ADVANCES IN EXPERIMENTAL MEDICINE AND BIOLOGY

Volume 88

AVIAN IMMUNOLOGY

Edited by Albert A. Benedict

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PLENUM PRESS • NEW YORK AND LONDON

Library of Congress Cataloging in Publication Data

International Conference on Avian Immunology, University of Hawaii, 1977.
Avian immunology.

(Advances in experimental medicine and biology; v. 88)
Includes index.
1. Chickens—Diseases. 2. Veterinary immunology. I. Benedict, Albert Alfred, 1921- II. Title. III. Series.
SF995.I57 1977 636.5'08'96079 77-2732
ISBN 0-306-32688-4

Proceedings of the International Conference on Avian Immunology held at the University of Hawaii, Honolulu, Hawaii, March 12–13, 1977

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I'd like to know
what this whole show
is all about
before it's out.

... Piet Hein

Preface

Many participants at this conference often have been asked the question, "Why do you work with chickens?". We agree with the argument that people are just curious, and like Mt. Everest chickens are here. In a more practical sense, the answer to that question makes reference to the clear-cut delineation of the T and B cells in birds. Indeed, the birth of chicken immunology probably occurred with the discovery of the immunological importance of the bursa of Fabricius. A justification for working with chickens no longer elicits a paranoid response, for the value of a phylogenetic approach for an understanding of the immune system is now obvious. The papers in this volume illustrate why the chicken is a valuable model for so many major concepts that are of general importance in immunology; such as, the ontogeny of T and B cells, the GVH reaction, the genetic basis of disease resistance, tumor immunity and regulation of the immune response.

Heard at this conference were views of avian immunology derived from diverse perspectives. The occasion afforded an opportunity for people with a common bond but from backgrounds as varied as medical schools, molecular biology and genetic institutes, animal disease research institutes, poultry research laboratories, animal science and biological science departments to review data, ask questions, and plan future experiments. We heard exchanges between those who were associated with the development of chicken breeds resistant to Marek's disease for commercial purposes with those involved in dissecting the major histocompatibility complex. The theorists also were given opportunity to propose theories.

The summation talks given by Jeanette Thorbecke, Max Cooper and Al Benedict will serve as the basis for these introductory remarks. We have made no attempt at being comprehensive, but we hope the flavor of the meeting is imparted. A. A. Benedict takes full responsibility for any inaccuracies in transcription from tape of the summations.

The ontogeny of lymphoid cells seems the most appropriate place to start. The early events in T and B cell ontogeny are still confusing. There seems to be no agreement on the data and on the semantics of the question of progenitor vs. stem cells. Nevertheless, we are beginning to understand more about progenitor cells which are committed to particular cell lines, and about stem cells in the sense of having almost unlimited capability of giving rise to undifferentiated progeny. An important future development will be to determine the nature of the substances that attract stem cells and which are produced by specialized thymus epithelium, and perhaps by the bursa. The way stem cells recognize these signals is an important question to answer.

Not predictable from mammalian models has been the observation that there is a lack of cells called into the bursa even before the signal for entry of stem cells has been shut off. A likely model suggested that after a certain point in development there were no longer any cells capable of migrating into the bursa and becoming B cells. A fascinating possibility is the suggestion that a cell comes into the bursa, is not committed, then can still wander into the thymus. This cell does not appear to have B cell characteristics; that is, immunoglobulin is not expressed on its surface.

Detection of some of the earlier stages in the B cell generation is now possible, and this is one of the main uses of the chicken model. Chickens have proved to be a source of pure B cells at a very early and defined stage in their life history, thus making available biological clues to analyze molecular events. It is going to be interesting to determine the physiological significance of the secretory phase early in the development of at least some B cells.

The combined data of papers on suppression answered at least tentatively some questions on the regulation of immunoglobulin synthesis. B cells are found in chickens adoptively transferred with suppressor cells (spleen cells) from bursectomized birds, but immunoglobulin secretion is depressed. Suppressor cells probably mediate their effects by acting directly on B cells; however, it was interesting that plasma cells and germinal centers disappear in recipients rapidly after transfer of suppressor cells. Neither the nature of the suppressor cells nor the B cell factor which recognizes the suppressor is known. In this connection, cells which suppress GVH reactivity and blastogenic responses to PHA are present in a subset of chicken thymus cells. Whether the suppressor cells are B cells which have taken up residence in the thymus is a prospect which needs looking into.

Disturbed immunoglobulin regulation is suggested in birds which have an inherited dysgammaglobulinemia, but suppressor factors have not been reported in these birds. This disease is characterized by a 7S immunoglobulin deficiency which occurs after several weeks of normal 7S immunoglobulin synthesis; thus this condition in birds may be a model for inherited, common variable ("late onset") immunodeficiency in humans.

Immune unresponsiveness also may be induced by antigen-antibody complexes, with the structure of the complexes being important in maintenance of tolerance. Both adherent cells and at least one other cell type seem to be susceptible to this kind of unresponsiveness.

The pervading influence of the major histocompatibility complex (MHC) in mammalian immunology is no less involved in avian immunology. It is not surprising that the B antigen is structurally similar to the mammalian counterparts, HLA and H-2. With the discovery of increasing numbers of serological, histogenetic, and GVH recombinants, and the finding of additional functions and cellular antigens associated with the MHC, a primitive map of the B complex is now possible. The region of the chromosome involved is divided into two parts, B-F and B-G. Compared to the H-2 of mice, the frequency of recombination in the B complex is lower, and there seems to be asymmetry in the arrangement of the chicken MHC. In some ways, the B complex arrangement corresponds more to the human than to the mouse MHC. The phylogenetic implications of these studies are exciting.

