Review Article

Autoimmune Disorders in Animals: Models of Human Counterparts

W. Jean Dodds

DVM, Hemopet, Garden Grove, California, USA

*Corresponding author: W. Jean Dodds, DVM; Hemopet, 938 Stanford Street, Santa Monica, CA 90403, USA, Tel: 714-891-2022 Ext 115, E-mail: info@hemopet.org

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Abstract

Companion animals, and especially dogs, have been studied as models of their counterpart human disorders for many decades. The large comparative data base that has accumulated includes defining the underlying genetic predisposition and gene loci involved and is frequently used to implement new research findings and diagnostics, as well as management and treatment. New therapies can be tested in clinical trials in dogs and other animal species before progressing to human clinical trials. The diverse family of autoimmune (immune-mediated) clinical disorders is particularly amenable to comparative research as they make up a significant percentage of all health conditions. In fact, among purebred inbred families of dogs, the prevalence of heritable autoimmune conditions continues to increase and even threatens the survival of some relatively rare breeds along with the more popular breeds, when a common sire influences the health of subsequent generations by the so-called “founder effect”.

The following review provides a summary of the factors affecting the prevalence and clinical expression of autoimmune conditions in animals and offers approaches for addressing issues that still need resolution.

Keywords: genetics, evolution, autoimmunity, biomarkers, oxidative stress

Introduction

Evolution of the Domestic Dog

Dogs have shared their environment with humans for thousands of years (estimated between 14,700-36,000 years), and most authorities believe that they developed from the now extinct gray wolves in Eurasia [1]. They were the first species to be domesticated and arose during the human hunter-gatherer period rather than from agriculturists. Of their approximately 19,000 genes, modern dogs share 99.8 % of them with wolf genes, whereas 122 dog-specific genes are located in the other 0.2 % [2]. Further, modern dogs have three specific genes that control digestion and utilization of starch, while wolves have only two of them, so evolution has adapted today’s dogs to eat and use more starch [1,2]. Modern dogs also have adapted genes for the central nervous system, stress response, and reproduction.

Largely because of their close association for thousands of years, dogs and human beings have common diseases, common genes, and a shared environment [1]. However, the dog genome has reduced genetic heterozygosity compared to that of people due to the line breeding and inbreeding commonly practiced, both in the
wild and after domestication to create purpose-bred dog lineages [2]. Consequently, domesticated dog breeds suffer from an even higher incidence and variety of the inherited diseases found in humans, such as cancers, diabetes, epilepsy, cardiovascular and autoimmune diseases [1, Figure 1, Tables 1a and b]. The clinical manifestation and disease progression is also similar between the two species, which has resulted in the common and successful use of animals as clinical and experimental research models of the parallel human condition [3-5].

There are nearly 400 modern domestic dog breeds today, each with unique histories and genetic profiles. Since the 19th century, these breed types have been refined by selective breeding and some outcrossing to create very specific breeds where the phenotype of early functional dogs was changed in appearance and was chosen to promote desirable behaviours [1].

**Shared diseases with humans**

**Autoimmunity and autoimmune diseases (Figure 1):** Distinguishing between self- and non-self-antigens is a vital function of the immune system and serves as a specific defense against invading microorganisms [3]. Failure of this self-tolerance leads to "autoimmunity", which literally means immunity against self and is caused by an immune-mediated reaction to self-antigens [3, 4]. Susceptibility of the host to pathological autoimmune states has a genetic basis in humans and animals, although numerous viruses, bacteria, chemicals, toxins and drugs have been implicated as the triggering environmental agents [4-6]. This mechanism operates by a process of molecular mimicry and/or non-specific inflammation and is most often mediated by T-cells or their dysfunction [3]. The resultant autoimmune diseases reflect the sum of the genetic and environmental factors involved. As stated in a landmark review from 1990, "perhaps the biggest challenge in the future will be the search for the environmental events that trigger self-reactivity"[3].

![Figure 1](image)

*Figure 1:* Upper right circle represents one or more effects of infectious agents, especially viruses, drugs, chemicals and toxins. Lower right circle represents physical, physiological and psychological stressors. Lower left circle represents hormonal factors especially of sex hormones.

The four main causative factors of autoimmune diseases are stated to be: Genetic predisposition; hormonal influences, especially of sex hormones; infections, especially of viruses; and stress events [3-6].
The following discussion reviews the components that function in a normal immune system and in autoimmunity.

