SYMPOSIUM INTRODUCTION

Biology's Best Friend: Bridging Disciplinary Gaps to Advance Canine Science

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Synopsis The rich history and global abundance of domestic dogs (*Canis familiaris*) present a unique opportunity and an ideal model for interdisciplinary research. Canine evolutionary history demonstrates unprecedented changes across all levels of biological organization. These include diversification from highly social, pack-dwelling wild carnivores (extant gray wolves, *C. lupus*), to increased dependence on humans (domestication), to modern in-home colonization featuring close physical proximity to humans (interspecies bonding). The young, emerging field of "canine science" comprises numerous biological disciplines including evolution, genetics, cognition, behavior, physiology, comparative medicine, and ecology, drawing on studies of both natural and experimental systems and scaling across all levels of biological organization, from genomes to ecosystems. However, limited connections bridge the diverse fields associated with canine science, although in every branch it is recognized that this species is one of the most phenotypically variable mammals. However, there has been growing interest in integrating the insights from genomic evolution with those from ecophysiology and ecology, thus facilitating a more biologically comprehensive perspective of dogs. In particular, integrative, mechanistic, and/or ecological studies have been generally underrepresented. To address these emerging interests, we have collected the most compelling questions in the field of canine biology and present avenues of current and future research. This article serves to both orient the reader to this special issue, as well as offer a forward-looking perspective from diverse biological sub-disciplines to highlight current and future goals in canine research.

Introduction

Domestication of gray wolves (*Canis lupus*) to ubiquitous household pet dogs (*C. familiaris*) has taken place over a remarkably short evolutionary time-frame (~15 ka; Janssens et al. 2018), yet many breeds (e.g., Chihuahua) are all but unrecognizable from their wild canid ancestor. Furthermore, the majority of the world's >350 modern breeds are less than 200 years old, and most have resulted from a strong, repeated selection of desirable traits,

transforming pack predators into loyal companions (Worboys et al. 2018). In addition to extreme morphological diversity (Fig. 1; Wayne 1986), dogs may also vary widely in life-history traits (Jimenez 2016), disease susceptibility (Karlsson and Lindblad-Toh 2008; Vaysse et al. 2011), and behavior (Mehrkam and Wynne 2014; Udell and Brubaker 2016; Lea and Osthaus 2018). Moreover, at an estimated population of one billion, dogs are the most globally abundant and widespread carnivore (Gompper 2014b), making the species particularly tractable for multidisciplinary research (Ostrander et al. 2017).

"Canine science" is composed of diverse biological disciplines including evolution, genetics, cognition, behavior, physiology, disease, and ecology, drawing on studies of both natural and experimental systems and scaling across all levels of biological organization, from genomes to ecosystems. Limited connections currently bridge the associated fields, yet there is growing interest in integrating insights from canine genomic evolution and phenotypic variability with those from ecophysiology and ecology. Canine science remains in its infancy, with generalizable whole-animal patterns only being established twenty five years ago (Patronek et al. 1997). Addressing current knowledge in the field in an interdisciplinary manner has the potential to transform how and what we study about dogs (Sykes et al. 2020). Others have recently reviewed anatomical, paleontological, genetic and behavioral variation during dog domestication (e.g., Smith and Van Valkenburgh 2020). Here, we focus on the domestic dogs' tremendous phenotypic variability, and how it can be addressed from an increasingly interdisciplinary approach.

Canine science: past advances and future directions

The dog–human relationship

Canine origins

Although many of the fundamental questions regarding dog domestication remain unresolved including where and the circumstances under which the relationship began, the timeframe over which it took place, and the number and location of potential independent domestication regions, four characteristics of dog domestication are now broadly accepted. First, dogs were the earliest species to undergo domestication and the only animal to enter into a domestic relationship with people during the Pleistocene (Larson et al. 2012). Second, no modern wolf populations from either Eurasia or the Americas are more closely related to modern dogs than others,

suggesting that the population from which dogs were derived is extinct (Freedman et al. 2014). Third, genetic evidence from modern and ancient dogs and wolves demonstrates that the first dogs in the Americas were part of a population that was domesticated in Eurasia (Ní Leathlobhair et al. 2018). Finally, thousands of modern dog nuclear genomes (Ostrander et al. 2019) and dozens of ancient genomes (Bergstrom et al. 2020) indicate that all modern and ancient dogs represent a genetically homogeneous group that possess degrees of ancestry from three major ancestral lineages, all of which were established at least 11,000 years ago: a western Eurasian lineage (mostly found in European, Indian, and African dogs), an east Asian lineage (e.g., dingoes) and an Arctic lineage (e.g., huskies and ancient American dogs; Ní Leathlobhair et al. 2018; Bergström et al. 2020).