The poultry industry has known for many years that hatchability, viability, and egg production have a genetic basis, and this was proved later to be somehow associated with B alleles. In the 1960's Marek's disease became a serious problem to the poultry industry. Through the efforts of a number of poultry research laboratories, resistance to Marek's disease was found to be influenced by certain B alleles. This was one of the earliest observations on the relationship between disease resistance and histocompatibility. As in other animal species, we heard that synthetic antigens are being used to characterize the MHC associated immune responses and, unlike results obtained in mammals, the immune response to the copolymer (T,G)-A--L in chickens exquisitely delineated the antigenic determinants of this immunogen based on responses controlled both by genes associated and unassociated with the B complex. The high degree of development of the chicken immune system to dissect the (T,G)-A--L determinants, and to respond to poly-glutamic acid which is essentially non-immunogenic in rabbits and mice (unpublished data) is curious in view of the finding that 7S antibodies synthesized to certain haptens do not have the high binding capacity of horse and rabbit antibodies. The later finding on the antibody binding site is more in line with phylogenetic expectations.

It was pointed out that it is an oversimplification to expect immune responses to be controlled by a single gene associated with the MHC. As mentioned earlier in regard to the anti-(T,G)-A--L response, many immune responses to a variety of immunogens probably will be shown to be controlled by two or more genes, some of which are not MHC associated. This is borne out in the pathogenesis of spontaneous autoimmune thyroiditis in the Obese strain of chicken in which many genetic traits seem to play a role. Perplexing are the East Lansing inbred line 6 chickens which are highly resistant to Marek's disease, whereas the East Lansing inbred line 7 chickens with the identical B allele are highly susceptible. These lines also differ quantitatively in their ability to respond to certain immunogens, and some of these quantitative differences in antibody production are associated with two autosomal loci, Bu-1 and Th-1, which determine alloantigens of B and T cells, respectively. Finally, for an immune response, the cooperation between T and B cells requires some histocompatibility identity. This later point needs clarification in view of reports of cooperation across the histocompatibility barrier.

The chicken model has been unique in tumor immunity as Marek's disease is the only naturally occurring malignancy that can be prevented by vaccination. Chickens vaccinated with the herpes virus of turkey develop a cell mediated cytotoxic response to tumor-associated surface antigen. Cell mediated immunity seems to be the chief factor in protecting against clinical manifestations of Marek's disease. In an attempt to develop a procedure to be used under field conditions to control lymphoid leukosis tumors, an androgen analog was fed to chickens. This treatment causes a progressive involution of the bursa, and therefore prevents development of lymphoid leukosis tumors.

In the chicken, cooperation between specific immune T cells and normal monocytes results in inhibition of growth of a carcinogen-induced transplantable fibrosarcoma. Particularly significant is the finding that tumor-specific immunity occurs locally even when induced with a delayed-type hypersensitivity reaction to antigens which do not cross-react with the tumor antigens.

"What chicken line are you working with?" was often asked at the conference. As expected, disparate findings may result from genetic differences. It seems that our current work with chicken lines is approaching the degree of sophistication evidenced in mouse genetics. Viable homozygous chicken lines are available for experimental purposes from a number of sources. We believe that it is crucial for the development of chicken immunogenetics that further efforts be made to characterize lines genetically, and to produce congenic lines. In view of the long generation time of

the chicken compared to the mouse, clever methods must be developed to enhance the rate of production of congenic lines.

It was good to hear that a committee is working on an internationally acceptable nomenclature for the B locus as this is urgently needed to classify inbred lines.

The structural and genetic identification of immunoglobulin allotypes has made available additional stable and easily detected genetic markers to characterize inbred lines. A system of nomenclature for both the 7S and 17S immunoglobulin allotypes was proposed. Perhaps not surprising was the observation that the genetic polymorphism of the 7S immunoglobulin allotype gene (CS-1) was about that observed for the Ig-1 gene of inbred mice. It appears that intracistronic recombination may account for the generation of the genetic polymorphism of the CS-1 gene alleles. It is pertinent to note that the chicken may be quite useful for studies on the genetic mechanism responsible for allotype expression because in several inbred lines low levels of inappropriate or "unexpected" allotypes were found. The presence of pseudoalleles has been proposed, which is in accord with a regulatory gene hypothesis for allotype expression.

Several uses of the chicken model were not discussed, some of which are experiments dealing with constraints on genetic models of immunoglobulin synthesis, kinetics and cellular events of in vivo immune responses, and idiotype explorations. Particularly important will be idiotype studies because of the value of looking at the generation of clonal diversity in the chicken model. We hope to have a Second International Conference on Avian Immunology when these and other subjects will be discussed.

This conference was made possible through the generous financial help of the University of Hawaii Foundation; the Graduate Division, College of Arts and Sciences, and Department of Microbiology of the University of Hawaii; the Hawaii Egg Producers Association and the Hawaii Fryer Council; also by the devoted care of Ms. Dolores Springer throughout the stages of planning, meeting, and book preparation. Our deepest gratitude to all of you.

Mahalo and Aloha

Honolulu, Hawaii
May, 1977

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