**Discussion**

**The normal immune system**

Immune competence is provided and maintained in the body by two lymphocytic cell systems, produced by the primary (bone marrow and thymus) and secondary (lymph nodes and spleen) lymphatic organs [4]. These descendants of the bone marrow pool of stem cells comprise a circulating or humoral immune system derived from B-cells (bursa-dependent or bone marrow-derived), and a cellular or cell-mediated immune system that derives from T-cells (thymus-dependent) [4, 7]. The basic body immune defense systems are the innate (non-specific) immediate short-term response to foreign invasion, and the adaptive (acquired) response that conveys immune memory like that produced by vaccines [5]. Natural killer (NK) cells are an integral part of the innate immune system, whereas T-helper (Th) cells are active in the adaptive immune response [7].

**B-Cell (Humoral) immunity:** B-cell immunity includes the circulating antibodies or immunoglobulins such as IgA, IgD, IgE, IgG, and IgM. These antibodies provide an important defense mechanism against disease in healthy individuals but can become hyperactive or hypoactive in a variety of disease states. Hyperactive or increased levels of immunoglobulins can occur in two ways: acutely, as a reaction to disease or inflammatory insult ("acute-phase" reaction); or chronically, as in autoimmune or immune-mediated diseases, chronic infections, and certain types of bone marrow and organ cancers [4-7].

Hypoactive or decreased levels of immunoglobulins can result from the rare genetically-based immunodeficiency states such as agammaglobulinemia or hypogammaglobulinemia, and from the immune suppression associated with chronic viral, bacterial, or parasitic infections, cancers, aging, malnutrition, drugs, toxins, pregnancy, lactation, and stress [4].

**T-Cell (Cellular) immunity:** T-cell or cell-mediated immunity is the cellular mechanism that comprises the coordinator and effector functions of the immune system. Cell-mediated immunity involves the lymph nodes, thymus, spleen, intestine (gut-associated lymphoid tissue), tonsils, and the mucosal secretory immunity conveyed by IgA. T-cells are classified as helper, cytotoxic, and suppressor cells. The helper cells "help" coordinate the immune response whereas the cytotoxic cells comprise the effector network that participates in removing virus and other infected cells from the body. The third class, suppressor T-cells, dampens the immune response when it becomes overactive or out of regulatory control. Finally, cooperation between the various T-cell classes and between T- and B-cells is an important component of the normal humoral and cellular immune responses [4].

Hyperactive cellular immune responses produce autoimmune and other immune-mediated diseases while hypoactive cell-mediated immunity causes immune suppression and incompetence in people and animals [Tables 1a and 1b]. Classical examples of this latter situation occur with retroviral infection such as human AIDS or the animal equivalents (e.g. feline immunodeficiency virus, feline leukemia virus, bovine leukemia virus, equine infectious anemia).

Recent studies in human and animal immunology have focused on responses mediated by T-helper 1 (TH1) and T-helper 2 (TH2) cell types [4, 7]. TH1 cells release interleukin (IL)-1, interferon, and tumor necrosis factor (TNF) after antigen stimulation. This cascade of effects leads to cell-mediated immune responses, which are responsible for macrophage activation, delayed-type hypersensitivity reactions, and defense against intracellular organisms. TH2 responses lead to release of IL-4, IL-5, IL-10, and IL-13, which stimulate B-cell proliferation and
antibody secretion [7]. Pathology associated with autoimmune, infectious and allergic diseases may be due to primary TH1- or TH2-like responses, and much recent research has focused on characterizing and modulating their responses. There is no doubt that TH1 lymphocytes participate in the development of autoimmune disease, but it seems that they do not play as an important role as had been thought. More recent research has demonstrated an increasing role of newly discovered cells such as TH17 (CD4+IL-17+) or T-regulatory cells (CD4+CD25FoxP3+) in the induction of autoimmune disorders [8].

**Causative factors of autoimmune diseases**

**Genetic predisposition:** The low genetic variation within breeds, discussed above, reflects the enrichment of several strong genetic factors, allowing efficient gene mapping with fewer individuals than in human populations, which naturally are much more diverse [1, 4-6, 9-11]. Efficient gene mapping of inherited canine recessive traits should be possible by studying just 20 disease cases and 20 controls [1]. For dominant traits, 50 cases and 50 controls should be sufficient, and for a complex trait, 100 cases and 100 controls should be able to identify alleles conferring a 5-fold increased risk. These predictions of identifying genetic disease risk have subsequently been shown to be correct for both monogenic and complex diseases [1].

