

The Pediatric Immune System of Dogs and Cats

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Abbreviations

B cells	Bursa of Fabricius-derived lymphocytes
CID	Combined immunodeficiency
GH	Growth hormone
MHC	Major histocompatibility complex
T cells	Thymus-derived lymphocytes
TH	Helper T cells
TNF-α	Tumor necrosis factor alpha
Treg	Regulatory T cells

Abstract

The immune system of humans and other mammalian species such as dogs and cats develops *in utero*, evolves until puberty, matures in adulthood, and culminates in geriatric senescence. During this growth and aging process, parallels exist between these species in the factors that influence and sustain health and trigger disease states. Understanding the fundamentals of the immune response in health and disease has laid the foundation and concepts of basic biology, biochemistry, physiology, psychology, and medicine. With immune dysfunction, the associated congenital and heritable traits of all mammals are expressed similarly. Consequently, studies of naturally occurring and experimentally induced immunological disorders in animals have served for decades as important models of human disease. Significant accomplishments include gaining landmark molecular and metabolic knowledge and the recent advent of genomics, gene editing, and gene therapy, which lead to effective management and treatment strategies.

Introduction

All mammals develop their immune responses *in utero* as a fetus, and the development continues until the onset of puberty and adolescence (1–10). During this critical period of early life, both the innate and adaptive (acquired)

immune systems evolve along with the functional roles of the pituitary-thyroid-hypothalamic axis, thymus gland and its gradual involution, Peyer’s patches, and the maturation of the microbiome in the gut (1, 3–11). This paper summarizes what is known about the developing immune system and its functions, outlines the primary causes of immunological dysfunction, and briefly discusses the heritable and acquired immunologic disorders recognized in young animals.

Overview

Veterinary practitioners are increasingly being presented with patients exhibiting immunological dysfunction and disorders (2–3, 10, 11–14). Beyond infancy, the onset of these conditions often follows from within a few days to 30–45 days after stress events (10, 12–15). Stressors include both physiological (eg, sex hormonal influences and changes, aging) and psychological (eg, separation anxiety, illness, adrenal fatigue syndrome, death of family member), and environmental or other exposures (8–15). This latter group includes examples such as vaccinations, use of certain drugs, parasiticides, chemical exposures to toxins, herbicides, pesticides, fertilizers, indoor cleaning supplies, certain indoor and outdoor plants, and food intolerances (2, 13–16).

Innate and Adaptive Immune Responses

An ability to respond to foreign substances and pathogenic microorganisms such as bacteria, viruses, and fungi is unique to each individual due to the complex nature of the principal components of the immune system (12, 17–23). The innate immune response is ready to go as the “first responder” of immune defense and protection (1, 3–10, 19, 20). It provides barriers to infection on and within the body’s surface, secretions, and gut, and includes the circulating soluble factors of the complement system, which offer further immune support of the defensive response to infection (2). While it does not express immunological memory like that of the adaptive immune system, the early postnatal innate immune response is determined by the maternal microbiota (4). The main cellular components of this response are enterocytes, goblet and dendritic cells, macrophages, neutrophils, mast cells, and eosinophils. Following different types of injury, damage-associated molecular patterns are generated by these cells. The elicited inflammatory response is characterized by chemokine and cytokine production, followed by the recruitment and activation of immune cells (2–9, 17–23). This response is essential to limit pathogen load and to maintain intestinal barrier function (5, 24). When pathogens are present in the gut lumen, mucosal macrophages, eosinophils, and mast cells release toxic and inflammatory mediators such as histamine, nitrogen radicals, tumor necrosis factor-alpha (TNF- α), and toxic enzymes such as lysozyme and peroxidase. However, this total response may be insufficient to avoid penetration of the bowel surface by pathogenic antigens, thus requiring activation of the adaptive immune system in a mutually cooperative fashion (5, 18, 20–23).

An acquired immune response develops after pathogen exposure within the gut lumen (2–10, 18–24). It is characterized by the long-term protection of immunological memory, which is crucial for the acquisition of oral immune tolerance (10, 13, 19, 24, 25). Adaptive responses are mediated by different cell populations such as macrophages, dendritic cells, mast cells, and lymphocytes using mechanisms such as antigen processing and presentation and the production of regulatory and effector molecules (5, 6–8, 18–22). These molecules include the small signaling proteins like cytokines, chemokines, and immunoglobulins that become activated against antigen invasion in combination with cell cytotoxic processes (1, 3–7, 13).

