Insects and Other Terrestrial Arthropods
Biology, Chemistry and Behavior

Ticks

Disease, Management and Control

Moges Woldemeskel
Editor

NOVA

INSECTS AND OTHER TERRESTRIAL ARTHROPODS:
BIOLOGY, CHEMISTRY AND BEHAVIOR

TICKS

DISEASE, MANAGEMENT AND CONTROL

MOGES WOLDEMESKEL
EDITOR

Nova Science Publishers, Inc.
New York

For permission to use material from this book please contact us:
Telephone 631-231-7269; Fax 631-231-8175
Web Site: http://www.novapublishers.com

LIBRARY OF CONGRESS CATALOGING-IN-PUBLICATION DATA

Ticks: disease, management, and control / editor: Moges Woldemeskel.
p. cm.
Includes index.
ISBN 978-1-62081-136-8 (hardcover)
1. Ticks--Control. I. Woldemeskel, Moges.
SF810.T5T55 2012
571.9'86--dc23

2012005426

Published by Nova Science Publishers, Inc. † New York

INSECTS AND OTHER TERRESTRIAL ARTHROPODS:
BIOLOGY, CHEMISTRY AND BEHAVIOR

TICKS

DISEASE, MANAGEMENT AND CONTROL

INSECTS AND OTHER TERRESTRIAL ARTHROPODS: BIOLOGY, CHEMISTRY AND BEHAVIOR

Additional books in this series can be found on Nova's website under the Series tab.

Additional E-books in this series can be found on Nova's website under the E-book tab.

PREFACE

Ticks and tick-borne diseases are among the major stumbling blocks to the development of livestock industry and entail heavy economic loses particularly in the tropics and subtropics. Ticks serve as vectors of several diseases and pose health hazards to animals and humans throughout the world. Attempts to control ticks and tick-borne diseases using different methods have been going on for several generations; however, ticks still cause insurmountable problems to the livestock industry and human and animal health. This book enlightens the reader on research and field experiences obtained from different parts of the world on the various chemical and biological approaches used in the control of ticks and tick-borne diseases. This book would serve as a valuable reference and guide for students, and researchers in biological and biomedical sciences and tick control authorities aimed at devising a sound tick control strategy.

Chapter 1 - Stress can be defined as a threat to homeostasis. Physiologic effects of acute stress include heightened awareness, increased heart rate, and muscle tone; all positive developments if the individual is being called upon to defend itself or escape. Chronic stress, however, can be detrimental to homeostasis. Ticks are external parasites and their blood-feeding behavior poses a significant economic burden to domestic animal agriculture worldwide. Direct negative economic effects of ticks on their hosts include loss of body weight and condition, lowered reproduction, and hide damage. These observed effects are due to a combination of a direct impact on homeostasis and lowered nutritional status via depression of intake. Additional hardships may result from disease transmission. Combating an external parasite burden may be considered a "cost of fitness" which incurs a drain on available energy. Protein-energy malnutrition has metabolic, endocrine and immune consequences especially with respect to parasitism. In this chapter, the effects of tick stress on grazing animals are discussed in relation to an interconnected series of physiological events involving multiple systems and indicators. Topics include: behavior, nutrition, metabolism, endocrine and immune factors, gastrointestinal function, and commensal bacteria. Recent research dealing with direct measurement of animal performance and metabolic indicators in cattle experiencing experimentally induced tick burdens will be discussed. Detection of tick stress via fecal analysis is presented as a means of bio-forensics.