**Species similarities and differences:** While most, if not all, of the autoimmune diseases seen in humans also have their counterparts or very similar disorders in animals, there are some exceptions. The genes involved in autoimmune disorders are located within the major histocompatibility complex (MHC), which codes for glycoproteins on the cell surface and plays a role in discriminating self-from non-self-antigens [3]. In humans, the MHC of the human leukocyte antigen (HLA) system is located on chromosome 6; for canines, the dog leukocyte antigen (DLA) system resides on chromosome 12; and for mice, the MHC is on chromosome 17 [1, 3-6]. However, differences in expression of their genomes in both healthy and diseased states are to be expected, as the dog and wolf have 78 chromosomes (39 pairs), humans have 46 chromosomes (23 pairs), and the laboratory mouse has only 40 chromosomes (20 pairs) [1,2].

Further, definitive diagnosis of a parallel disorder may not be possible in animals if the assay and reagent tools need to be species-specific and are not available or too costly. In the field of comparative hemostasis, for example, this author had to develop specific immunoassays for coagulation factor proteins such as coagulation factors VIII, IX and von Willebrand factor by first purifying them from canine plasma, before being able to study their specific amounts and molecular patterns in health and disease, as well as the pathophysiology of canine hemophilia A and B and von Willebrand disease [5]. These comparative studies have long been recognized as one of the most successful examples of studying naturally-occurring animal models of human disease, and even led to an infusion in this author’s clinical research facility of the first recombinant human clotting factor VIII which was given to a dog with hemophilia A [5]. [His bleeding time was normalized within six minutes and remained so for the next 36 hours; this resulted in large-scale production of safer prophylactic clotting factor concentrates for hemophilic people throughout the world at a time when HIV infection and AIDS became prevalent. It was an exciting time indeed!].

**Multiple organ and tissue systems involved:** The more commonly recognized autoimmune disorders in animals include those affecting: endocrine glands, namely the thyroid (thyroiditis), adrenals (Addison’s disease), pancreas (diabetes), and parathyroid; bone marrow and hematologic cells, namely the marrow stem cells, erythrocytes, platelets, and leukocytes; muscle, including myasthenia gravis, masticatory muscle myositis, polymyositis, and dermatomyositis; the eyes, with keratoconjunctivitis sicca (dry eye), uveitis, pannus, and uveodermatologic syndrome (Vogt-Koyanagi-Harada, VKH); skin, with pemphigus disorders, systemic lupus erythematosus, and vitiligo; neurologic tissue, including immune-complex meningoencephalitis; the kidneys, with
immune-complex glomerulonephritis, and systemic lupus erythematosus; and the joints, with rheumatoid arthritis (Table 1) [9-22).

**Table 1**: Genetically Based Immune Disorders in Animals

<table>
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<tr>
<th>Autoimmune Diseases</th>
<th>Immune Deficiency Diseases</th>
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<tr>
<td>Endocrine</td>
<td>Defects in Mechanical Barriers</td>
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<td>Eye</td>
<td>Defects in Nonspecific Host Defenses</td>
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<td>Gastrointestinal</td>
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**Hormonal influences and endocrine disorders**

**Autoimmune thyroditis**: Autoimmune thyroid diseases constitute 30% of all the auto-aggressive diseases in humans, and are classified as being organ-specific, of which Hashimoto's thyroiditis (chronic lymphocytic thyroiditis) that leads to hypothyroidism, and Graves' disease that causes hyperthyroidism are the most clinically important [9, 11-14]. Hypothyroidism is the more common; a complex clinical condition found in both humans and dogs and thought to be caused by a combination of genetic and environmental factors [3-5, 9]. The hyperthyroidism of Graves' disease has not been recognized as a clinical entity in dogs, despite that fact the type-specific thyroid autoantibodies are produced by both conditions in humans [9].

The spectrum of Hashimoto's thyroiditis also includes focal and fibrous thyroiditis, primary myxedema, and Hashitoxicosis. Graves' disease is associated with the related autoimmune phenomena of ophthalmopathy and dermopathy. Other associated autoimmune disorders commonly include: idiopathic thrombocytopenic purpura, immune-mediated hemolytic anemia, and antigen-antibody complex nephritis (like systemic lupus erythematosus) [9, 17]. Non-thyroidal endocrine autoimmune deficiency disorders also have been classified as part of the spectrum of thyroid autoimmune disease [9]. Further understanding of postpartum and neonatal thyroid disorders has led to recognition that thyroid disorders in the infants of women with autoimmune disease is related to the levels and types of anti-thyroid antibodies acquired from the mother. Simple adolescent and multinodular goiters, as well as some cases of sporadic cretinism, can be part of the expanded spectrum of autoimmune thyroid disease [9].

