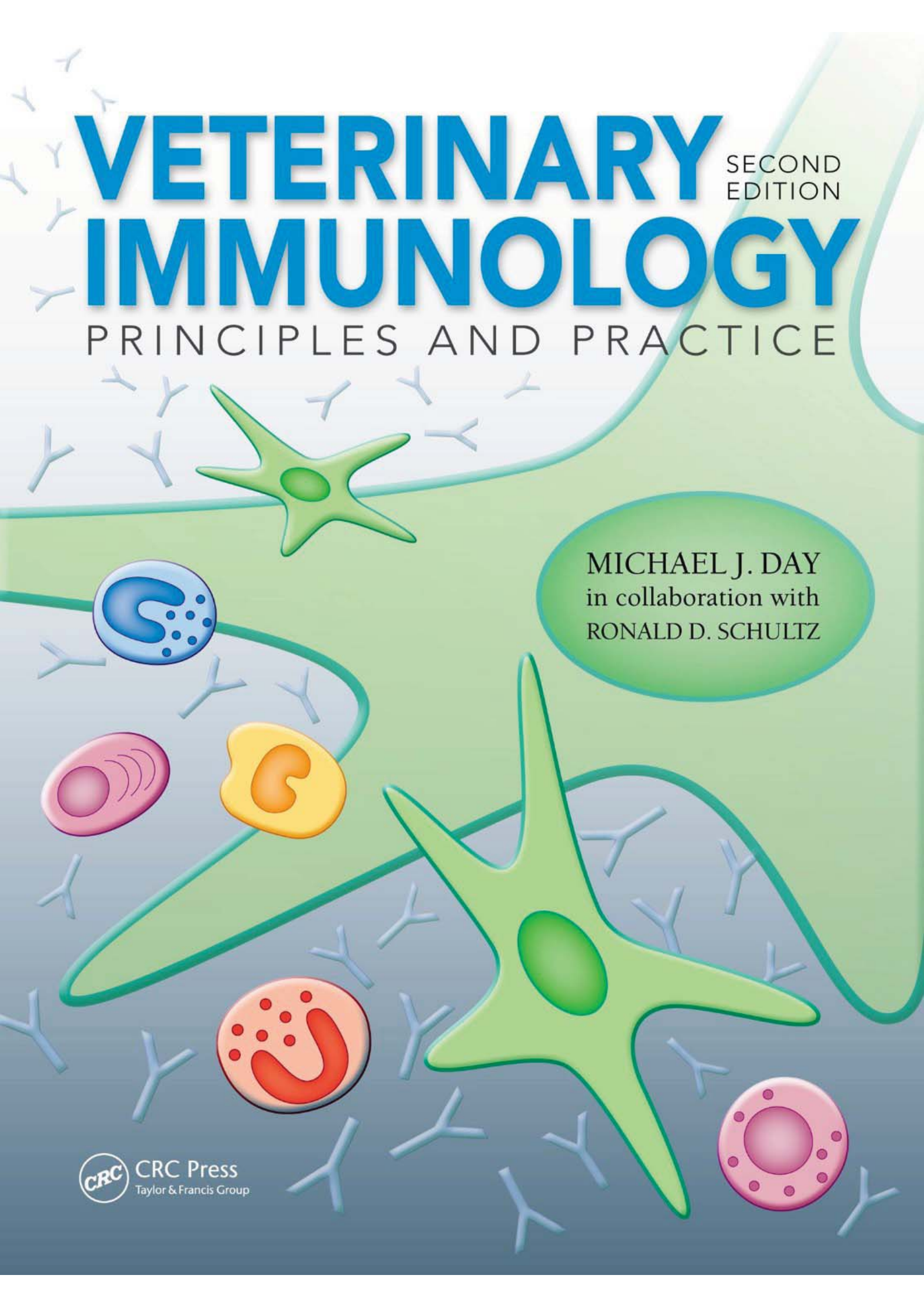
VETERINARY IMMUNOLOGY

SECOND EDITION

PRINCIPLES AND PRACTICE

MICHAEL J. DAY
in collaboration with
RONALD D. SCHULTZ



CRC Press
Taylor & Francis Group

Veterinary Immunology – Principles and Practice

Second Edition

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CRC Press
Taylor & Francis Group
Boca Raton London New York

