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Introduction

Byron H. Waksman

The overwhelming preoccupation of the immunological community with lymphocytes, their markers, their structural and biochemical characteristics, and their functional attributes is reflected in this volume of *Progress in Allergy*. Of the four reviews, three deal explicitly with lymphocytes. Drs. Cantor and Weissman consider the now very strong evidence for extensive heterogeneity of these cells, even within such narrower categories as T and B. Oppenheim and Rosenstreich attempt to reduce to some sort of order the mountain of recent information on lymphocyte stimulation and the factors which affect triggering. Wedner and Parker consider the conflicting evidence that cyclic nucleotides may play a key role in lymphocyte triggering. Even the review of Goldstein deals with a closely related topic, the lysosomal activities of macrophages.

These reviews are written against a background of increasing crisis in communication within the field of Immunology. The mass of current research in the various specialties of the field is simply staggering [1]. The number of new specialties with their own journals continues to increase – witness *Immunogenetics* and *Journal of Immunogenetics*, appearing since I last introduced a volume of *Progress in Allergy* in 1973. A similar increase continues in general journals and review volumes – *Annales d'Immunologie* (part of *Annales de l'Institut Pasteur*), *Contemporary Topics in Molecular Immunology*, *Clinical Immunobiology*, *Research in Immunochemistry and Immunobiology*. There is a suggestion that at least this curve is levelling off, since new journals have appeared at a slower rate in the last 2–3 years than previously.

The increase in review volumes is itself a proof of the felt need for better communication. In fact a rapidly increasing part of such communica-

tion takes place at specialized and often rather small meetings, symposia, and workshops, both international and national. In addition we are witnessing a rapid proliferation of annual courses offered by national societies such as the American Association of Immunologists and the British Society of Immunology, by individual university groups such as that at SUNY, Buffalo, by the International Union of Immunological Societies (in conjunction with WHO), and by other umbrella organizations, e.g. WHO/UNESCO/ICRO. One may count in 1975 at least seven of these, which of course take place all over the world. Training in Immunology has been formalized by the creation of graduate programs devoted to this discipline. The Doctorate Records file of the NRC Commission on Human Resources (United States) first recognized Immunology as a separate Ph.D. field in 1972. In that year there were 18 such degrees granted. In 1973 there were 49 and in 1974, 71 [2].

The growth of Immunology is taking place not only at a basic but also at an applied level. It was possible, a decade ago, to foresee the gradual substitution of clinical immunologists, concerned with a wide range of problems in infectious disease, allergy, rheumatology, and hematology, for the more classical allergists, whose interest and competence were limited to atopic disease. This change is now in full swing, and the level of the new activity may be judged by the many books which have appeared devoted entirely to clinical immunology (I will not attempt to list these here), as well as the review series mentioned above.

The flow of technical and conceptual breakthroughs in fundamental Immunology has not diminished. In a previous introduction (1971) I listed identification of lymphocyte subpopulations, topographic and genetic mapping of lymphocytes, the nature of immunocompetence, the mechanisms of thymus differentiation and of transformation and triggering of immunocompetent lymphocytes as major new areas of research. In 1973, the list included helper and suppressor effects of lymphocytes, the characterization of diffusible 'lymphokines' and their role in these effects, the study of pharmacologic receptors (cholinergic, α- and β-adrenergic, etc.) on lymphocytes and their relation to triggering and to the function of microtubules, microfilaments, and the cyclic nucleotides as second messengers, and the use of continuous lymphocytic cell lines and hybridization techniques to study the genetic control of differentiated lymphocytic functions.

Perhaps the most exciting of recent developments has been the change in our understanding of the major histocompatibility complex, originally thought to be simply a genetic locus governing cell surface structures

(histocompatibility antigen, thymocyte-specific antigen, MLC antigen, etc.) [3]. This chromosomal region, with space for as many as 1,000 genetic loci, has been shown to include genes governing immune responsiveness to a variety of antigens (perhaps by governing a surface receptor molecule on T-lymphocytes), cell interactions (both lymphocyte-lymphocyte and macrophage-lymphocyte), a variety of diffusible regulatory mediators (for both cooperation and suppression), and several complement components, and it is becoming clear that the entire region must be derived from a cluster of genes governing an ancestral recognition system. While the MHC is on a different chromosome from the structural genes governing antibody formation, β_2-microglobulin, an integral component of several of the MHC products, shows peptide sequence homologies with γ-chain domains, and it seems that immunoglobulins also must be derived from such an ancestral system.

MHC products are present on many types of cells (or free in the circulation or released from activated cells) and the system obviously concerns a general cellular property. It is no accident that recognition phenomena resembling graft rejection are recognizable in lower forms such as echinoderms and tunicates [4]. One may speculate that similar but perhaps more primitive recognition phenomena, in earlier phylogenetic forms [5], will soon be identified as being determined by the ancestral MHC.

Several other new areas of rapid advance could be cited, among them the three-dimensional analysis of the antibody combining site, identification of a new group of reactions involving humoral antibody and blood cells acting on metazoan parasites, the functions of thymus hormone. However, enough has been said to show that Immunology is alive and well and moving rapidly forward.