Dogs exhibit a range of immune-mediated conditions including lymphocytic thyroiditis which very closely parallels the Hashimoto's thyroiditis of humans [1, 10-14]. Studies of 173 dogs including affected Doberman
Pinschers, English Setters and Rhodesian Ridgebacks, as well as several other breeds, revealed that they express a rare dog leukocyte antigen (DLA)-class II haplotype that contains the DLA-QA1*00101 allele [12, 13].

A more recent multi-breed analysis of predisposing genetic risk factors for hypothyroidism in dogs studied three high-risk breeds, Gordon Setter, Hovawart and Rhodesian Ridgeback [14]. Using a genome-wide association approach and meta-analysis, a major hypothyroidism risk locus shared by these breeds was identified on chromosome 12 [14]. Further characterization of the candidate region revealed a shared ~167 kb risk haplotype, tagged by two SNPs in almost complete linkage disequilibrium. This breed-shared risk haplotype included three genes (LHFPL5, SRPK1 and SLC26A8) and did not extend to the DLA-class II gene cluster located in the vicinity. These three genes have not been identified previously as candidate genes for hypothyroid disease. This finding provides for future possibilities in screening dog breeds to assist in breeding programs and treatments, as well as contributing to better understanding of the genetic etiology of human hypothyroid disease, which is one of the most common endocrine disorders [14].

The levels of IL-17, one of the major effector cytokines of the Th17 system, and IL-23, that has been implicated in the generation, survival and expansion of Th17 cells, are also altered in hypothyroidism [8].

**Addison's disease:** Also known as immune-mediated hypoadrenocorticism, it occurs in certain dog breeds with a greater incidence than the population as a whole, as well as in individual breeds. Predisposed breeds include the Alaskan Klee Kai, Bearded Collie, English Setter, Eurasier, Great Dane, Labradoodle, Leonberger, Nova Scotia Duck Tolling Retriever, Old English Sheepdog, Pharaoh Hound, Pomeranian, Portuguese Water Dog, Soft-Coated Wheaten Terrier, Standard Poodle, and Weimaraner [15-18].

The mode of inheritance may differ from breed to breed and in some dog families remains unclear, whereas the mode of inheritance is believed to be autosomal recessive in the Standard Poodle, Nova Scotia Duck Toll and Portuguese Water Dog [15-18, 20]. The mean age of onset of this disorder in all affected dogs is 4-5 years, whereas the median age of onset in Nova Scotia Duck Tollers is 2.6 years. In some affected breeds, males appeared to be as equally affected as females, whereas in other breeds, Addison's disease is more common in females, and in young or middle-aged adults [19].

Classical signs of Addison's disease are non-specific and include: muscle weakness and general lethargy (listlessness), in which affected dogs will be unable to jump up on the couch or bed, have trouble climbing stairs, lie down a lot or show a lack of enthusiasm for activities involving physical exertion; vomiting and diarrhea, sometimes with blood present; hyperpigmentation, shown as small patches or spots of darker skin around the armpits, mucous membranes or inside the cheek; joint pain, which may manifest as whimpering or yelping during walking or as a limp; poor appetite; and shivering or muscle tremors [19-20]. The cause is either insufficient production of cortisol, which determines how the body handles stress, and helps regulate how the body uses nutrients and maintains proper cardiovascular functions, or aldosterone, which helps to regulate blood pressure and allows the kidneys to maintain a proper water-to-salt balance in the body [11].

The Portuguese Water Dog studies presented convincing evidence that establishes Addison's disease as an inherited disorder in this breed with an estimate of heritability of 0.49 (± 0.16); there were no differences in risk for disease across sexes (p > 0.49) [18]. Breeders of these dogs should apply these findings as they plan future matings in order to select against producing affected dogs.

**Autoimmune polyglandular syndromes:** The autoimmune polyglandular syndromes are a group of syndromes comprising a combination of endocrine and non-endocrine autoimmune diseases, which differ in their component diseases and in the immunologic features of their pathogenesis [3, 21]. The underlying autoimmune
reaction produces autoantibodies against endocrine tissues, cell-mediated autoimmunity, or both; it then leads to inflammation, lymphocytic infiltration, and partial or complete destruction of affected glands. More than one endocrine gland is involved, although clinical manifestations are not always simultaneous.