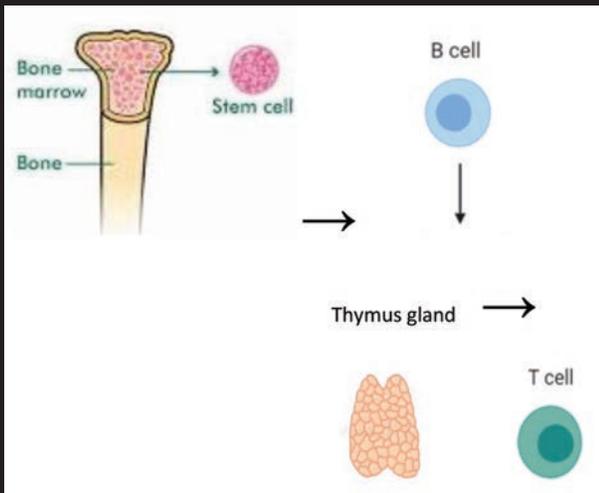
Lymphocytes located between the gut epithelial cells contribute to surface barrier integrity and regulatory functions, although they can also become pro-inflammatory (20, 24). These lymphocytes are predominantly thymus-derived (T cells), involved in the defense against viruses (17–23). They promote regrowth of healthy intestinal epithelial cells following cytolysis of epithelial cells during viral infection, thereby maintaining epithelial integrity. They release gamma interferon and TNF- α as a response to an infection, which then stimulate inflammation and intestinal barrier dysfunction (1, 5, 7, 8, 18, 23, 24). Interferons are proteins that form part of the body’s natural defenses by signaling any invasion of viruses, other microbes, and even cancer cells. They then trigger the production of killer immune cells to fight the invaders (18, 23).

Dendritic cells receive antigens from goblet cells and macrophages and migrate to the draining mesenteric lymph node to activate T cells, resulting in either an immune tolerance or reactive response. Following activation, T lymphocytes can differentiate into different subsets based on their cytokine environment: helper T cell (T_H)1, T_H 2, T_H 17, T_H 19, T_H 22, and regulatory T cells (Treg) (1, 8, 18). These cells are found throughout the lamina propria of the gut, with large numbers in Peyer’s patches, the appendix in humans and other primates, and other scattered lymphoid follicles, and provide an immune defense to protect the body against foreign invasion. Having a high proportion of Treg cells or gut-associated lymphoid tissue in the intestine compared to any other part of the body is crucial for producing oral tolerance (1, 18, 23, 24). T cells, which mature in the thymus gland, only recognize viral antigens outside the infected cells. In contrast, B cells, which mature in the bone marrow (or bursa of Fabricius in birds), recognize the surface antigens of bacteria and viruses (18–24).

The Thymus

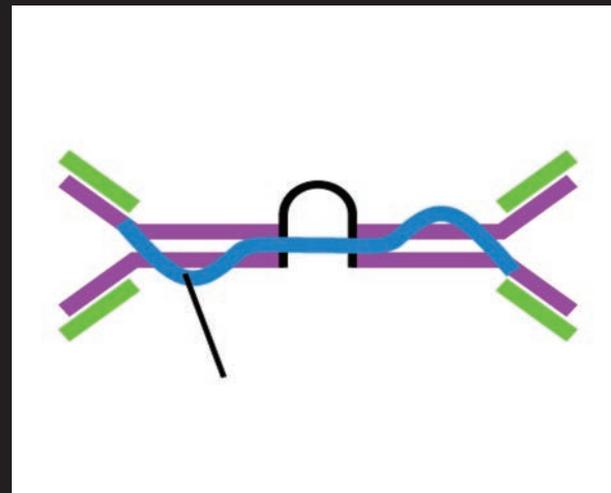
The thymus is a primary lymphoid organ that serves a vital role in the training and development of T cells that defend the body from potentially deadly pathogens including bacteria, viruses, and fungi (3, 6–10). The T lymphocytes orchestrate the development of the adaptive immune response (**Figure 1**). An important role of the thymus is the induction of central immune tolerance (3, 6–10, 19). The thymus starts decreasing in size at birth in many species except dogs, cats, and mice, and the area

Figure 1



Stem Cell Origin of B- and T-Cells and Thymus Gland.

Figure 2



Immunoglobulin A Molecule with Secretory Piece (in blue).

occupied by the thymus is replaced with fatty tissue. This process of involution speeds up after puberty such that by geriatric age, the body is unable to make new T cells (3–8, 12). The thymus gland can involute transiently with stress, infections, pregnancy, and malnutrition (3–8, 24, 26).

