

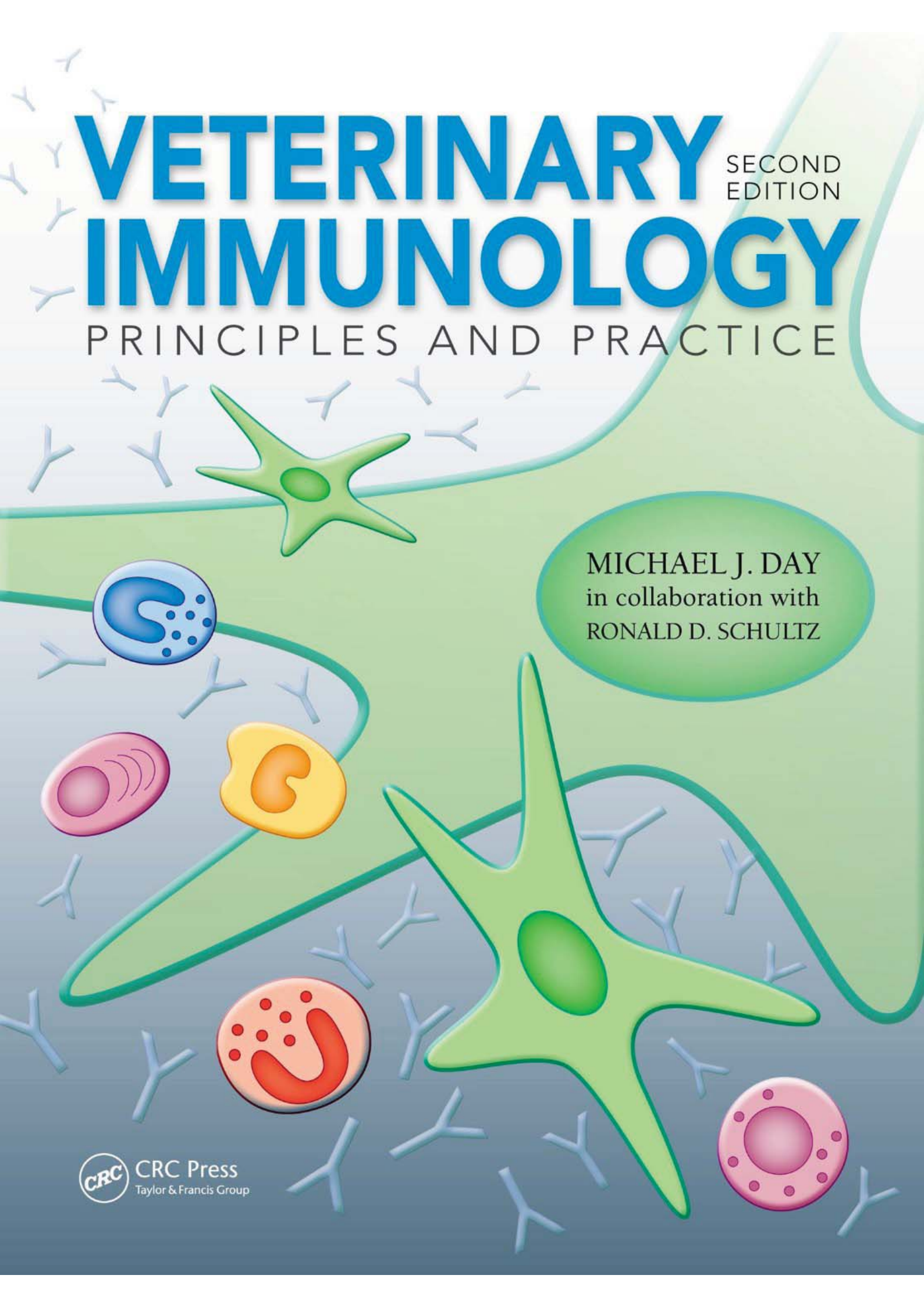
# VETERINARY IMMUNOLOGY

SECOND EDITION

PRINCIPLES AND PRACTICE

MICHAEL J. DAY  
in collaboration with  
RONALD D. SCHULTZ

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# Veterinary Immunology – Principles and Practice

*Second Edition*

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# Foreword

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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)

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*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)

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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













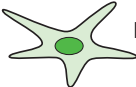





<b>AchR</b>	acetylcholine receptor	<b>CFT</b>	complement fixation test
<b>AD</b>	atopic dermatitis	<b>C<sub>H</sub></b>	constant region of the heavy chain
<b>ADCC</b>	antibody-dependent cell-mediated cytotoxicity	<b>CH<sub>50</sub></b>	total haemolytic complement (assay)
<b>AGD</b>	agar gel diffusion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

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



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

# Key to symbols

	T cell		Neutrophil		Endothelium or capillary		MHC class I
	B cell		Eosinophil		Immunoglobulin		Fc receptor
	Plasma cell		Mast cell		T-cell receptor		Antigen
	Dendritic cell (APC)		Natural killer cell		Antigenic peptide		
	Macrophage (APC)		Platelets		MHC class II		

# 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 colostrum 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