In that regard, the common endocrine disorder of autoimmune thyroiditis is more frequent in individuals who suffer from other so-called “auto-aggressive diseases”, for example, Addison’s disease, diabetes mellitus type 1, rheumatoid arthritis, or systemic lupus erythematosus [3, 9, 12].

In humans, this syndrome is classified by three types [21]:

Type 1 usually begins in childhood. It is defined by the presence of two or more of: chronic mucocutaneous candidiasis, hypoparathyroidism, and adrenal insufficiency (Addison’s disease). Type 2 (Schmidt’s syndrome), usually occurs in adults and is three times more common in females than males; it manifests as adrenal insufficiency, hypo- or hyper- thyroidism and type 1 diabetes mellitus. This is the form of polyglandular autoimmunity that occurs in dog breeds such as the Nova Scotia Duck Tolling Retriever, Leonberger, Old English Sheepdog, Portuguese Water Dog and Standard Poodle [10, 11]. Lastly, the Type 3 disorder is seen mostly in middle aged women with hypothyroidism and at least one of the other autoimmune disorders but does not involve the adrenal cortex.

Viral and other infections: Immune-suppressant viruses of the retrovirus and parvovirus classes have recently been implicated as causes of bone marrow failure, immune-mediated blood diseases, hematologic malignancies (lymphoma and leukemia), dysregulation of humoral and cell-mediated immunity, organ failure (liver, kidney), and autoimmune endocrine disorders especially of the thyroid, adrenal glands, and pancreas [3-6, 10, 11].

Viral disease and recent vaccination with single or combination modified live-virus vaccines, especially those containing distemper virus, adenovirus 1 or 2, and parvovirus, are increasingly recognized contributors to immune-mediated blood disease, bone marrow failure, and organ dysfunction [3-5, 23-27]. Potent adjuvanted killed vaccines like those for rabies virus also can trigger immediate and delayed adverse vaccine reactions, termed vaccinosis [26-27]. Genetic predisposition to these disorders in humans has been linked to the leucocyte antigen D-related gene locus of the major histocompatibility complex and is likely to have parallel associations in domestic animals [25].

Drugs associated with aggravating immune and blood disorders include the potentiated sulfonamides (trimethoprim-sulfa and ormetoprim-sulfa antibiotics); the newer combination or monthly heartworm, flea and tick preventives; and anticonvulsants, although any drug has the potential to cause side-effects in susceptible individuals [4].

Stress events: Numerous physical, physiological and psychological disorders in humans have been linked to a recent stress event [3, 4]. These include: depression, anxiety, heart attacks, stroke, hypertension, immune system disturbances that increase susceptibility to infections, a host of viral linked disorders ranging from the common cold and herpes to AIDS and certain cancers, as well as autoimmune diseases like rheumatoid arthritis and multiple sclerosis [3]. Additionally, stress can have direct effects on the skin (rashes, hives, atopic dermatitis) and gastrointestinal system (gastric reflux, peptic ulcer, irritable bowel syndrome, ulcerative colitis); can contribute to sleep disturbances such as insomnia, and degenerative neurological disorders like Parkinson’s disease. Similar disorders affect the organ systems of companion animals and even livestock [4].

Immunohematological effects of vaccines: Combining viral antigens, especially those of modified-live virus type which multiply in the host, elicits a stronger antigenic challenge to the animal and presumably mounts a more effective and sustained immune response [4, 22, 26]. This more potent immunologic challenge, could adversely
affect the immunocompromised animal or even the healthy animal genetically predisposed to react adversely to viral exposure upon repeated encounters with other environmental stimuli [4, 26].

The rising incidence of leukemia and lymphomas in an increasing number of dog breeds is a case in point [4, 5, 22, 26]. A similar and disturbing increase in the incidence of hemangiosarcomas, primarily in the spleen, but also in the heart, liver and skin, is affecting more dogs especially of certain breeds like the German Shepherd Dog, Golden Retriever, Irish Setter, Old English Sheepdog and Vizsla [6]. They occur most often in middle age or older dogs of medium to large breeds. This age of onset suggests that both genetic and environmental factors play a role, which can promote the immune suppression or dysregulation that contributes to the failure of immune surveillance mechanisms. These mechanisms protect the body against the infectious and environmental agents which induce carcinogenesis and neoplastic change [4-6, 22].