More About Early Life Immune Responses

B cell activation allows antibodies to recognize the Class II major histocompatibility complex (MHC) markers. T cell activation involves T_H cells that recognize Class II MHC markers, cytotoxic T cells that recognize Class I MHC markers, and Treg cells. Further, the regulatory and effector molecules of the adaptive immune response sustain the antigen-antibody binding function that release effector cytokines (small cell signaling molecules) and their specific family of chemokines that direct chemotaxis and attract cells to sites of inflammation and infection (1, 3–8, 24, 26). Examples of important chemokines are the interferons, interleukins, and TNF- α (6, 7, 13). Equally important for this evolution of the early life immune response is the protective effect of maternally-derived immunity in neonatal dogs and cats, and fetal mice and humans (3–7, 25, 26).

Mucosal Surface Immunity

In mammals, IgA secretions provide mucosal surface immunity as a mechanical barrier to invasion by foreign particles and microbes (**Figure 2**). Areas include

sebaceous glands on the body surface, intact skin, tears, salivary secretions, sweat, mucous from the nose and upper respiratory tract, ear wax, cilia in the trachea, the gastrointestinal tract and especially the stomach, and the genitourinary tract (7, 12, 15).

The Thyroid Gland

Thyroid hormones are essential for growth and brain development in human infants and all other animals (2, 11, 17, 25, 27–30). The formation and maturation of the pituitary-thyroid-hypothalamic-axis of newborns begin *in utero* with fetal dependence on maternal thyroid hormones early in the pregnancy (26). As the fetal thyroid gland begins to produce thyroid hormones in the mid-pregnancy period, this maternal reliance decreases and remains at lower levels until birth. After birth, placental detachment and the environmental temperature change lead to a rapid increase in circulating neonatal thyroid-stimulating hormone, resulting in subsequent increases in thyroxine and triiodothyronine concentrations. In mothers with autoimmune thyroid disorders, placental transfer of maternal autoantibodies occurs and can affect the thyroid function of the neonatal fetus (11, 17, 25, 27–30). Hypothyroidism is the most common endocrine disorder of dogs, and up to 90% of cases result from the autoimmune lymphocytic thyroiditis akin to human Hashimoto's disease that progressively destroys the thyroid gland over 12–18 months (6, 27, 28). Because this form of thyroid disease is heritable, it has significant genetic implications for canine breeding stock.

Accurate diagnosis of the early stages of thyroid dysfunction and autoimmune thyroiditis offers genetic and clinical options for prompt intervention and case management (28). Congenital hypothyroidism with goiter has been recognized in Toy Fox Terriers and several other breeds including Scottish Deerhounds, Rat Terriers and other terriers, and Giant Schnauzers (29, 30). As the thyroid gland regulates the metabolism of all cellular functions, reduced thyroid function can produce a wide range of clinical and behavioral manifestations. Since many of these clinical signs mimic those resulting from other causes, recognition of the condition and interpretation of thyroid function tests can be problematic (15, 27, 28).

An association between aberrant behavior and thyroid dysfunction occurs in humans and dogs starting around puberty (15, 27, 28). Typical clinical signs in dogs include unprovoked aggression towards other animals or people (especially children), sudden onset of seizure disorder in adulthood, disorientation, moodiness, erratic temperament, periods of hyperactivity, hypo-attentiveness, depression, fearfulness and phobias, anxiety, submissiveness, passivity, compulsiveness, and irritability. After episodes, most animals appear to come out of a trance-like state and are unaware of their bizarre behavior (27, 28). Treatment with thyroxine replacement usually corrects this aberrant behavior (28).

The normal reference ranges for thyroid analytes of healthy adult animals tend to be similar for most breeds of dogs. Exceptions are the sighthound and giant breed types of dogs which have lower basal levels. Similarly, because young animals are still growing and adolescents are maturing, optimal thyroid levels are expected to be in the upper half of the adult reference ranges (15, 27, 28).

Nutrients Essential for a Healthy Immune System

From the fetus to newborn and onwards through puberty, adolescence, and aging, wholesome nutrition is the most crucial factor for maintaining human and animal health (2, 6, 20, 24, 31, 32). It provides direct and indirect factors that promote and sustain the complex immune response. Without good nutrition, the weakened body is potentially subject to more infections from pathogenic organisms (18, 20, 24, 31–34). Malnutrition and protein deficiency of the mother lead to intrauterine growth retardation and reduced thymic function such that the

pediatric offspring have a poor immunological response to vaccination (1,8–10, 20, 26, 34).