With regard to the timeframe, numerous claims have been made for a domestication trajectory that began approximately 40,000–35,000 years ago. Morphological analyses of canid remain at sites such as Goyet (Germonpré et al. 2009, 2013; Galeta et al. 2021) and Předmostí (Germonpré et al. 2012, 2015) have been marshaled to suggest that people and wolves were interacting to a degree that led to skeletal shape changes mirroring those seen in modern dogs. Although the early Pleistocene canids could represent an initial shift in human-wolf relationships, the first generally accepted archaeological dog (based upon morphological, genetic, isotopic, and contextual evidence) was excavated from a co-burial with humans at the site of Bonn-Oberkassel in Germany, and has been dated to ~15,000 years ago (Janssens et al. 2018).

Regardless of the timeframe, location, or number of independent wolf populations that were part of a domestication process, humans and dogs have shared a significant degree of their evolutionary and cultural history. For example, the close association between dogs and people has been demonstrated by longitudinal studies revealing that when human diets incorporated larger quantities of animal-derived proteins, the same shift in isotopic values was also evident in local dogs (Sykes et al. 2020). At the population level, recent genetic analyses of ancient dog remains have shown how the spatiotemporal patterning of mitochondrial lineages correlates with the dispersals of specific human cultural groups. A study of mitochondrial signatures derived from ancient Near Eastern and European dogs demonstrates that a specific haplogroup arrived into Europe as dogs dispersed alongside farmers out of the Near East (Ollivier et al. 2018). A separate movement of people

Fig. 1. Dogs: The Cabbage of the Animal Kingdom? (**A**) Dogs (*C. familiaris*) are the most phenotypically diverse animal species in the world (Vaysse et al. 2011). (**B**) Cabbage (*Brassica oleracea*) is the most phenotypically diverse plant species in the world and has been called The Dog of the Plant World (Mabry et al. 2018; Gallagher et al. 2019). (**C**) Therefore, we propose that dogs are The Cabbage of the Animal Kingdom. Nicaraguan dog photo courtesy of Debra Bardowicks.

and dogs has also been shown to have occurred in the North American Arctic where dogs carrying a specific genetic signature accompanied Paleo-Inuit groups as they moved into the region ∼5000 years ago (Ameen et al. 2019). Finally, a mitochondrial assessment of the first dogs in New Zealand also revealed a close association between newly arriving people and the dogs that accompanied them (Greig et al. 2015).

Each of these lines of inquiry demonstrates that dogs, more than any other species, are humanity's oldest and closest vertebrate companions. Even the earliest records indicate that humans cared about the health and wellbeing of their animals (Guthrie 1939; Dotson and Hyatt 2008). This ancient interest likely arose concurrently with domestication itself (Mark 2020). What would eventually become known as veterinary practice was undertaken by 3000 BCE for dogs and other domesticates in the ancient civilizations of China, Mesopotamia, Egypt, and India centuries

before it arrived in Greece, Rome, and eventually Europe. It was not until the Enlightenment of the 18th century that veterinary medicine once again gained attention and momentum lost during Medieval times. The first formal institute for the study of veterinary medicine was established by 1762 in Lyons, France, and during the next century, another 17 such institutes were founded in rapid succession across Europe, largely in response to the enormous economic toll of numerous plagues among domestic animals (Guthrie 1939). The swift establishment of formalized veterinary education coincided with the Victorian-era proliferation in dog breeds (Howell 2015; Olmert 2018; Worboys et al. 2018), often reflecting small numbers of founders.

Today, domestic dogs are both prolific and diverse: there are approximately 350 dog breeds recognized by the Federation Cynologique Internationale, the world's largest canine organization. Each dog breed is characterized by unique features, often

related to appearance and behavior, and the genomic diversity of domestic dog breeds is an indispensable resource for advancing understanding of mammalian biology and genetic health (Ostrander et al. 2019).