CRC Press is an imprint of the
Taylor & Francis Group, an **informa** business

CRC Press
Taylor & Francis Group
6000 Broken Sound Parkway NW, Suite 300
Boca Raton, FL 33487-2742

Printed on acid-free paper
Version Date: 20140219

International Standard Book Number-13: 978-1-4822-2462-7 (Paperback)

Library of Congress Cataloging-in-Publication Data

Day, Michael J., 1960- author.
Veterinary immunology : principles and practice / authors, Michael J. Day, Ronald D. Schultz. -- Second edition.
p. ; cm.
Includes bibliographical references and index.
ISBN 978-1-4822-2462-7 (pbk. : alk. paper)
I. Schultz, Ronald D., author. II. Title.
[DNLM: 1. Animal Diseases--immunology--Case Reports. 2. Immune System Diseases--veterinary--Case Reports. SF 757.2]

SF757.2
636.089'6079--dc23 2014005392

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http://www.crcpress.com

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Foreword

Veterinary immunology is one of the most recent, and the most important, basic and clinical sciences in veterinary medicine. Veterinary immunology became an important part of the veterinary curriculum approximately 40 years ago when most veterinary medical students were introduced to concepts of basic immunology during their first or second year of veterinary school. Clinical immunology was either a minor part of the basic immunology course or it was taught at a later time as part of the medicine courses. During the past 40 years, information regarding basic and clinical immunology in veterinary medicine has increased beyond the scope of a single course. However, this textbook, *Veterinary Immunology – Principles and Practice*, *Second Edition*, includes both basic and clinical concepts of veterinary immunology.

The author is a veterinary immunologist engaged in both basic and clinical research studies in immunology and immunopathology. The book provides not only the veterinary medical student, but also the graduate veterinarian, with excellent information on the basic and clinical aspects of veterinary immunology. The basic aspects of the science are made easily understandable to those with limited or no knowledge of immunology. At the same time the book provides an excellent insight into the complexity of diseases caused by or prevented via innate and/or adaptive immunity. The book is equally valuable to those with little or no understanding of clinical medicine and to those with an excellent knowledge of basic clinical medicine. This is accomplished through the author's unique presentation style in which the basic concepts of immunology are introduced and explained, often in the context of the mechanism for an immune-mediated disease or the immunological mechanism for prevention or treatment of a disease. The author has also 'sifted and winnowed' through the complexities of basic medical immunology in order to provide the reader with factual information that applies to most veterinary species. This text, unlike many introductory immunology texts available for medical students and undergraduate or graduate students in the biological sciences, does not focus on the myriad of information on the immunology of the mouse, a favourite species of many immunologists who perform *in-vivo* studies. Ironically, most immunologists are of the opinion that because the mouse's immune system is easily manipulated for *in-vivo* and *ex-vivo* immunological studies, it serves as a model for all other species. Unfortunately, this is often not true and many of the veterinary species differ significantly between each other as well as with the mouse regarding basic and clinical mechanisms of diseases caused by and/or prevented via their immune system. The species differences, when known, are defined in this text. Information on differences among species should make this text a valuable reference for all immunologists, especially those with an interest in real animal studies. Information is included on food animal species, but the focus in the clinical immunology sections is on companion animal species, especially the dog and cat. The author has published a more detailed book, *Clinical Immunology of the Dog and Cat*, which is beautifully illustrated with graphs and figures including histopathology sections of immune-mediated diseases in these species. Similarly, this text is very well illustrated, but for obvious reasons does not contain the detail found in the *Clinical Immunology of the Dog and Cat*.

I especially like this book because the veterinary immunology course taught to second-year veterinary medical students at the University of Wisconsin-Madison first presents the 'Basics of Veterinary Immunology' via eighteen didactic lectures, followed by 'Clinical Immunology' via twelve 'Clinical Correlates'. In addition, there are approximately 50 hours in the course that cover laboratory exercises such as vaccinating calves and puppies, performing clinical immunology tests for the diagnosis of diseases of companion and food animals, and other laboratory procedures (phagocytic tests, lymphocyte function tests and multiple serological tests). This book provides a very helpful way of understanding these diagnostic tests, animal immunization and immune-mediated diseases.