The creation of immune tolerance, control of inflammation, and responses to the beneficial bacteria in the microbiome are interrelated and linked to specific immune mechanisms (4, 5, 15, 24, 31, 32). Certain nutrients act as antioxidants and cofactors at the level of cytokine regulation, whereby a balance between the production of reactive oxygen species, free radicals, and endogenous antioxidant defense mechanisms is essential (15). Health is achieved by understanding molecular, individualized, functional nutrition (31–34). Nutrients that play a functional role include vitamins D, E, and C, carotenoids (lycopene and beta-carotene), plant polyphenols, resveratrol, and others (18, 32, 34–40). Omega-3 fatty acids and beta-glucans provide essential benefits for growth (15, 36–38).

Foods “speak” to the body at the cellular level, although scientists have just begun to understand how diet affects the deepest level of cells (30–34). Further, many foods



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one considers healthy can be sending unhealthy messages to genes and the genome (31, 39). Thus, for people and the animals we share our lives with, foods should be pre-selected to promote optimal gene expression and prevent intestinal dysbiosis, the dysfunction of the gut microbial community (15, 30–34, 36–40). This translates to the need for choosing clean, pure, organic foods to avoid health problems related to pesticides, genetically modified organisms, antibiotics, and other human-made hazards such as contaminated foods, toxins, chemicals, heavy metals, and foreign objects that infiltrate our food system (15, 30–35).

Oral Tolerance to Foods

Immune responses directed against gut microbiota result in inflammatory bowel diseases, “leaky gut,” and ulcerative colitis (33–35, 38). Failure to induce tolerance to food proteins is thought to result in food allergy (hypersensitivity) and the more common food sensitivities and gluten intolerance (38). Tolerance to food proteins induced via the small intestine affects local and systemic immune responses, although tolerance to gut bacteria in the colon does not reduce systemic responses (34). Diagnostic assessment of food intolerances is problematic in all species, although accurate systems currently utilize saliva or feces (31–33, 39, 40). Food allergies can be suppressed via a Treg cell pathway after fecal microbiota transplantation (15, 31, 32).

The Microbiome and Health

The microbiome is the genetic material of all the prokaryotic microbes—bacteria, fungi, protozoa, viruses, and archaea—that live on and inside the human and animal bodies (15, 24, 31–34). The number of genes within the microbes of the microbiome is 200 times the number present in the mammalian genome (24). All mammals depend on it to stay alive throughout life as it protects against infection, breaks down food to release energy, and produces vitamins. It is believed by some to be present before birth and impacts maternal-offspring health outcomes, maintains the gut-brain axis, and interacts with the immune system. The microbiome plays a role in many diseases, including metabolic disorders, autoimmune and motor neuron diseases, autism, and cancers (5, 15, 18, 20–24, 31–37). Observable benefits include a reduction in the severity of eczema and other skin disorders, improved protein

digestion (measurable by absent or reduced intestinal gas) in young humans and animals consuming protein-rich diets, and alleviation of constipation in seniors (15, 33, 34).

Lifestyle and environmental factors such as diet, hygiene, exercise, and natural change in the microbiome itself impact the composition of the microorganisms that colonize human and animal bodies throughout life (4, 5). Compositional and functional alterations of the gut microbiome are associated with multifactorial diseases including inflammatory, autoimmune, metabolic, neoplastic, and neurodegenerative (11, 15, 24, 33–36, 38–40). It is possible to restore the microbiome to improve health and well-being utilizing fecal microbiota transplantation, also called microbiome restorative therapy.

Highly diverse microbiome ecosystems are contributing factors that support stability, resistance, and resilience of the microbial community, which contributes to health and reduces the incidence of microbial pathogens. A balanced microbiome improves the quality of life across all life stages (35). In that regard, young people and animals require the same nutrients as mature and older individuals, but in different amounts to support optimum growth and development

Functional Foods and Superfoods (Targeted Nutrition)

Functional foods are whole foods that have a complex and nutrient-rich composition and provide well-being beyond what the body needs to survive (36–38). Superfoods are usually rich in phytochemicals, known for having disease-fighting properties (34). Examples include foods calming to the gut like prebiotics such as spirulina and inulin found in garlic (*Allium sativum*), chickory (*Cichorium intybus*), burdock (*Arctium lappa*), and dandelion (*Taraxacum officinale*), and probiotics such as raw green tripe, lactobacillus, yeast, yogurt, and fermented products such as kefir; lactulose to aid digestion; fructooligosaccharides and mannanoligosaccharides to promote digestibility, especially in the German Shepherd Dog breed; medicinal mushrooms including the anti-cancer properties of turkey tail (*Trametes versicolor*), reishi (*Ganoderma lucidum*), cordyceps (*Cordyceps sinensis*), shiitake (*Lentinula edodes*), and maitake (*Grifola frondosa*); bee products (honey, propolis, royal jelly and pollen); resveratrol (grapes and Japanese

knotweed [*Fallopia japonica*]); phospholipids (phosphatidylserine); immune modulators (beta-glucans); essential fatty acids (omega-3 and -6 fatty acids); and medium-chain triglycerides such as contained in coconut oil (36–39).