Canine genetics mapping studies

Because humans have engaged in strong phenotypic selection for specific dog morphologic and behavioral traits, individual breeds often have limited gene pools (Drögemüller et al. 2008; Boyko 2011; Parker et al. 2017) and the canine genome is characterized by extensive linkage disequilibrium (Sutter et al. 2004; Lindblad-Toh et al. 2005). Large numbers of individuals are not needed for simple genetic mapping studies; rather, a modest number of unrelated individuals can yield the same results. In addition, large numbers of markers are similarly not needed. As a result, initial genome wide association studies (GWAS) in dogs, particularly those seeking to identify genes controlling simple traits, have utilized only modest numbers of markers (e.g., 150,000 or fewer single nucleotide polymorphisms [SNPs] in most cases; Lindblad-Toh et al. 2005; Vaysse et al. 2011; Hayward et al. 2016) from 200 to 300 dogs. By comparison, human GWAS often utilize over a million markers and hundreds of thousands of individuals.

While the above strategy has been successful, as canine geneticists move away from the "low hanging fruit" of single-gene traits and tackle the problem of complex traits, newer strategies are required. To that end, dense collections of markers based on the analysis of whole-genome sequencing (WGS) of hundreds of dogs now exist (Plassais et al. 2019). Building a dataset of WGS from 722 canines, including domestic breeds, village dogs, and wild canids, over 90 million canine SNPs and insertion–deletions (indels) variants have been identified. This dataset has proven useful for the identification of multiple loci controlling body size, weight, leg length, ear size and shape, and fur-associated traits (Plassais et al. 2019; Whitaker and Ostrander 2019; Parker et al. 2020), often verifying previous reports such as those of associated with body size (Sutter et al. 2007; Rimbault et al. 2013; Plassais et al. 2017).

The above data are useful for identifying regions and points of variation responsible for major morphologic differences. In general, breed differences are controlled by small numbers of genes of large effect. The data are also useful for better understanding the complex functions of some genes. GWAS aimed at identifying genes that are particularly important for large body size includes *IGSF1* and *IRS4*, both of which are members of the GH-IGF1 superfamily

and thyroid hormone pathways (Plassais et al. 2017). These pathways are known to play a role in body size morphology, but the dog data provide a new system for examining genetic variation and morphology. These data also demonstrate how genes underlying complex morphological traits, when perturbed in humans, cause disease.

For studies such as the above to advance, four things are needed. First, many additional canine genomes need to undergo WGS. This is underway via the Dog10K project (Ostrander et al. 2019), which aims to sequence 10,000 canines with rapid data release. A deep phylogenetic tree of domestic dogs has been generated (Parker et al. 2017) and breeds from each of the 23 clades are represented, with a goal of sequencing 10 dogs of each domestic dog breed. Also, while sets of village dogs have already undergone WGS, this should continue, as the data have proven invaluable (Boyko et al. 2009; Shannon et al. 2015; Pendleton et al. 2018). These are dogs that are not members of a breed and have not been under the same sort of high-intensity human selection. Second, new reference genomes need to be developed. The original reference genome, from a boxer named Tasha, utilizes short reads (Lindblad-Toh et al. 2005). New long read technologies permit higher fidelity assemblies with fewer gaps. Currently, multiple reference assemblies are being generated from distinct dog breeds and other canids. Third, genome studies need to be more inclusive of copy number variation and other repeats (Serres-Armero et al. 2017). Only then can a deep understanding of the role of regulatory elements in the canine genome be achieved. Finally, the success of any genetic study is intimately tied to phenotyping. Although breed standard measures are often used for genetic studies of morphology, they inevitably fall short for genetic studies of behavior. One large well-used behavioral survey exists (Hsu and Serpell 2003), which has contributed significantly to our understanding of heritability and behavior. But well-developed and validated behavioral assays are needed to identify genes controlling individual traits.

Dogs as pets

In a mere few decades, the estimated global dog population has grown to approximately 1 billion (Gompper 2014b). Free-roaming dogs (or "village dogs," those not permanently restrained or under human control) are thought to account for half to three-quarters of the global canine population (Boyko et al. 2009; Hughes and Macdonald 2013), although dogs' mobility makes estimation difficult.