Chapter 2 - The feeding period of hard ticks often exceeds one week and makes tick infestation a considerable intervention to host physiology. A broad range of inflammatory and immune reactions take place locally at the feeding site as well as systemically within the host body. Active modulation of the host immune response by tick saliva is thus required for the tick to complete its blood meal. Upon attachment, the tick inoculates its saliva containing a repertoire of bioactive molecules that help ticks to attach to the host, to overcome host hemostasis, and to prevent host pain and itching and the concomitant scratching. Furthermore, the tick must deal with the host innate immunity during primary infestation and with innate and adaptive immunity in subsequent infestations. The immunomodulatory properties of tick saliva and the roles of individual salivary components at the tick-host interface are described in this chapter, dealing with virtually all levels of nonspecific and specific host immune mechanisms. In addition, tick-borne pathogens, including the Lyme disease spirochete *Borrelia burgdorferi*, exploit the pharmacologic activities of tick salivary molecules to successfully maintain their life cycle. Identification of molecules responsible for this phenomenon, termed saliva-assisted transmission (SAT), can help in the design of an efficient transmission-blocking vaccine. Moreover, understanding of the immunity-based processes within the tick-host-pathogen interface opens a relatively new field for the development of drugs to treat various immunity-related diseases.

Chapter 3 - The tick *Ixodes ricinus (I.ricinus)* is the most multi-competent vector in Europe, responsible for significant diseases of humans and livestock throughout the northern hemisphere. Quantitative analysis of tick-borne disease risk and potential tick control depends on a full understanding of the tick's complex seasonal dynamics, for which a realistic model is an invaluable tool. The effects of individual environmental factors on population dynamics can be investigated in ways not easily possible by experimental manipulation of *in situ* populations. A population model for *I. ricinus*, based on a modified stage-classified Leslie matrix, gives a good fit to field data from UK sites and, after modification of a single parameter, also replicates divergent seasonal patterns in central Spain. This modification with respect to diapause, which is required before the model is more generally applicable across wide geographic areas, highlights gaps in the authors' knowledge of tick biology. The model is generally robust, but most sensitive to changes in parameters related to density-dependent mortality.

This model can be used to explore the relative impact of changes in climate, host density and acaricide-treated hosts on tick abundance and seasonality to identify the causes of apparent recent increases in tick populations, and to predict potential effects of future environmental change. The rise in temperature in 1989 across Europe could have increased the inter-stadial development rate of ticks, thereby reducing the cumulative effect of daily mortality rates and potentially raising population levels. An earlier onset of tick questing activity in warmer springs could increase contact between ticks and humans during recreation in the countryside in spring holidays. These tick population effects are more marked where initial background climate is more limiting, especially along latitudinal and altitudinal boundaries. At the same time, the observed increase in deer abundance is predicted to drive tick populations up, most markedly where deer are initially at low densities. Where host densities are already high, however, further increases may reduce the population of questing ticks as they find hosts more rapidly, even though the overall tick population (and therefore pathogen transmission potential) increases. Culling high-density deer populations could, therefore, initially cause an apparent increase in questing ticks, while adding more large hosts (e.g. sheep) would effectively reduce the number of questing ticks, and therefore the risk to humans. If such sheep were treated with acaricide, tick populations are predicted to decrease rapidly. Tick control in designated areas may be achieved by using sheep in this way as 'lethal mops', as occurred in the past.

Chapter 4 - Ethiopia has the largest livestock population in Africa, and lies in the tropics encompassing wide ranges of agro-climatic zones including the cool central highlands, wet tropical forest in the west and southwest and dry arid and semi-arid areas in the east, south and southeast. Therefore it would represent various climatic zones and livestock production systems in tropical Africa. Ticks are the main ectoparasites infesting domestic and wild animals and are among the major stumbling blocks in livestock production in Ethiopia and tropical Africa. Ixodid and argasid ticks collected from cattle, sheep, goats, camels, equines and a few from wild animals in Ethiopia are described. In this chapter, forty-four tick species in 9 genera recorded in different agro-ecological zones of the country and their possible role in disease transmission are briefly described. The identified ticks infesting domestic and wild animals belonged to the genus *Rhipicephalus* (15 species), *Hyalomma* (9 species), *Amblyomma* (8 species), *Haemaphysalis* (4 species), *Aponomma* (2 species), *Boophilus* (2 species), *Ornithodorous* (2 species), *Ixodes* (1 species), and *Argas* (1 species). Understanding the distribution, seasonal dynamics and the host range on various tick species infesting domestic and wild animals is very important to envisage and implement sound and effective tick- and tick-borne disease control strategies.