Immune Deficiency States

Immune deficiency diseases are a group of disorders in which normal host defenses against infection are impaired. These include disruption of the mechanical barriers by invasion from pathogenic organisms or foreign antigen, defects in nonspecific host defenses, and defects in specific host defenses (2, 3, 6, 41–46).

Immune defects occur in mechanical barriers such as normal bacterial flora and healthy, intact eyes and skin. Primary ciliary dyskinesia, also known as immotile cilia syndrome and Kartagener's syndrome, has an autosomal recessive inheritance in humans, dogs, and mice. It is characterized clinically by chronic respiratory tract disease, male sterility, and middle ear infections that begin in early life, and has been reported in at least 19 dog breeds (41, 46). About half of affected humans also have situs inversus and dextrocardia, a reversal in the location of the internal organs and heart.

Examples of defects in non-specific host defenses include complement deficiency and functional white blood cell disorders. Cyclic hematopoiesis is a congenital disorder of gray Collies affecting all bone marrow elements. A similar condition occurs in humans (41). Cyclical decreases in each of the blood cell elements occur at different times within the same affected individual, although each cycle's periodicity remains the same. The defect lies within the bone marrow itself, as transplantation of affected dog marrow to histocompatible normal dogs produces the disease in the normal marrow, and the reverse procedure corrects the defect of abnormal dogs. Affected Collies have chronic recurrent severe bacterial infections, especially of the respiratory and gastrointestinal tracts. Hemorrhage from thrombocytopenia also occurs, and affected pups often die as neonates, rarely living beyond 3 years of age. Using lithium carbonate in affected humans and dogs works well to prevent infection and maintain production of hematopoietic cells, but it must be given continuously.

Chediak-Higashi syndrome is an inherited autosomal recessive condition of humans, blue Persian cats, and

Hereford cattle (41). Affected individuals characteristically have giant, red-colored lysosomal granules within white blood cells and numerous tissues. The hair and eye color are diluted because enlarged melanin granules are found in the hair shaft and eyes. Congenital cataracts, photophobia, and retinal changes are frequent, and there is an associated platelet dysfunction and bleeding tendency. Affected cats have an increased susceptibility to bacterial infections, as their neutrophil chemotactic function is impaired.

Canine granulocytopenia syndrome was reported in a family of Irish Setters with abnormal leukocyte function and a leukocyte adhesion defect (41). The flaw is inherited as an autosomal recessive trait, and affected dogs have life-threatening bacterial infections and a short life span. Recurring pyoderma and osteomyelitis are common.

Pelger-Huet anomaly is a benign condition of humans and animals not associated with a known clinical problem (41). It is transmitted as an autosomal dominant trait. Dog and cats have been described as having incomplete segmentation of the nucleus of neutrophils and eosinophils. Affected nuclei appear round or bean-shaped.

Third component of complement deficiency is inherited as an autosomal recessive trait in humans, several dog breeds, and an inbred strain of guinea pigs (41). Affected dogs suffer from increased bacterial infections and septicemias, especially involving gram-negative bacteria and *Clostridia* spp.

Defects in specific host defenses include immunosuppression caused by bacteria, viruses, and parasites, and combined immunodeficiency (CID). Severe CID classically occurs in humans, dogs, and Arabian horses (41, 43). The horse defect has a greater than 2% frequency and is inherited as an autosomal recessive trait. Affected Dachshunds in Australia developed fatal *Pneumocystis carinii* pneumonia between 9 and 12 months of age. A family of Basset Hounds had a form of CID with X-linked inheritance. Affected dogs were prone to viral and bacterial infections, especially of *Mycobacterium avium*. These dogs produced only IgM immunoglobulins, had low lymphocyte counts, and died at a young age.

Selective IgA deficiency was reported in a large breeding kennel of Beagles and is commonly seen in the Chinese

Shar-Pei and German Shepherd breeds (41, 42). The Beagles had chronic recurrent respiratory tract infections with *Bordetella*, parainfluenza virus, and parvovirus despite proper vaccination. Chronic ear infections and dermatitis were also present, and occasionally animals developed seizures. Each of these clinical manifestations also occurs with human IgA deficiency, in which serum levels of IgA are undetectable or very low, but immunoglobulins and T cell function are normal. Respiratory infections in these dogs were attributed to inadequate secretory IgA levels at mucosal surfaces. Affected Shar-Peis had recurrent staphylococcal dermatitis, demodectic mange, thyroid disease, otitis externa, flea allergy, cystitis, food intolerance, bronchitis, and atopy (2, 42).