Worldwide, dog prevalence is ∼12 dogs per 100 people, but this ratio varies considerably even among neighboring countries (Sykes et al. 2020). Dog ownership is projected to expand fastest in developing countries where higher living standards and discretionary income make pet ownership affordable (Tahir 2017). In the global veterinary services market, the growth of Asia Pacific's market recently surpassed that of both North America and Western Europe. China's growing urban population and increase in pet ownership is largely driving this demand for veterinary services (Thibaud 2017). American pet ownership has more than tripled since the 1970s, and today two-thirds of US households own a pet (APPA 2020a). Dogs continue to dominate in pet popularity; over 38% of American households own at least one dog—the highest ownership rate since AVMA began measuring it in 1982 (AVMA 2018), and the highest per-capita ownership in the world (Herzog 2019). All told, the USA is the home to over 77 million dogs (up 10% from 2011), with shelter and rescue groups as the largest constituents (AVMA 2018).

Dogs are increasingly viewed as family members across much of the developed world; a 2016 study revealed that the majority (85%) of American dog-owning households considered their pets "members of the family," up from 51% in 2002 (AVMA 2002, 2018). A strong correlation exists between the perceived degree of human–dog bonding and pet spending. For example, households who consider dogs to be family averaged three times the annual veterinary visits compared with households who considered dogs property (Burns 2008). The average American dog owner spends approximately $1400 per dog annually on basic expenses, and in aggregate, global spending on dogs accounts for 42% (∼USD 93 billion) of the entire international pet care industry revenue share (APPA 2020b).

Such costs appear well-justified. Bred and trained human assistance dogs (e.g., therapy, guide, medical, and service dogs) can measurably increase the well-being of individuals with physical disabilities or chronic conditions (e.g., Winkle et al. 2012; Rodriguez et al. 2020). Numerous studies have documented that similarly, companion dogs can enhance their owners' health, sense of psychological well-being, and longevity (collectively termed *zooeyia*; Bryce [2021]; reviewed in Wells 2007; Casciotti and Zuckerman 2016; but see Herzog 2011). Furthermore, dogs have provided critical, direct benefits to people during the SARS-CoV-2 (a.k.a. COVID-19) global pandemic. Promising pilot data from numerous laboratories suggest that dogs can accurately distinguish urine, saliva (Essler et al. 2021) or armpit sweat samples (Grandjean et al. 2020) from COVID-19 positive patients versus those from healthy individuals, with detection reliability approaching that of PCR diagnostic testing. The pandemic has also highlighted the at-home benefits of canine companionship: the stricter the social isolation, the higher the rates of dog adoption, with no associated increase in dog abandonment (Morgan et al. 2020).

Canine–human bonding

It is not surprising that another major area of research in recent years has been dog–human relationships and their role in dogs' success and welfare in anthropogenic environments. Early studies attributed that success to a hypothesized "human-like" social cognition evolved during domestication (Hare and Tomasello 2005). However, demonstrations that other species, including wild canids, have the capacity to bond with humans (Lenkei et al. 2020) and excel on human guided tasks (Udell et al. 2008), coupled with findings that development, learning, and environment play a significant role in the presentation of social skills in dogs (e.g., D'Aniello and Scandurra 2016) have moved the field in a new direction. Instead of acting on cognitive abilities directly, recent evidence suggests that domestication may have altered dogs' social development, and ultimately the degree of social focus (vonHoldt et al. 2017). For example, structural variants in GTF2I and GTF2IRD1 genes are more common in dogs compared with wild canids, and these alterations correspond with a general increase in focus on social stimuli (vonHoldt et al. 2017). This same genetic region has been implicated in the development of Williams–Beuren Syndrome in humans, a condition characterized by excessive gregariousness and hypersociability (Kaplan et al. 2001).

However, a predisposition toward hypersociability is only one piece of the puzzle. Increasing recognition that the social behavior of dogs can be highly flexible and variable has opened the door for more discussion of individual and population differences as well (Udell et al. 2014). While the great majority of early work on the dog–human relationship was focused on pets, more diverse data have provided new insight into the origins of dogs' social behavior. Data from free-roaming dogs suggest that while some human-directed behaviors appear to be incredibly similar across dog populations (e.g., inhibition of individual problem solving, and increases in looking toward humans when presented with a novel task [Brubaker et al. 2019]) there are