Chapter 5 - Canine babesiosis is an important worldwide, tick-borne disease caused by hemoprotozoan parasites of the genus *Babesia*. It is a small pleomorphic intraerythrocytic parasite that can cause erythrocyte destruction and hemolytic anemia. The parasite is transmitted through the bites of ixodid ticks, such as *Rhipicephalus sanguineus*. Definitive diagnosis of canine babesiosis is based on medical history and clinical signs together with the identification of *Babesia* spp. within infected erythrocytes, positive serologic results, or detection of amplification of nucleic acid extracted from blood or tissues. Subjects with high mortality can be identified using several prognostic factors. Combination of babesicidal agents and antibiotics, and supportive cares are integrated as treatment program for canine babesiosis. Tick (vector) control is the key to prevent canine babesiosis. This chapter describes the current information regarding epidemiology, pathogenesis, and pathophysiology of the clinical manifestations associated with tick-borne canine babesiosis, and the methods of diagnosis, prognostic factors, treatments and prevention of canine babesiosis.

Chapter 6 - Cutaneous dermatophilosis is a severe skin disease of domestic animals caused by the bacterium *Dermatophilus congolensis* (*D. congolensis*). Although the disease is caused by *D. congolensis*, several risk factors are associated with the pathology and pathogenesis of the disease. Tick infestation is among the major risk factors, which play a very important role in the establishment, transmission and progression of the disease. Dermatophilosis and tick infestation entail heavy economic losses in animal production due to treatment costs, management of the disease and condemnation of skin and hides in various parts of the world, particularly in the tropical countries. In this chapter, the role ticks play in the pathology and pathogenesis of dermatophilosis and the effect of tick control in the management of the disease will be covered.

Chapter 7 - Tick resistance to acaricides is an increasing problem in tropical Africa. It poses a real economic threat to the livestock and veterinary pharmaceutical industries. New acaricides are extremely expensive to develop. Therefore, the present acaricides should be seen as an ever-diminishing resource, which should be protected by all means possible. To alleviate tick resistance problems through resistance management regimens, it is very important to determining the pattern of resistance to ticks in a given area. A field survey was carried out at selected communal and commercial farms in the Eastern Cape and Northwest

Provinces of South Africa to monitor the levels of field ticks (B. decoloratus, R. evertsi evertsi, R. appendiculatus and A. hebraeum) resistance to Amitraz, Cypermethrin and Chlorfenvinphos.

On the communal farms high levels of tick resistance were detected to Cypermethrin as well as partial resistance to Chlorfenvinphos whilst no resistance was detected against Amitraz. On the commercial farms, however, ticks were equally resistant to Amitraz, Cypermethrin and Chlorfenvinphos. The populations of B. decoloratus on these farms had developed higher levels of resistance to the test acaricides than the populations of R. evertsi evertsi, R. appendiculatus and A. hebraeum. Higher level of tick resistance to Amitraz was observed on commercial farms than on communal farms. However, there was no significant difference in tick resistance to Chlorfenvinphos and Cypermethrin at both the commercial and communal farms. It was summarized that inappropriate use of acaricides on the commercial as well as the communal farms might have resulted in higher tick resistance to the currently available acaricides.

This chapter describes the levels of tick resistance to acaricides at selected commercial and communal farms in South Africa, compares the *in vitro* adult and larval test methods and discusses the acaricide management strategies, which may increase the lifespan of the presently used acaricides.

Chapter 8 - Different approaches have been used in Mexico during several years for the control of the cattle tick *Rhipicephalus (Boophilus) microplus,* the vector of two very important diseases of cattle: babesiosis, caused by the haemoprotozoans *Babesia bovis* and *B. bigemina* and anaplasmosis caused by the haemotropic rickettsia *Anaplasma marginale*. The most frequently used methods in Mexico include strategic acaricidal baths, which when used improperly have generated tick populations resistant to some acaricides, use of anti-tick commercial vaccines, and the more recently proposed use of entomopathogenic fungus for biological control of ticks. These methods utilized in Mexico have shown various degrees of success. In this chapter the efficacy of the aforementioned methods of tick control and their drawbacks are discussed. Furthermore, the tendencies for the use of alternative new control procedures, for example the use of the fly *Megaselia scalaris* as a biologic control method as well as the practice of integrated control strategies is described.

