodeficiency diseases? The agammaglobulinemic chickens closely resembled patients with X-linked agammaglobulinemia, a condition described much earlier and documented as having normal thymus development. We know now that the disease results from mutations in Bruton’s tyrosine kinase, a gene not expressed in T lymphocytes.

The same is true for transplantation therapy and dissection of the molecular bases for autoimmune diseases.

Cooper and colleagues were certainly correct when they deemed the chicken a “fortunate model.” It not only allowed the separate surgical ablation of B and T cell production but also was useful in establishing the origin of non-IgM isotypes from IgM producing B cells (7). However, it was immediately obvious that there must be an organ in mammals with function comparable to the bursa of Fabricius. Some years were required to learn that it resides in hemopoietic tissues such as the bone marrow, where Cooper and colleagues (8, 9) found that precursors of B lymphocytes could be identified on the basis of their initial synthesis of Igµ H chains.

As partial testimony to the impact of this “Pillars of Immunology” article and other work begun by Cooper et al., this report has been cited 685 times and as recently as last year. Only about a third of the citations were from labs in the United States, indicating how widely these data have affected the field of immunology. In fact, while many highly cited papers involve research methods or are referenced as important work in review articles, 80% of the articles citing Cooper’s manuscript can be designated as research articles. Indeed, it can be said that this publication served as the catalyst for many exciting new directions.

The last 40 years have brought many improvements in technology, sometimes allowing questions to be answered before we have them clearly formulated. This classic study was well conceived, and it is impressive that multiple experimental approaches were effectively used to assess immune competence. It is fun reading because it captures the excitement of the times and reminds us how “fortunate models” should be exploited.

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References


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