also important differences (Bhattacharjee et al. 2017). For example, pet dogs follow human points more reliably at older ages (Wynne et al. 2008). In contrast, in free-roaming populations, puppies more readily follow human points than older individuals, suggesting that these trends may have more to do with context and environment than aging (Bhattacharjee et al. 2017). Exploring social plasticity as a feature of dogs' success in human environments has great potential to change the way we think about and study social behavior in dogs going forward, and also paves the way for more research aimed at improving the success and wellbeing of individual dogs, who are not always well represented by averaged data (Brubaker et al. 2019). For example, research suggests that stronger, more secure attachments can benefit both dogs and humans, resulting in greater persistence, task performance, lower stress levels and in some cases better therapeutic outcomes (Wanser and Udell 2019), but there is still much to learn about the factors that predict or facilitate the development of secure attachments. There is also a need to understand what role humans play in the social lives of dogs, compared with the role of bonded conspecifics. Sipple et al. (2021) address this question, comparing the degree of social support a bonded human or bonded conspecific provides for a dog in an unfamiliar environment.

Dog diversity in form and function

We recognize that dog phenotypic and functional diversity has many aspects that are impossible to cover comprehensively within the scope of this article. Here, we attempt to give a general overview of phenotype and aging, followed by a more specific discussion of functional and metabolic mechanisms that may underlie these observations.

Lifespan and aging in dogs

Canine epidemiology has received considerable attention over the past decade, both for veterinary studies as well as comparative medicine and epidemiology. Unlike many model organisms, dogs sharing the human environment are affected by many of the same diseases, receive comparable medical care in developed nations, and have large amounts of health and environmental data readily available. Under the Center for Disease Control's *One Health* paradigm, companion dogs present a valuable model for human epidemiology. Additionally, because companion dogs age roughly 7–10 times faster than their owners, it is reasonable to assume that they will show the effects of exposure to environmental risk factors on disease risks much sooner than would be the case in humans (Gilmore and Greer 2015; Pitt and Kaeberlein 2015; Creevy et al. 2016; Kaeberlein et al. 2016; Hoffman et al. 2018).

While veterinary epidemiology has yielded large amounts of data on various individual diseases and their associated risk factors, lifespan has not received nearly as much attention. This disparity is somewhat disappointing in that regardless of environmental, genetic, or phenotypic risk factors, every dog will eventually succumb to a life-limiting event or disease, and barring animal welfare concerns, lifespan is therefore ultimately a more meaningful outcome in epidemiology than individual disease risks (Urfer and Kaeberlein 2019).

Measuring lifespan in dogs poses several challenges. The common practice of measuring it based on data from deceased dogs results in right-censored data and underestimates actual lifespan (Urfer 2008). Measuring lifespan based on teaching hospital data (Fleming et al. 2011) or animal insurance data (Egenvall et al. 2005, 2010) tends to favor more involved husbandry, more affluent owners, and complex diseases. Measuring lifespan based on data from veterinary practice chains introduces bias regarding a particular clientele that favor these practices (Urfer et al. 2019), and measuring it based on data from independent practices raises issues with standardized data collection and evaluation (Lewis et al. 2018). It has been known for quite some time that age-to-age comparisons between dogs and humans are not linear, and that the oft quoted "seven human years to one dog year" is not an accurate reflection of comparative aging between the species (Hoffman et al. 2018). Recently, Wang et al. (2020) undertook a quantitative translation of dog-to-human aging through conserved remodeling of the canine DNA methylome. Their work shows a nonlinear relationship that translates dog-to-human years and aligns the timing of major physiological milestones between the two species at distinct ages as marked by associated physiological changes (infant, juvenile, mature, senior, etc). Ultimately, it is fair to say that there is no such thing as an unbiased set of dog lifespan data—and yet, when comparing results from studies based on all these methods of data collection, some universally valid patterns have emerged and raise interesting questions for future research.

In general, mammals tend to follow a pattern where larger species live longer than smaller species, but within the same species, smaller individuals live longer than larger individuals (Samaras et al. 2002; Demetrius et al. 2009; Jimenez 2016). Domestic dogs are no exception to this; however, their extraordinary diversity in body size (spanning almost two

orders of magnitude) makes them a particularly interesting model for studying the influence of size on lifespan. Here, most of the observed lifespan differences are due to an earlier increase in mortality in large dogs when compared with small ones, which appears to be at least partially caused by large dogs developing age-related diseases such as cataracts and tumors early in life (Galis et al. 2007; Greer et al. 2007; Urfer et al. 2011; Kraus et al. 2013). However, there are some intriguing exceptions to these observations that may be helpful in further probing how and why small and large dogs age differently.