Growth hormone and immune deficiency were described in a colony of inbred Weimaraners with congenital growth hormone (GH) deficiency, a small thymus, and depletion of T lymphocytes. Affected dogs were immunodeficient dwarfs that exhibited a wasting disease, unthriftiness, recurrent infections, and retarded growth. German Shepherd Dogs with this disorder have a combined deficiency of GH, thyroid-stimulating hormone, and prolactin, requiring GH to help support and improve their immune health (46). A parallel syndrome is recognized in immunodeficient dwarf mice. When treated with bovine GH or a thymus gland extract (thymosin), affected pups responded dramatically by growing and developing normal T cell lymphocyte responses.

Lethal acrodermatitis is an autosomal recessive condition of English Bull Terriers and results from impaired absorption and metabolism of zinc (41). Affected pups are lighter in color at birth and develop diarrhea and recurrent respiratory tract and skin infections. The footpads become crusty and crack, nails are incompletely formed, and purulent dermatitis affects the feet and body orifices. Skin biopsies show changes characteristic of zinc deficiency. Impaired T cell function occurs, and serum zinc levels are usually low. Zinc supplementation does not appear to help, and affected animals usually die by 15 months of age (41).

Immune Hypersensitivity

Hypersensitivity reactions can be divided into 4 types (1, 13, 19, 41, 47). Type 1 includes common immune disorders such as asthma, allergic rhinitis, eczema, urticaria, and anaphylaxis. Types 2 and 3 involve autoimmune

or low-affinity antibodies; T cells play an accomplice role, and TH2 cytokines promote them. Type 4, delayed hypersensitivity, is caused by over-stimulation of lymphocytes and macrophages via TH1 cytokines, resulting in chronic inflammation and cytokine release. All these reactions can occur in the very young (13, 19, 25, 47, 49).

Autoimmunity

An imbalance between pro-inflammatory and anti-inflammatory immune components can lead to autoimmune conditions, which reflect the failure of self-tolerance (47–49). The body's immune system is genetically programmed to attack its own tissues mistakenly. Some of the more common immune-mediated disorders include the hematological conditions of hemolytic anemia and immune thrombocytopenia (a combination known as Evan's syndrome in people and dogs), hemolytic disease of the newborn (like Rhesus blood type incompatibility in infants, or the equivalent blood type incompatibilities in foals, puppies, or kittens), immune-complex glomerulonephritis, autoimmune thyroiditis in dogs akin to human Hashimoto's disease, and Addison's disease in several dog breed families. The combination of thyroiditis and Addison's disease in people, called Schmidt's syndrome, also occurs in dogs (2, 27, 47).

Mercury-induced inflammation is also called ASIA, the autoimmune/inflammatory syndrome induced by adjuvants. It causes autoimmunity, including thyroiditis, multiple sclerosis, immune-complex kidney diseases, chronic fatigue syndrome, and myalgia (2, 27, 28, 47–50). Mercury is still used in dental fillings and as the preservative thimerosal in rabies and other vaccines (14, 48–51). Nickel, gold, silver, aluminum, and chromium appear to function similarly (48–51). Immunomodulation and allergic, delayed hypersensitivity have been reported and can manifest as contact dermatitis and other signs. Genetic predisposition is involved in animals and likely in people, and predisposing factors include the patient's endocrine status and chronic infections (1, 2, 48).

Vaccines and Vaccinosis

Modern vaccine technology has afforded effective protection of humans and other species against serious infectious diseases (13, 14, 16, 27, 47, 62). More lives have been saved, and more livestock and companion animal health and productivity have been safeguarded than any other

medical advance (14). Smallpox has been eradicated, as has nearly all polio and measles in people. Endemics of canine distemper virus, infectious hepatitis virus, adenovirus, and parvovirus have been significantly reduced, although not in wildlife reservoirs. Feline panleukopenia virus, a devastating parvovirus disease of cats, has been mostly controlled, except in areas with a surfeit of stray cats and some purebred catteries. Rabies and foot and mouth disease no longer exist in Europe, and Rinderpest has been eradicated in Africa (14).

This advancement brings an increased risk of adverse reactions (vaccinosis), some serious, chronically debilitating, or even fatal (14, 47, 62). Thus, the benefit needs to be more effectively balanced against the risk. Only about 40% of veterinarians are estimated to follow the current World Small Animal Veterinary Association, AVMA, AAHA, Canadian Veterinary Medical Association, or British Veterinary Association vaccine policy guidelines (14). Despite comments by some colleagues and the public, there is no such thing as an “up to date” or “due” vaccination. More animals in the community need to be vaccinated to increase the degree of herd (population) immunity to the required minimum of 70–80% to protect the rest of the group that are unvaccinated for communicable diseases. Concerned veterinarians also can offer separated vaccine components, since the published data show more adverse reactions when multiple vaccines are administered together (14, 27, 47).