Chapter 9 - The tick *Rhipicephalus (Boophilus) microplus* is a bovine ectoparasite that causes severe economic losses in herds in tropical and subtropical areas due to parasitism and disease transmission. Tick control is currently based mainly on the use of chemicals. However, alternative strategies are required due to the ability of ticks to develop resistance, the demands of consumers for chemical-free foods, and the environmental impact of chemical acaricides. In accordance with this scenario, the use of fungi to biocontrol ticks is an efficient and important tool. The entomopathogenic and acaricidal fungus *Metarhizium anisopliae* is the most studied fungus for the biocontrol of *R. microplus*. Various studies on different aspects of the use of *M. anisopliae* to control ticks and other pests have been published during the decade. Such knowledge is crucial in the search for more efficient strains and for optimizing new formulations for large-scale use of this efficient, economic and environmentally safer form of tick control. Here The authors focus on the biocontrol of the tick *R. microplus* based on the use of *M. anisopliae*, including the different fungal isolates, their virulence, the biochemical and molecular aspects of the pathogenesis and the control strategies.

Chapter 10 - Ticks are vectors of various protozoan and bacterial diseases. Ticks transmit infectious diseases such as Lyme disease, Japanese spotted fever, Rocky Mountain spotted fever, Colorado tick fever, and others. It is significant to check for the presence of a tick bite, because immediate and precise treatment may reduce the morbidity and the mortality due to tick-borne diseases. The management of tick-bite should not be limited to the treatment of only the tick-bite lesions. Physicians need to examine and consider the possibility of consequent hazardous tick-transmitted infectious diseases. As the distribution of ticks is dependent on the environment, it is recommended for physicians to know the types of ticks prevalent in their surroundings, the time ticks bite their victims, and the types of tick-borne disease transmitted by a given tick species prevalent in the surrounding. Recently, dermoscopy is used for detecting and examining the tick-bite lesions and the involved biting tick. It also helps to determine whether or not the tick has been completely removed from the lesion. Dermoscopy is useful for easy initial classification of the tick species, which will suggest the strategy for treatment. Now, the term entodermoscopy is proposed for the new field connecting entomology, infectiology and dermatology.

CONTENTS

In: Ticks: Disease, Management and Control
Editor: Moges Woldemeskel
ISBN: 978-1-62081-136-8

Chapter 1

THE PHYSIOLOGY OF TICK-INDUCED STRESS IN GRAZING ANIMALS

Douglas R. Tolleson,[1,*] Pete D. Teel,[2] Gordon E. Carstens[3] and Thomas H. Welsh, Jr[3]

[1]University of Arizona, School of Natural Resources and the Environment, Arizona, US
[2]Texas A and M University, Department of Entomology, Texas, US
[3]Texas A and M University, Department of Animal Science, Texas, US

ABSTRACT

Stress can be defined as a threat to homeostasis. Physiologic effects of acute stress include heightened awareness, increased heart rate, and muscle tone; all positive developments if the individual is being called upon to defend itself or escape. Chronic stress, however, can be detrimental to homeostasis. Ticks are external parasites and their blood-feeding behavior poses a significant economic burden to domestic animal agriculture worldwide. Direct negative economic effects of ticks on their hosts include loss of body weight and condition, lowered reproduction, and hide damage. These observed effects are due to a combination of a direct impact on homeostasis and lowered nutritional status via depression of intake. Additional hardships may result from disease transmission. Combating an external parasite burden may be considered a "cost of fitness" which incurs a drain on available energy. Protein-energy malnutrition has metabolic, endocrine and immune consequences especially with respect to parasitism. In this chapter, the effects of tick stress on grazing animals are discussed in relation to an interconnected series of physiological events involving multiple systems and indicators. Topics include: behavior, nutrition, metabolism, endocrine and immune factors, gastrointestinal function, and commensal bacteria. Recent research dealing with direct measurement of animal performance and metabolic indicators in cattle experiencing experimentally induced tick burdens will be discussed. Detection of tick stress via fecal analysis is presented as a means of bio-forensics.