One such exception is canine cognitive dysfunction (CCD), which is an age-related dementia that shares many biological and clinical traits with human Alzheimer's disease (Landsberg et al. 2012; Oates 2014; Ozawa et al. 2016; Dewey et al. 2019; Majdic and Prpar Mihevc 2019). Unlike other age-related diseases, larger dogs do not appear to be affected by it at earlier ages than small dogs—in fact, our own preliminary data show no CCD cases in old dogs weighing more than 50 pounds, and other studies appear to confirm this (Watowich et al. 2020). This implies that the canine brain is somehow isolated from the usual size-related differences in aging that we find in most other organs. The mechanisms behind this phenomenon merit further investigation.

It is also worth noting that even in dogs of similar size, there can be considerable variability in lifespan. For example, in a recent study of 2.3 million dogs seen in corporate veterinary hospitals, the median lifespan of Great Pyrenees was 2.5 years longer than the median lifespan of Great Danes, and the median lifespan of Rottweilers was 3 years shorter than the median lifespan of Labrador Retrievers (Urfer et al. 2019). These large differences in lifespan cannot be explained by differences in body size, and they warrant further study to determine underlying physiological mechanisms that may differ in these dogs compared with other breeds, which will likely improve our understanding of the mechanisms of aging and age-related disease and how they interact with body size. In addition, further exploration into genotype-environment interactions and their effects on lifespan is warranted, such as investigating the effects of selection and training on physical fitness traits.

Canine exercise physiology

Some dogs are known for their capacity for exercise, whether as professional athletes, dedicated working dogs, or pets that interact with their owners through vigorous play. As a result, exercise stress is common in the lives of dogs and much of our current knowledge of mammalian responses to exercise stress has been built on the foundation of canine exercise physiology research. Dogs were used as models of mammalian cardiorespiratory and metabolic function throughout the mid- to late 20th-century, and during this time several laboratories produced seminal studies examining the basic cardiorespiratory and metabolic responses to acute exercise. In particular, Musch et al. (1985, 1987) detailed the cardiovascular responses to acute exercise, and the laboratory of David Wasserman produced several studies detailing the metabolic responses of dogs to exercise stress (Wasserman and Cherrington 1991). Included in these studies were the effects of athletic conditioning, and although there were clear successes in experimentally increasing the fitness of dogs in a laboratory environment, it became apparent much later that the degree of conditioning that was achieved in these studies was substantially less than what an athletic dog was capable of achieving and as a result, these studies did not fully illustrate the scope and variability that is possible within canine responses to exercise stress.

The considerable exercise capacity of athletic dogs began to be revealed in a scientific context in the late 20th century. A pivotal advance in this field was the movement of scientific investigation into the field and the use of professional canine athletes as research subjects, as these dogs represent populations that have undergone intense purposeful selection. Sled dogs participating in ultra-endurance racing (races lasting for days to weeks and covering up to 1600 km) were frequently the subject of these studies. One of the first investigations to demonstrate the feasibility of conducting high-quality scientific studies on exercising dogs documented the extraordinary capacity for sustained exercise, with dogs consuming up to 12,000 kcal/day ($\sim$480 kcal/kg/day) for multiple consecutive days during competition (Hinchcliff et al. 1997). Highly conditioned canine athletes can have an average maximal aerobic capacity (VO_{2MAX}) of 200 mL O_2/kg/min (Banse et al. 2007), with individual dogs approaching 300 mL O_2/kg/min (M. S. Davis, unpublished data). Other intensively trained dogs such as military working dogs were also studied (Miller et al. 2015b; Phillips et al. 2015). Much of this work challenged the current dogma of how mammalian exercise is supported metabolically (Davis et al. 2014; Miller et al. 2017).

Perhaps the most intriguing aspect of canine exercise physiology is the metabolic plasticity of dogs intensively trained for endurance exercise, with these dogs being able to adapt from a glycogen-depleting phenotype to a glycogen-sparing phenotype in just a

few days (McKenzie et al. 2008). However, underlying genes are also important. Huson et al. (2011, 2012) mapped two loci important in the success of sled dogs, controlling heat tolerance and cardiac function, a group of breeds defined by their athleticism. Also, Kim et al. (2018) demonstrated, in a comparison of athletic breeds (e.g., retrievers, hunting dogs, and racing dogs) *versus* terriers, that genes affecting physiology (heart and muscle) were under the greatest selection in the athletic breeds.