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Development and Function of Subpopulations of Thymocytes and T Lymphocytes

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I. Introduction

There is a large body of experimental evidence delineating subpopulations of thymus cells on the basis of size, surface antigens, proliferative potential, susceptibility to various physical and chemical agents, and immunological function. There is also increasing evidence that the thymus may give rise to functionally distinct subpopulations of peripheral T cells. In this review, we shall attempt to define thymus and T cell subpopulations in terms of functional and intermitotic life span, distinctive surface characteristics, anatomic locale, homing properties, and immunologic function in the production of cell-mediated and humoral immunity. We do not attempt an exhaustive review of the literature, but limit our analysis to two key aspects

of the problem: the intrathymic maturation sequence, and the existence of (and interaction between) peripheral T cell subpopulations.

We attempted to complete the literature review by mid 1973, and to limit the references to papers which were most definitive for the topics in question. Necessarily, we excluded papers which contributed to, but were not central to our discussion, and also probably missed several papers central to our topic by misadventure.

II. Identification and Characterization of Thymic Precursors

A. Bone Marrow Origin of Thymic Precursor Cells

Much of our current understanding of the development of the thymus derives from early experiments on the role of the thymus in murine leukemogenesis [88, 128, 143, 154]. Two systems were initially studied – spontaneous leukemogenesis in AKR and C58 mice, and radiation-induced leukemias in C57Bl and A strain mice. In the course of studying the mechanisms involved in radiation-induced C57Bl leukemia, KAPLAN and co-workers [29, 129] noted that whole body sublethal doses of irradiation led to rapid involution of the thymus, and that rapid regeneration of thymus weight and architecture could be induced by thigh shielding [29] or injection of syngeneic bone marrow cells [29], but not by injection of thymocytes or implantation of muscle [29]. Cytogenetic evidence that most mitotic cells in the regenerating thymus were indeed derived from bone marrow was provided by FORD *et al.* [81] using (allogenic) cells bearing a cytogenetic marker, T_6 [43], and GENGOZIAN *et al.* [89] using rat bone marrow cells identified in the thymus by both cytogenetic and thymus antigen markers. However, it remained possible that these donor cells proliferated in the host thymus as a result of stimulation by host transplantation antigens. Definitive proof of proliferating donor BM cells in a syngeneic host thymus awaited the development of a line of CBA mice bearing the T_6 chromosome marker. In this model, syngeneic chromosomally marked donor bone marrow cells were observed to divide in irradiated host thymuses in the regenerative phase [82]. Since over 95% of thymic lymphocytes are derived from recently dividing cells (see sect. III), observation of chromosome markers identifiable only in mitotically active cells is useful for studying thymus regeneration. Unirradiated thymus *grafts*, which undergo an initial phase of cell death followed by a regenerative phase, also show host-type mitotic cells in the majority by 2–3

weeks [112, 157] derived from BM precursors [65]. In the irradiated host injected with bone marrow cells, the cells in the regenerating thymus express the genetic potential of the donor and not the host, at least with regard to the specificity in the induction of graft-versus-host (GVH) disease [182] and the expression of thymus-specific alloantigens [180, 201] and heteroantigens [89].

1. Rate of Entry of Precursor Cells into the Thymus

Only a few experiments have been performed in which the entry and proliferation of bone marrow precursors into the uninjured thymus under relatively physiological conditions have been assayed. FORD *et al.* [83] irradiated the lower quarter of mice and then transfused them with syngeneic T_6 marked bone marrow which rapidly colonized the irradiated femoral, but not the unirradiated humeral marrow cavities. Donor-type mitoses were first apparent in the thymus at 5 weeks, reaching maximum values at about 9 weeks. Similarly, unirradiated CBA hosts were transfused with syngeneic T_6 marked bone marrow cells [160]. Donor mitoses rapidly appeared in bone marrow, but donor mitotic cells were not apparent in the thymus until 4 weeks postinfusion, their levels rising until at least 12 weeks. In another approach, BRAHIM and OSMOND [28] pulse-labeled bone marrow by a single intracavitary injection of ^{3}H-TdR into the femorae and tibiae of guinea pigs (while clamping off the venous return and simultaneously injecting ^{1}HTdR into the heart), and found substantial numbers (1.8%) of labeled polymorphonuclear granulocytes appearing in the blood 2–5 days later. Very few labeled cells (at most 16 per whole thymus section) were seen in the thymus in the ensuing 12 days; those were localized preferentially in the juxtamedullary cortex. These studies suggest that although bone marrow serves as a source of cells capable of proliferation in the thymus, and that although these cells are important in the relatively rapid repopulation of the experimentally involuted thymus, their rate of immigration into the intact thymus in normal animals is quite low. It has been reported that massive antigenic stimulation may slightly, but significantly accelerate this inflow of bone marrow cells in the intact host [161].

2. Differentiation of Thymic Precursors in Allogeneic Hosts

A related question of some clinical importance involves whether stem cells are capable of differentiating to thymocytes and immunocompetent T lymphocytes in allogeneic, immunosuppressed hosts. Although there is good evidence that this differentiation does occur [98], it is not clear whether immunocompetent cells reactive to the transplantation antigens of the host are