* Correspondence:E-mail address: dougt@cals.arizona.edu.

INTRODUCTION

Stress can be defined as a threat to homeostasis, some event which the body perceives as harmful and thus requires defensive action. The concept of stress in biological terms was first proposed by Selye [1]. His observation that rats receiving frequent injections developed (among other symptoms) enlarged adrenals regardless of what the injections contained, led others to determine that the hypothalamus, the anterior pituitary, and the adrenals function to produce hormones responsible for the physiological actions now known as the "stress response". In general, this response involves processes which prepare the body for "fight or flight". Included among these processes are: tachycardia, vasoconstriction in the skin, vasodilation in skeletal muscle, and temporary/short-term cessation of "non-essential" processes such as digestion or immune function.

The endocrinology of stress involves catecholamines released from the adrenal medulla as a result of sympathetic nervous system stimulation and, a feedback driven cascade of hormones produced by an interrelated group of tissues known as the hypothalamic-pituitary-adrenal (HPA) axis. Briefly, upon perception of a stressor, the hypothalamus secretes corticotrophin releasing hormone (CRH) which acts upon the anterior pituitary gland's corticotroph cells to stimulate adrenocorticotropic hormone (ACTH) synthesis and secretion. The adrenal cortex subsequently releases glucocorticosteroids (e.g. cortisol and corticosterone) in response to ACTH. Some of the physiologic effects of acute stress were previously alluded to: heightened awareness, increased heart rate and muscle tone, all positive developments if the individual is being called upon to defend itself or escape. Chronic stress, however, can be detrimental to homeostasis. Classic work by Sapolsky [2] with baboons has illustrated the long-term effects of stress on overall health and well-being. Immunity is, of course, a significant player in this process.

THE IMMUNE SYSTEM

One of the most exciting and rapidly expanding fields in the life sciences is immunology. Though driven primarily by interest in combating disease, research into the immune system has also helped expose the intricate connections among various systems in the body. Disciplines such as psychoneuroimmunology, for instance, deal with the actions of such neuroendocrine tissues as sympathetic neurons and HPA hormones on metabolism and the immune system [3]. In addition to indirectly affecting immune function by potentially shunting resources away from immune tissues during a stressful situation, direct effects of glucocorticoids on various immuno-active cells have been demonstrated [4]. Mononuclear cells contain receptors for glucocorticoids [5]. Glucocorticoids inhibit major histocompatibility II expression [6] and tumor necrosis factor production [7] in macrophages. Cortisol [8] reduced lymphocyte production in swine. Hormones of non-adrenal origin have direct effects on immune tissues as well. Growth hormone and insulin-like growth factor 1, for instance, in addition to their better-known metabolic functions, also expedite maturation of lymphocytes in bone marrow [9] and thymus [10]. The communication between the immune system and other physiological systems is bi-directional. Cytokines, the chemical messengers produced by immune cells, influence many metabolic functions; for example protein synthesis and muscle maintenance. Interleukin-1, Interleukin-6, and tumor necrosis factor-α are among the cytokines considered to be "pro-inflammatory". Insulin-like growth factor-1, both circulatory and intramuscular, is reduced by elevated concentrations of these cytokines [11]. Thyroid hormones are important regulators of basal metabolic rate. Pro-inflammatory cytokines diminish the response of thyroid-stimulating hormone to thyrotropin-releasing hormone [12], thus affecting peripheral thyroid hormone levels and ultimately basal metabolism.