Individual capacity to adopt multiple different metabolic phenotypes in a short period of time appears to be related to the ability of the successful canine athlete to preserve a high rate of cellular protein synthesis during exercise stress (Miller et al. 2015b) combined with the ability to adopt alternative approaches for providing metabolic energy (Miller et al. 2015a; Davis et al. 2018) and managing metabolic byproducts (most notably, heat). The use of professional canine athletes in exercise physiology and as models in biomedical research is further described by Davis (2021).

Dog body size and life-history

Body size in vertebrates often correlates with ecological and life-history traits (Blackburn and Gaston 1994; Bakker and Kelt 2000) as well as with cellular and molecular determinants of whole animal metabolic rate, including heart rate, mitochondrial density, and maximal activities of rate-limiting enzymes (Dobson and Headrick 1995). Domesticated animals are often freed from key constraints associated with natural selection (e.g., resource acquisition), while body size and reproduction are manipulated via artificial selection. As a result, the amount of energy spent on maintenance, including cell-based rates of metabolism, may be altered (Kozłowski et al. 2020). With body sizes ranging from the 2 kg Chihuahua to the 90 kg Great Dane, a 44-fold difference in body size dictated by a small genetic variance within a single species (Jimenez 2016; Parker et al. 2017), the domestic dog is the ideal study model to address the question of how body mass and metabolic parameters have co-evolved across levels of organization. In mammals, changes in body size lead to cellular metabolism changes (Kozłowski et al. 2020). Determining body size metabolic consequences in a single species is lacking in the literature. The development of a framework and understanding of how a single species resolves issues of scale, from the whole organism to the cell, will elucidate higher order principles that control cellular organization and function, and link these patterns to whole-animal phenotypes at rest and exercise.

With whole-animal correlations to aging rates only recently established (Deeb and Wolf 1994; Patronek et al. 1997; Michell 1999), progress toward a mechanistic approach to answer the inevitable query of slow aging rates in small dogs with high mass-specific metabolic rates remains challenging. Some have postulated that faster growth rates in large breed dogs could lead them to be burdened with increases in oxidative damage during early life, leading to higher rates of diseases associated with free radical damage, and hence, early mortality (Galis et al. 2007; Kraus et al. 2013). However, Jimenez (2016) found that smaller breeds have faster growth rates compared with larger breeds, although larger breeds spend more of their lifespan in a growing phase compared with smaller breeds. At the cellular level, using primary fibroblast cells isolated from young and old dogs, previous work has found that basal levels of oxygen consumption and proton leak change similarly in small and large breed dogs, where older dogs have higher rates of both variables, although no differences in mitochondrial content were found (Jimenez et al. 2018). To that end, others have demonstrated that primary fibroblast cells from dogs have lower mitochondrial membrane potential in longer-lived breeds, suggesting more uncoupling (Nicholatos et al. 2019). Rates of mitochondrial efficiency and uncoupling seem to show some plasticity in dogs. For example, respiratory leak in permeabilized skeletal muscle fibers from biopsies of Alaskan sled dogs when they were unconditioned or after conditioning increased with increasing temperatures, and after athletic conditioning (Davis and Barrett 2021). This study also found a significant negative correlation between uncoupling protein (UCP3) expression and oxidative phosphorylation efficiency, suggesting that large breed dogs, when exercised, have plasticity in coupling efficiency. Additionally, Jimenez et al. (2018) found that reactive oxygen species (ROS) production was not correlated with breed sizes or breed lifespan, but limited data exist on ROS production rates in exercising or physiologically stressed dogs. Furthermore, Jimenez and Downs (2020) found that small breed domestic dogs have more circulating lipid peroxidation (LPO) damage compared with large breed dogs, opposing the conventional lifespan predictions of keeping increases in damage at bay for animals that have long lifespans. Thus, the generally recognized patterns of oxidative stress, as they seem to be described in the aging literature, do not seem to match as a primary mechanistic process associated with, at least, aging rates in dogs. Jimenez (2021) reviews the current literature on whole-animal and cellular metabolism across body sizes of domestic and wild canids.