Adaptive immunity to viruses develops before that of bacteria, fungi, and parasites and is highly effective (12, 17–23). Animals adequately immunized against the clinically important viral diseases have sterilizing immunity that not only prevents clinical disease but also eliminates infection (56). The duration of immunity generated is long-lived and often lifelong (13, 25, 55, 62). Only the presence of antibodies can prevent infection, such that an animal with a positive serum antibody test is protected. Vaccinating that animal would not cause a significant increase in the antibody titer, and hypersensitivity to vaccine components (eg, fetal bovine serum) may develop. Furthermore, the animal does not need to be revaccinated, and revaccinating could cause an adverse reaction or hypersensitivity disorder (13, 14, 47).

Vaccine adjuvants act to accelerate, prolong, or enhance antigen-specific immune responses (41–62). They are

added into vaccines to improve their immunogenicity, but this increases the risk of autoimmune and inflammatory adverse events following vaccination. While killed, inactivated vaccines containing adjuvants make up about 15% of the veterinary biologicals given, they have been associated with 85% of the post-vaccination reactions, primarily because of the adverse effects of the adjuvants (14, 41, 62). Simultaneous administration of even 2 to 3 adjuvants can overcome genetic resistance to autoimmunity (49). Adjuvants impact the CNS by changing gene expression, resulting in impaired brain development and immune function. This is of particular concern for children and young animals (41, 61). Vaccines and their adjuvants have been implicated as triggering events for those host individuals carrying the genetic predisposition to adverse vaccine reactions (47). These vaccinosis events are well-recognized to affect humans, companion animals, domestic livestock, and wild and zoo animal species.

For neonates, infant children, young companion animals, and livestock, there is an urgent need to remove heavy metals like aluminum and mercury from vaccines (48–51). Currently, neonatal children receive 17 times more aluminum from vaccines than allowed if doses were adjusted for body weight (50). Weight is ignored in human vaccine dosing, as the priority is to enhance immune efficacy by adding heavy metal adjuvants. Experts now urge that aluminum and mercury not be given in infant vaccines until after brain maturation (6–7 months of age but preferably 12 months) (48–52). Experts also recommend that heavy metal and other adjuvants like squalene and monophosphoryl A be removed when other additives like zinc and calcium phosphate can be used instead. However, zinc can cause skin irritation and even tissue necrosis at the injection site (48–51).

Sugar-like molecules such as inulin, curdlan, and trehalose have recently been shown to be safe and effective vaccine adjuvants when given in the first 4 weeks of human infant life (51–52). The discovery and implementation of novel adjuvants to enhance the immune response to vaccines should be encouraged, although the need for more effective quality control of contaminants is paramount (52, 53). The more recently available and developing recombinant DNA and RNA vaccines circumvent this problem. The environmental impact of shed vaccines should also be recognized and addressed. The common practice of over-loading

the young infant and animal with multiple vaccines needs to be curtailed, as they are often given even when the infectious disease agents they are directed towards are rare or no longer present (14, 50). The mistaken belief that the typical combination vaccine cocktail given to companion animals is necessary and safe needs to be re-examined in light of the numerous scientific reports and relevant recommendations of expert groups. Alternatives to automatically giving booster vaccinations to properly immunized individuals include spacing vaccine boosters from annually to every 3 or more years and measuring serum antibody titer levels periodically instead (14, 50).

Serum antibody titer testing assesses the immunologic status of animals against the clinically significant infectious diseases, determining if vaccine boosters are required or advisable (14, 25, 54–56, 58–62). Protection against these viral diseases of companion pets is indicated by a positive titer result, and once an animal's titer stabilizes, it should remain constant for many years. Viral vaccines prompt an immune response that lasts much longer than that elicited by protein molecule antigens (14, 19, 56). Further, any measurable antibody level reveals the presence of committed immune memory cells that respond immediately with an anamnestic response to protect the individual from that infectious agent (14, 25). Titer measurements also determine if an individual vaccine is effectively immunizing animals (56). A negative result usually means a failure to reach the threshold of providing sterile immunity. However, a negative titer is not the same as a zero titer, and the animal may be protected by the other arms of the immune system such as secretory and cell-mediated immunity (14, 25, 56). Published studies show that 90–98% of properly immunized dogs and cats have measurable titers (14, 19, 25, 56).