This second edition of *Veterinary Immunology – Principles and Practice* is a book for veterinary students worldwide. It is also an excellent review and update for veterinarians who graduated five or more years ago and want or need to know more about basic and clinical veterinary immunology.

Ronald D. Schultz

Preface (First Edition)

Veterinary Immunology – Principles and Practice has the simple aim of providing undergraduate veterinary students with core knowledge of veterinary immunology, while emphasizing the clinical relevance of this subject area. Veterinary students often struggle with the complexity of the immune system and find it difficult to relate immunological concepts to veterinary practice. In many universities, immunology is taught to veterinary undergraduates at a superficial level and the subject is also often delivered by basic scientists with an inappropriate focus on murine or human systems. Despite this, immunology is a key subject in the veterinary curriculum; it links together subject areas such as biochemistry, microbiology, parasitology and pathology with clinical medicine. One of the main clinical applications of immunology is the practice of vaccination, and all graduating veterinarians must have a solid understanding of the principles of vaccinology.

There are relatively few textbooks of veterinary immunology to support the delivery of undergraduate courses in this subject. I hope that *Veterinary Immunology – Principles and Practice* will fill a key niche in providing students with an affordable and practical reference that will also have relevance as they progress through a practice career. The key features of this book include:

- A sufficient level of detail of core knowledge without this being diluted by minutiae.
- Clear definition of learning objectives and bullet-point summaries of key points, with key words highlighted throughout the text in bold font and listed in a glossary.
- An affordable price for a full colour text supported by numerous diagrams and photographic images.
- An emphasis on clinical examples with a series of 15 clinical case studies that present core information related to clinically significant immune-mediated diseases. This aspect is truly unique to this text and is found in no other reference book on this subject. These case studies should very clearly indicate to the student the major clinical relevance of immunology. They provide a bridge between this book and the more practitioner-orientated *Clinical Immunology of the Dog and Cat*. Both of these texts share fundamental aspects of presentation (e.g. diagrammatic symbols), which should make it straightforward to progress from one to the other.

This book is born from the lecture course in veterinary immunology that I have delivered over the past 20 years to students at the University of Bristol. I am delighted to have had the opportunity of working with Professor Ron Schultz on this project. Ron has made insightful suggestions on the text and ensured that the content also covers the curriculum needs of students in North America. I am very grateful to Ron for sharing his vast experience in veterinary immunology and helping shape this major new resource. Both of us share a passion for this subject and the teaching of it to veterinary undergraduates. However, it is our belief that *Veterinary Immunology – Principles and Practice* will not only have relevance to the student market, but should serve as a simple reference for veterinarians already in practice.

I would like to acknowledge the support and enthusiasm for this project from Michael Manson and Commissioning Editor Jill Northcott. This is my fourth book for Manson Publishing, but the first truly undergraduate textbook. My thanks go to the production team of Kate Nardoni (project manager), Susan Tyler (illustrator) and Peter Beynon (copy editor) for their professional input into the finished product.

M. J. Day
January 2011

Preface (Second Edition)

I was delighted with the response to publication of the first edition of *Veterinary Immunology – Principles and Practice* in 2011. The book was very well received by veterinary students and has now become the adopted text in numerous veterinary schools throughout the world. The text achieved its goal of providing a concise and affordable book supported by high-quality colour illustration. Many colleagues who teach veterinary immunology were highly complimentary about this new resource and offered constructive suggestions for changes to a second edition. Teachers of the subject were also very pleased with the opportunity, provided by the publishers, to obtain teaching sets of the images and diagrams used in the book.

Immunology is a rapidly developing subject area and in order for this textbook to remain current the text of the second edition has been widely updated with advances in knowledge since 2011. The format and style of the text remains the same, but the second edition contains around 20 new and updated figures, one new table and two new clinical case studies. New developments in fundamental and clinical veterinary immunology are reported, with expanded information on commonly used diagnostic test procedures and the inclusion of newly arising diseases such as bovine neonatal pancytopenia.

I have been delighted to have the opportunity once more of collaborating with my friend and colleague, Professor Ron Schultz, on this second edition. I would also like to acknowledge my Commissioning Editor, Jill Northcott, and the production team of CRC Press.