STRESS AND THE IMMUNE SYSTEM

Venkatraman and Pendergast [13] in a review of the effects of stress on the immune system state:

> ...stress leads to a proportional increase in stress hormone levels and concomitant changes in several aspects of immunity, including the following: high cortisol; neutrophilia; lymphopenia; decreases in granulocyte oxidative burst, nasal mucociliary clearance, natural killer cell activity, lymphocyte proliferation, the delayed-type sensitivity response, the production of cytokines in response to mitogens, and nasal and salivary immunoglobulin A levels; blunted major histocompatibility complex II expression in macrophages; and increases in blood granulocyte and monocyte phagocytosis, and pro- and anti-inflammatory cytokines. In addition to providing fuel for exercise, glycolysis, glutaminolysis, fat oxidation and protein degradation participate in metabolism and synthesis of the immune components. Compromising, or overusing, any of these components may lead to immunosuppression.

Specifically, chronic stress suppressed Immunoglobulin G titer to keyhole limpet hemocyanin in hamsters [14]. Matalka [15] reviews evidence that acute stress induces the production of pro-inflammatory cytokines (i.e. promotes a T_h1 response), while chronic stress causes dysregulation in immune function by shifting the cytokine pattern in favor of a T_h2 response. Chronic heat stress reduced white blood cell counts and antibody production in laying hens [16], while acute cold stress enhanced the innate immune response in growing chicks [17]. Beef steers grazing endophyte infected fescue have been reported to exhibit decreased phagocytic activity and expression of major histocompatibility complex II [18]. However, Rice et al. [19] found that antibody titers to Conconavilin A tended to be higher and were higher ($P < 0.05$) against sheep red blood cells in cattle grazing infected fescue versus those consuming the non-infected variety. The effect of "stress" on immunity is thus not a "one size fits all" phenomenon. Rook [20] states that, feedback from cytokines on the HPA axis helps the body to control the immune response. Cortisol plays an important role in regulating immunity and inflammation, but as with many other vital physiological functions a delicate balance must be maintained; either too much or not enough can be harmful.

GASTROINTESTINAL TRACT

The gastrointestinal tract (GIT) is a hollow tube extending from the oral cavity to the anus. The function of the GIT is digestion, absorption, and excretion of food residues. Basic architecture varies among species but in mammals generally the components are: the mouth, esophagus, stomach, small intestine, cecum, large intestine, and associated structures such as the liver, pancreas, and gall bladder. Since the small intestine is the primary area for immune activity in the GIT, the discussion in this section will focus on the immunological activities of this organ.

The small intestine is composed of three sections: the duodenum, jejunum, and ileum. It is the longest section of the GIT (~ 50 m in bovines, 4 m in canines, 6 m in humans) and the major site of nutrient absorption. The duodenum, jejunum and proximal ileum are the sites where most digestion and absorption occur [21]. On cross-section, from the serosa to the lumen, the small intestine consists of the longitudinal and circular outer muscular layers, followed by the sub-mucosa and finally the mucosa lining the lumen. The mucosa is the "front line" for both nutrient absorption and immunity. The absorptive surface area of the small intestine is greatly expanded by: 1) folding of the sub-mucosal layer (*valvula conniventes*), 2) the presence of finger like outward projections known as villi upon these folds, 3) and lastly, the villi are in turn lined with epithelial cells possessing a luminal cell surface covered by microvilli. The microvilli are also referred to as the brush border. The net result of the above convolutions and projections is a surface area of approximately 250 m^2 in the adult human [22]. The columnar absorptive cells, enterocytes, line the lumen of the small intestine. These are replaced every 3 to5 days by new cells produced from the simple tubular glands between the villi called crypts of Lieberkuhn. The second most numerous cells found here are goblet cells, important for their mucus secreting functions.

Digestion beyond that which occurs in the upper sections of the GIT is carried out by specific enzymes on the cell surface of the enterocytes, in a layer of glycoproteins known as the glycocalyx. The net result is a population of molecules of a size and configuration appropriate for absorption. Absorption is often accomplished by nutrient dependent mechanisms coupled to Na/K transport, an energy consuming process responsible for much of the net energy of maintenance in animals. Undigested and unabsorbed feedstuffs are passed along the tract through the colon, and ultimately excreted through the anus along with resident microbes, various digestive secretions and sloughed epithelial cells [23, 24].