Factors Affecting Vaccine Responses

Published studies have found several factors that affect the immune response to vaccines (14, 55–62). These include the virus strain used to create the vaccine; pet size, with smaller pets generating higher serum antibody titers than the larger and giant breeds; age, as very young pets and infants do not mount vigorous antibody responses, especially when vaccinated in the presence of residual maternal immunity or when iron deficient; the number of vaccines given; and duration of immunity (14, 41, 62). Varying degrees of serologic antibody responses were found depending upon the dog or cat breed types and

gender in humans and pets, with the heightened immune responses in females providing stronger vaccinal immunity but predisposing them to more immune-mediated disorders than males (41, 62).

Recommendations for Vaccinating Puppies and Kittens

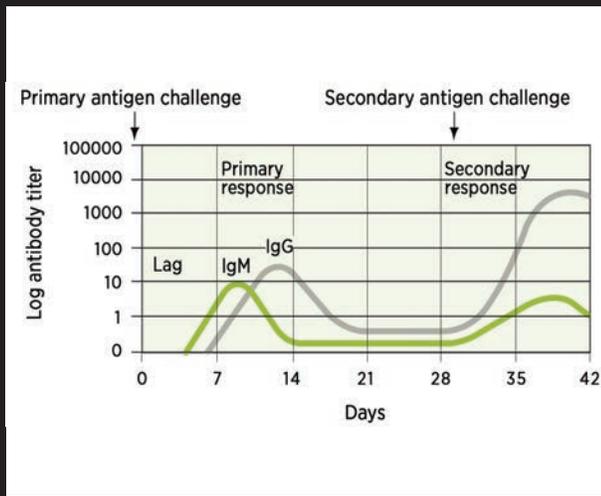
Puppies should receive modified-live virus or recombinant “core” vaccines (canine distemper, adenovirus, and parvovirus), preferably either at 9–10 and 14–16 weeks of age (minimum protocol), or at 9, 12, and 16–18 weeks. As infectious hepatitis is rarely seen as a clinical entity anymore in North America, it can be omitted from the puppy “core” vaccines, especially considering its addition to the vaccine given to young puppies causes suppression of their immune system for up to 14 days (13, 14). Kittens can be immunized earlier at 8 and 12 weeks of age, as their immune systems mature earlier (14, 27, 47).

Rabies vaccines for dogs are all adjuvanted killed products. They are given as required by law, preferably always separately from other vaccines and as late as legally allowed, usually after 20–24 weeks of age. Rabies vaccines that do not contain thimerosal or other heavy metals are preferred and safer, and vaccines with adjuvants like gentamicin and amphotericin B are available (61, 62). Cats have the option to receive non-adjuvanted recombinant rabies vaccines (14).

Other vaccines for puppies are optional, depending on the circumstances and local disease risk (14, 25, 47, 51). Leptospirosis vaccines protect against only 4 of the 7 clinically significant serovars and are second to rabies vaccines in their risk of hypersensitivity and other adverse effects (14, 16, 58). A 2015 study that examined, and displayed in a table, owner-reported adverse events following leptospirosis vaccines found dogs that received a 4-serovar vaccine had a significantly higher incidence rate of adverse events than for dogs receiving any other vaccines (12). Therefore, the preferred use of this vaccine is in endemic clinical exposure risk areas.

Following the primary response to an initial antigen or vaccinal exposure, a secondary, much larger, immediate response occurs to protect the individual (**Figure 3**). Between 10–14 weeks of age, socialization can occur in the back yard or at pet training classes with known friends

Figure 3



The Anamnestic IgM and IgG Immune Response to Antigen Exposure.

and healthy pets. Until fully vaccinated, puppies and kittens should not walk on unfamiliar or public grounds and can be placed in carrying crates if they need to travel (14, 27, 47).

Commentary

Scientific advances in biochemistry, physiology, and medicine during the 21st century have culminated in an impressive library of benefits to improve the health and longevity of human and animal lives. Studying and comparing mammalian development among humans and various domesticated and wild species, as demonstrated with the depth of detail of the pediatric immune system discussed in this paper, there is little doubt that we now know and appreciate far more about mammalian development. This knowledge base has been accumulated by biomolecular teamwork leading to the current advances in nanotechnology and the so-called “-omics” era of proteomics, metabolomics, transcriptomics, nutrigenomics, pharmacogenomics, 3D printing, and imaging. These advances address epigenetic programming of the genetic “blueprint” map and reveal the efficacy and exciting potential of future developments in genomics, gene editing, and gene therapy for preventing and treating diseases of the immune and other systems.

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