It is now over 15 years since I first began working with Manson Publishing on the production of my first book, *Clinical Immunology of the Dog and Cat*. This second edition of *Veterinary Immunology – Principles and Practice* would have been my sixth Manson publication, but as the final manuscript for this edition was submitted, Michael announced his retirement and the transfer of Manson Publishing to CRC Press. I would like to acknowledge my long and fruitful collaboration with Michael and wish him the very best for the future.

M. J. Day
May 2014

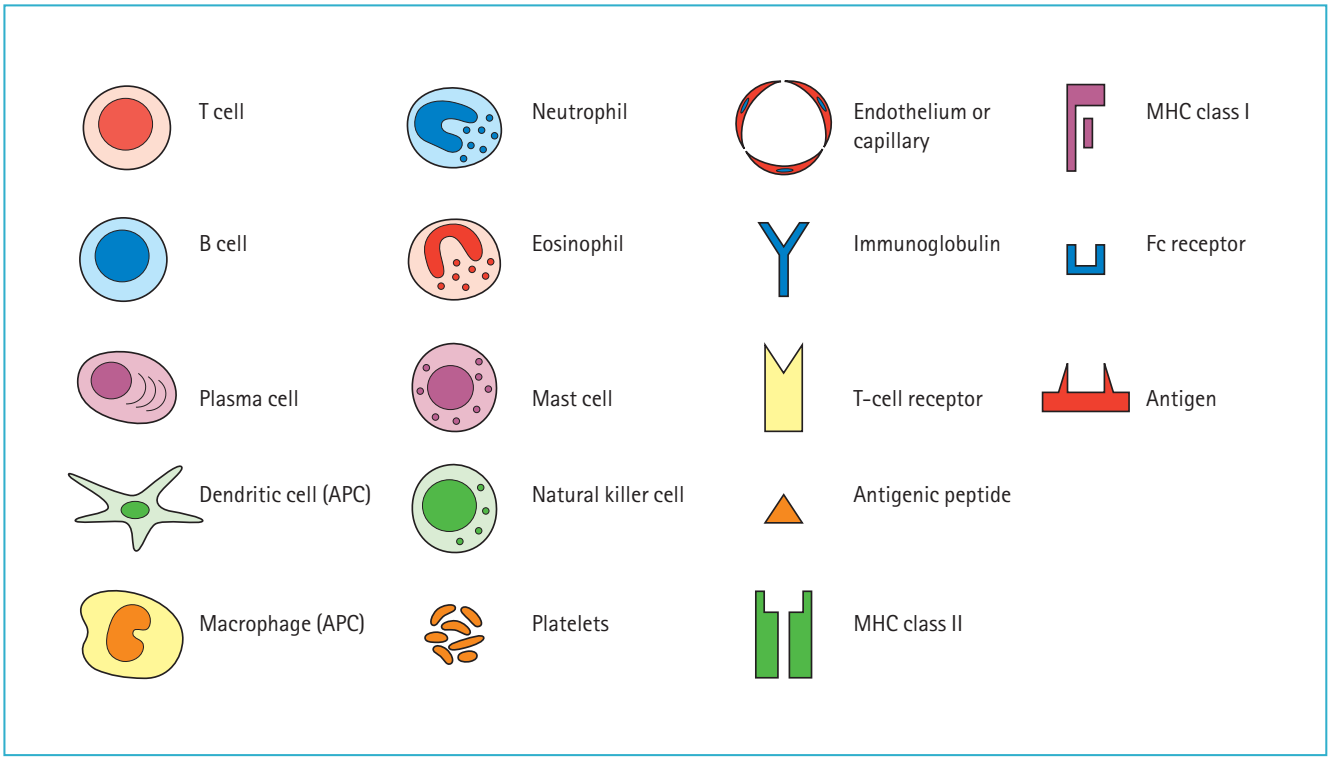
Abbreviations

AchR	acetylcholine receptor
AD	atopic dermatitis
ADCC	antibody-dependent cell-mediated cytotoxicity
AGD	agar gel diffusion
AIDS	acquired immune deficiency syndrome
AIHA	autoimmune haemolytic anaemia
AINP	autoimmune neutropenia
AITP	autoimmune thrombocytopenia
ALL	acute lymphoblastic leukaemia
ALP	alkaline phosphatase
ANA	antinuclear antibody
APC	antigen presenting cell
APTT	activated partial thromboplastin time
ASIT	allergen-specific immunotherapy
AST	aspartate aminotransferase
BALT	bronchial-associated lymphoid tissue
BCR	B-cell receptor
BLAD	bovine leucocyte adhesion deficiency
BLV	bovine leukaemia virus
BNP	bovine neonatal pancytopenia
BoLA	bovine leucocyte antigen
BSA	bovine serum albumin
BVDV	bovine viral diarrhoea virus
CADESI	canine atopic dermatitis extent and severity index
CALT	conjunctiva-associated lymphoid tissue
CAV	canine adenovirus
CD	cluster of differentiation
CDR	complementarity determining region
CDV	canine distemper virus
CFT	complement fixation test
C_H	constant region of the heavy chain
CH_{50}	total haemolytic complement (assay)
C_L	constant region of the light chain
CLA	cutaneous lymphocyte antigen
CLAD	canine leucocyte adhesion deficiency
CLE	cutaneous lupus erythematosus
CLIP	class II-associated invariant chain peptide
CLL	chronic lymphoid leukaemia
CMI	cell-mediated immunity
CNS	central nervous system
ConA	concanavalin A (mitogen)
COX	cyclooxygenase
cpm	counts per minute
CR	complement receptor
CRP	C-reactive protein
CTLA-4	cytotoxic T lymphocyte antigen-4
DAF	decay accelerating factor
DAMP	damage-associated molecular pattern
DAT	direct antiglobulin test
DEA1	dog erythrocyte antigen 1
DLA	dog leucocyte antigen
DNA	deoxyribonucleic acid
DOI	duration of immunity
DTH	delayed-type hypersensitivity
EAE	experimental autoimmune encephalomyelitis
EBP	eosinophilic bronchopneumopathy
ELA	equine leucocyte antigen
ELISA	enzyme-linked immunosorbent assay
ELISPOT	enzyme-linked immunospot
EPI	exocrine pancreatic insufficiency