As important as the digestive functions of the GIT are to the animal, they are by no means the only important functions. The body is exposed to many potential antigens through ingestion of food and associated microbes. The gut epithelium is often described as being in a constant state of controlled inflammation. As such, the commensal microbial population exists in a delicate balance with the body's immune defenses.

IMMUNE FUNCTION OF THE GASTROINTESTINAL TRACT

The GIT provides three barriers against infection: 1) physical structure, 2) innate immune system, and 3) adaptive immune system. Each is interrelated and dependent upon the other two. The physical barrier [25] consists of primarily the mucosa and associated layers. The epithelia, as previously mentioned, line the lumen of the tract and come into immediate contact with microbes and digesta. Tight junctions between cells here allow passage of water and ions but effectively block diffusion of macromolecules and microorganisms. The glycocalyx of columnar epithelial cells and mucus from goblet cells help shield the inner layers from direct microbial attachment and invasion. Paneth cells are found at the base of the luminal crypts and have both secretory (IgA) and phagocytic (lysozyme) functions. Also found in the epithelia are membranous or microfold (M) cells [26], which have specialized adaptations for transporting antigens. The lamina propria is the site of Peyer's patches (discrete clusters of lymphoid follicles), and in the sub-mucosa are numerous primary follicles as well as active germinal centers. The Paneth cells, M cells, and Peyer's patches are thus not only part of the physical barrier to infection, but also play an active part in the innate immune barrier.

INNATE IMMUNITY IN THE GASTROINTESTINAL TRACT

Innate immunity occurs in the gut associated lymphoid tissue. This somewhat amorphous collection of cells is designed to not only defend against intrusion by potentially harmful microbes, but perhaps equally significant also, to not attack helpful organisms. Several cell types and mechanisms within cells exist to accomplish this unique balance. Nicoletti [25] has recently reviewed the origin, structure, and function of M cells. These special cuboidal epithelial cells can be found adjacent to enterocytes but possess a distinct morphology. The M cells exhibit considerably less microvilli than do other epithelial resident cells and the characteristic thick glycoclayx is noticeably absent. Such adaptations facilitate active phagocytosis of large particulate matter within their area. This feature obviously serves to eliminate invading bacteria by internalizing and presenting them to macrophages, but also exposes the body to exploitation by certain microbes which use this route to gain entry to the underlying tissue [27, 28]. Another interesting feature, which differentiates M cells from prototypical intestinal epithelial cells, is the deep invagination of the basolateral membrane. Intraepithelial pockets are thus formed which create intimate contacts between the M cell and specific antigen presenting cells (APC) which home to this area. Such modification of the basolateral membrane also results in shortened transit for endocytotic vesicles within the M cells.

In addition to being interspersed throughout the gut epithelia, the M cells form areas of high concentration (> 50%) immediately above the Peyer's patches. These areas are referred to as follicle-associated epithelium [29]. Kiyono and Fukuyama [26] have presented a thorough review of the origin, structure, and function of the Peyer's patch. The Peyer's patches are dome-shaped structures within the lamina propria, somewhat analogous to the deep cortex and follicles of a lymph node but with no afferent or efferent lymphatic vessels [30]. They are in fact clusters of these follicles. Similar in form and function to lymph nodes, they are thus sites of antigen encounter for activation and induction of B and T cells and have areas of concentration of each type of lymphocyte. Immigration of naïve B and T cells from primary lymphoid tissues occurs via high endothelial venules which lace the lamina propria. Amplification of both effector and memory cells is another similar function of Peyer's patches to that of the lymph nodes, resulting in enhanced IgA secretion and cytotoxic killing. Antigen presentation occurs via macrophages and dendritic cells (DC) which have been in close contact with the invaginated basal membrane of M cells. These APCs, especially DC are an integral link between innate and adaptive immunity.