Accordingly, clinicians need to be aware of this potential and offer alternative approaches for preventing infectious diseases in susceptible animals [26, 27]. Appropriate alternatives to current vaccine practices include: measuring serum antibody titers; avoidance of unnecessary vaccines or over-vaccinating; caution in vaccinating ill, geriatric, debilitated, or febrile individuals; and tailoring a specific minimal protocol for dogs or families of breeds known to be at increased risk for immunological reactions [26-27].

Future Perspectives

Revisiting the scientific era

There is little doubt that animals will continue to be used in the foreseeable future as representatives of the normal and disease states of humans and other vertebrates. Biomedical research today has evolved from clinical observations of humans and other species with resulting hypotheses tested in laboratories in the 1940s, through more molecular approaches and the concept of gene therapy in the 1960s, to the 1970s, when molecular science and genetics became mainstream; and laboratory animal welfare and issues surrounding the safety and efficacy of vaccines surfaced. Since then, the 1980s and 1990s saw clinical and drug therapies evolve from bench and clinical studies in laboratory animals to clinical trials and use of these therapies first in laboratory animals, then for clinical veterinary use, and eventually for human therapies. Also, in the 1990s, more emphasis was placed on developing non-animal mathematical and other models for studying scientific phenomenon.

Animal welfare and the institutional review committee

The largest groups of animals studied over the past decades are rodents and rabbits, largely because of their readily availability as purpose-bred laboratory animals of defined genetic backgrounds and also because of their size and affordability. Studies of non-human primates and companion animal species are by their nature less frequently performed not only from cost and availability factors, but also because of public and societal concern for their humane use and welfare. Studies of the naturally-occurring diseases of companion and other animals that serve as models for the human counterpart disorders are more readily accepted, as long as the studies are non-invasive, minimally or preferably not harmful, and have received full peer review by an Institutional Animal Care and Use Committee. This author was involved at the inception of this type of national research review policy on animal welfare and continues to champion its purpose.

The concepts of Russell and Birch, namely, the 3R’s (Reduction, Refinement, Replacement) of animals used in research were promulgated and, after considerable dissention from the biomedical community, eventually embraced by law at the federal level (USDA Animal Welfare Act; NIH Guide for the Care and Use of Laboratory Animals) – both still actively enforced today. Similarly, the 3S’s of biomedical research (good Science, good Sense, and good Sensibility) were promoted. Self-regulation was unquestionably the way to convince biomedical scientists
to practice the 3R’s and 3S’s. All the institutional regulations and federal oversight would have little impact unless the investigators themselves understood why and believed that they should treat animals as sentient beings. Today, all institutions receiving federal funding must comply with prevailing laws and guidelines, and private industry has followed suit.

Fast forward to today – in the 2000s, the human, dog and cat genomes were sequenced, which launched the advent of gene therapy, while stem cell therapy for humans and animals became mainstream in clinical medicine. Even the “holy grail” of evidence-based medicine is being challenged today. This concept has recently been revised to become evidence-based practice. Evidence-based practice represents a more complete discipline that combines research science and publications with the art of medicine, namely clinical and patient experience plus expert opinion [4, 6, 11].

The ‘Omics era

We have entered an “omics” era today for establishing scientific validity and efficacy. We employ genetics to offer the DNA genomic “blueprint”; epigenetics which comes from studying DNA methylation and RNA histones; transcriptomics for investigating RNA; proteomics to assess proteins, and metabolomics to understand the metabolites generated. Even more recently we have coined the terms “pharmacogenomics” and “nutrigenomics” to focus on the molecular mechanisms that prevent, control, mitigate, and treat diseases in individual people and individual animals using drugs and nutraceutical therapies, respectively [6, 11, 29].

Conclusions

Over the past decades, a large comparative data base has accumulated for a variety of disorders affecting both humans and companion animals. The diverse family of autoimmune (immune-mediated) clinical disorders is particularly amenable to comparative research as they make up a significant percentage of all health conditions. In fact, among purebred inbred families of dogs, the prevalence of heritable autoimmune conditions continues to increase and even threatens the survival of some relatively rare breeds along with the more popular breeds, when a common sire influences the health of subsequent generations. This data base is frequently used to implement new research findings and diagnostics, as well as management and treatment. New therapies can be tested in clinical trials in dogs and other animal species before progressing to human clinical trials.

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