ER	endoplasmic reticulum
ES	excretory–secretory (proteins)
Fab	antigen-binding fragment (of Ig)
FAD	flea allergy dermatitis
Fc	crystallizable fragment (of Ig)
FcR	Fc (Ig heavy chain) receptor
FeLV	feline leukaemia virus
FHV	feline herpesvirus
FIP	feline infectious peritonitis
FISS	feline injection site sarcoma
FITC	fluorescein isothiocyanate
FIV	feline immunodeficiency virus
FLA	feline leucocyte antigen
FOCMA	feline oncornavirus-associated cell membrane antigen
GALT	gastrointestinal-associated lymphoid tissue
G-CSF	granulocyte colony-stimulating factor
GITR	glucocorticoid-induced TNF-receptor-regulated (gene)
GMCSF	granulocyte–macrophage colony-stimulating factor
GMP	guanosine monophosphate
GnRH	gonadotrophin-releasing hormone
GTP	guanosine triphosphate
GVHD	graft-versus-host disease
GWAS	genome-wide association study
HAI	haemagglutination inhibition
HAT	hypoxanthine, aminopterin and thymidine
HEV	high endothelial venule
HGPRT	hypoxanthine–guanine phosphoribosyl transferase
HIV	human immunodeficiency virus
HLA	human leucocyte antigen (human MHC)
IBD	inflammatory bowel disease
IBH	insect bite hypersensitivity
IBR	infectious bovine rhinotracheitis
ICAM-1	intercellular adhesion molecule-1
IDST	intradermal skin test
IEL	intraepithelial lymphocyte
IEP	immonoelectrophoresis
IFA	immunofluorescent antibody (test)
IFN	interferon (e.g. IFN-γ)
Ig	immunoglobulin
IGHA	gene encoding the IgA heavy chain
IL	interleukin
IMHA	immune-mediated haemolytic anaemia
IMP	inosine monophosphate
IMNP	immune-mediated neutropenia
IMTP	immune-mediated thrombocytopenia
iTreg	induced Treg (cell)
IVIG	intravenous immunoglobulin (therapy)
JAK	Janus kinase
KCS	keratoconjunctivitis sicca
KIR	killer cell immunoglobulin-like receptor
KLH	keyhole limpet haemocyanin
LAD	leucocyte adhesion deficiency
LAK	lymphokine-activated killer (cell)
LFA-1	lymphocyte function-associated antigen-1
LGL	large granular lymphocyte
LPS	lipopolysaccharide
M cell	microfold cell
M1/M2	subtypes of macrophages
MAC	membrane attack complex
MAdCAM	mucosal addressin cell adhesion molecule
MALT	mucosa-associated lymphoid tissue
MAMP	microorganism-associated molecular pattern
MASP	MBL-associated serine protease
MBL	mannan-binding lectin
MCH	mean cell haemoglobin
MCHC	mean cell haemoglobin concentration
MCP	membrane co-factor protein
MCV	mean cell volume
MDA	maternally derived antibody
MHC	major histocompatibility complex
MMP	matrix metalloproteinase
mRNA	messenger RNA
MS	multiple sclerosis
NADPH	nicotinamide adenine dinucleotide phosphate
NALT	nasal-associated lymphoid tissue

NET	neutrophil extracellular trap
NF-AT	nuclear factor of activated T cells
NFκB	nuclear factor κB
NI	neonatal isoerythrolysis
NK	natural killer (cell)
NKT	natural killer T (cell)
NLR	NOD-like receptor
NO	nitric oxide
NOD1/2	nucleotide-binding oligomerization domain 1/2
NOD	non-obese diabetic mouse
NOS	nitric oxide synthase
nTreg	natural Treg (cell)
NZB	New Zealand black mouse
OLA	ovine leucocyte antigen
OSP	outer surface protein
OVA	ovalbumin
PALS	periarteriolar lymphoid sheath
PAMP	pathogen-associated molecular pattern
PBMC	peripheral blood mononuclear cell
PBS	phosphate buffered saline
PCR	polymerase chain reaction
PCV	packed cell volume
PEG	polyethylene glycol
PHA	phytohaemagglutinin
PI	persistently infected
pIgR	polymeric immunoglobulin receptor
PRR	pattern recognition receptor
PT	prothrombin time
PTH	parathyroid hormone
PVDF	polyvinylidene fluoride
PWM	pokeweed mitogen
PWMS	post-weaning multi-systemic wasting syndrome (of pigs)
RAG	recombination activating gene
RAO	recurrent airway obstruction
RBCs	red blood cells
RF	rheumatoid factor
rHuGCSF	recombinant human granulocyte colony-stimulating factor
rHuGMCSF	recombinant human granulocyte–monocyte colony-stimulating factor
rHuIFN-α	recombinant human IFN-α
RIG	retinoic acid inducible gene (receptor)
RNA	ribonucleic acid
ROS	reactive oxygen species
RT-PCR	reverse transcriptase polymerase chain reaction
SAA	serum amyloid A
SCID	severe combined immunodeficiency/ immunodeficient
SI	stimulation index
SLA	swine leucocyte antigen
SLE	systemic lupus erythematosus
SLIT	sublingual immunotherapy
SNP	single nucleotide polymorphism
SPC	summary of product characteristics
SRBC	sheep red blood cell
SRID	single radial immunodiffusion
STAT	signal transducers and activators of transcription
TAM	tumour-associated macrophage
TAP	transporter protein (TAP1/TAP2)
Tc	T cytotoxic (cell)
TCR	T-cell receptor
TFh	T follicular helper (cell)
Tg	thyroglobulin
TGF	transforming growth factor
Th	T helper (cell)
TLR	Toll-like receptor
TMS	trimethoprim–sulphonamide
TNF	tumour necrosis factor
TNS	trapped neutrophil syndrome
TPMT	thiopurine methyltransferase
Treg	T regulatory (cell)
TSH	thyroid-stimulating hormone
UPC	urine protein:creatinine (ratio)
VEGF	vascular endothelial growth factor
V_H	variable region of the heavy chain
V_L	variable region of the light chain
VN	virus neutralization
WHO	World Health Organization
X-SCID	X-linked severe combined immunodeficiency

Key to symbols



CHAPTER 1

An Overview of the Immune System: Innate and Adaptive Immunity and the Inflammatory Response

OBJECTIVES

At the end of this chapter you should be able to:

- Distinguish between innate and adaptive immunity.
- Discuss how gene duplication within the immune system provided an evolutionary advantage.
- Give examples of innate immune mechanisms of the skin and mucosal surfaces.
- Describe the main features of acute and chronic inflammation.
- List the components of the adaptive immune system.
- Understand the key role of the dendritic cell in linking innate and adaptive immunity.
- Understand why it is necessary to regulate the immune system.
- Define the concept of immunological memory.
- Briefly describe the evolution of the immune system.

INTRODUCTION

Immunology is a relatively young and rapidly developing science that has established itself as a fundamental cornerstone of human and veterinary clinical medicine. There are not many veterinary activities that do not have an immunological aspect. The husbandry of neonatal domestic livestock and the essential requirements for colostral immunity, the crucial role of vaccination in protecting the population and the individual from infectious disease, the laboratory diagnosis of a wide range of disorders, the consequences of chronic disease for immune function and the myriad of immune-mediated diseases caused by disturbance of immune homeostasis are all examples of how basic knowledge of the immune system impacts on the daily practice of veterinary medicine. The aim of this textbook is not only to provide this basic knowledge of immune function, but also to clearly relate this to clinical practice.

This chapter will briefly review the history of immunology and broadly consider the different elements of the immune system and how they interact to create a unified whole. The focus here will be on the innate immune system, with an introduction to adaptive immunity, which will be discussed in detail in subsequent chapters.

HISTORY OF IMMUNOLOGY

A perusal of the relatively short history of the discipline of immunology reveals just how integral veterinary immunology has been to the development of this science. This brief summary cannot do full justice to the progressive discoveries that have led to our current state of knowledge. Most texts record the birth of immunology, at least in the Western world, as related to the introduction of the concept of vaccination by Edward Jenner. In 1796 Jenner performed his famous experiment whereby he

collected fluid from a cowpox vesicle on the hand of the dairymaid Sarah Nelmes, and inoculated this into the arm of the 8-year-old boy James Phipps. Although James developed cowpox lesions, he was protected when subsequently challenged 2 months later with virulent smallpox. It has recently been suggested that a similar experiment may have been conducted some 20 years before Jenner by the Dorset farmer Benjamin Jesty. The next major developments in immunology were attributed to Louis Pasteur, who developed vaccines to fowl cholera (1879), anthrax (1881), swine erysipelas (1892) and rabies (1885). It is noteworthy how many of the early developments in immunology related to animal diseases.

In fact, the history of immunological developments can be easily appreciated by studying a list of Nobel prizes awarded in this discipline (*Table 1.1*). These chart the progressive recognition of antibody, phagocytic cells and complement through to the current appreciation of the molecular interactions that underpin immune function. Of note is the 1996 award to Peter Doherty, a 1962 graduate of the University of Queensland School of Veterinary Science, who undertook postgraduate studies on ovine 'louping-ill' at the Moredun Research Institute in Scotland, further demonstrating the role that veterinarians have had in the development of immunology. In the current century, veterinary immunology remains a flourishing field of research with its own journals (e.g. *Veterinary Immunology and Immunopathology*), conferences and societies such as the American Association of Veterinary Immunologists (of which Dr Schultz was the first President). A major recent achievement in veterinary immunology was the declaration in 2011 that the world was free of rinderpest virus infection following successful vaccination campaigns. This is only the second occasion that a major infectious disease has been eliminated, the first being the eradication of smallpox in 1979.

TABLE 1.1. NOBEL PRIZES IN IMMUNOLOGY

1901	Von Behring	Discovery of serum antibody
1905	Koch	Immune response in tuberculosis
1908	Mechnikov and Ehrlich	Phagocytosis and antitoxins
1913	Richet	Anaphylaxis
1919	Bordet	Complement
1960	Burnet and Medawar	Immunological tolerance
1972	Edelman and Porter	Antibody structure
1977	Yalow	Development of radioimmunoassay
1980	Benacerraf, Dausset and Snell	Discovery of the major histocompatibility complex
1984	Jerne, Kohler and Milstein	Production of monoclonal antibodies
1987	Tonegawa	Mechanism of antibody diversity
1990	Murray and Thomas	Transplantation
1996	Doherty and Zinkernagel	Major histocompatibility complex restriction
2011	Steinman	Role of the dendritic cell in adaptive immunity
2011	Beutler and Hoffman	Activation of innate immunity