Ecology of dogs

Foraging ecology of large canids

Free-ranging dogs are ubiquitous members of a large predator guild whose impacts are a burgeoning area of research across academic disciplines. As such, understanding the ecology of dogs requires concurrent consideration of the ecology of other large canids. For example, there is a growing literature on the foraging ecology of wild large canids—defined by Ripple et al. (2014) as a group of carnivorans comprising the African wild dog (*Lycaon pictus*), dhole (*Cuon alpinus*), Ethiopian wolf (*Canis simensis*), gray wolf, maned wolf (*Chrysocyon brachyurus*), red wolf (*Canis rufus*), and the long-feral Australian dingo— that is important for understanding how dogs interact with native species across the globe. Most of the early work on foraging in this group focused on their consumptive effects, which stem from the removal of individuals from prey populations (e.g., Estes and Goddard 1967). This emphasis is hardly surprising, given that the hunting behavior of many large canids is both visceral and readily observed, and that these species can compete with humans for wild game, target livestock, and sometimes pose a threat to humans (Lozano et al. 2019). More recently, research on foraging in this group has broadened to explore non-consumptive (i.e., fear-based) effects on prey (Fleming et al. 2017), intraguild interactions (Palomares and Caro 1999), and broader community consequences (Morris and Letnic 2017). Looking ahead, exciting research frontiers include implications of large canid non-consumptive effects for prey demography, scavenging (Wirsing and Newsome 2021), indirect consequences of changes to their foraging, and how their effects are shaped by humans.

Considerable attention has been devoted to the non-consumptive effects of large predators, including canids, on prey behavior (Say-Sallaz et al. 2019), but much less to what is known as predator risk effects, or deleterious effects of stress and opportunity costs (for foraging and reproduction) that stem from defensive investment (Creel and Christianson 2008). Not surprisingly, therefore, Sheriff et al. (2020) found little evidence for risk effects on prey population size caused by large-bodied predators in open systems. Future studies addressing this lacuna are key to our understanding of when, and to what extent, the effects of large canids on prey demography transcend those caused by the act of, or even operate in the absence of, predation. They will also improve our capacity to predict the full ecological consequences of large canid declines and recovery.

The evidence for large canids triggering trophic cascades, or effects that propagate downward through food webs (Ripple et al. 2016), is debated (Fleming et al. 2017). Clarity about these indirect effects, which can have profound implications for ecosystems (Estes et al. 2011), has been hindered by several factors that represent fruitful avenues for future work. First, many trophic cascades studies involving large canids, and especially those examining non-consumptive mechanisms, have focused on gray wolves and taken place in a few protected areas in North America (Say-Sallaz et al. 2019), limiting their scopes of inference. Second, few such studies are designed as experiments (Ford and Goheen 2015). Third, trophic cascades are complex (Peterson et al. 2014) and yet, in particular where non-consumptive mechanisms are concerned, most studies of these phenomena have addressed subsets of the interacting species that might shape them (Montgomery et al. 2019) and overlooked features of the interacting players and setting on which the outcome of the cascade might depend (Wirsing et al. 2021).

Whereas most prior work on the effects of large carnivore foraging has occurred in areas with a limited anthropogenic footprint, much of the remaining habitat for these species includes humans as an important ecosystem player (Watson et al. 2018). Moreover, there is a growing awareness that humans can alter large predator effects in ecosystems (Guiden et al. 2019), raising questions about the applicability of research on large predators in areas where human impacts are minimized. Nevertheless, work on the relationship between humans and predator–prey interactions is in its infancy (Kuijper et al. 2016). Rapid expansion in this research area is likely because of the urgent need to predict the impacts of humans on ecological communities as they expand into the wilderness and the effects of large canids, and other predators, as they recolonize areas that are dominated by humans.

Ecology of dogs in natural communities

Applied ecologists are increasingly aware of the potential impacts of dogs, both unowned and owned, on animal populations. While the scope and scale of these impacts are still unclear, generalizations regarding the role of dogs have emerged. Concerns include dogs acting as predators or competitors, dogs acting as prey for native large predators and in-turn driving human–wildlife conflict, dogs hybridizing with native *Canis* species, and dogs acting as reservoirs for pathogens (Gompper 2014a). A burgeoning number of case studies have expanded the spatial scale of

these problems from locally important issues to problems that are relevant globally. Two general assumptions are increasingly accepted: (1) dogs are bad for wildlife; (2) dogs need to be better managed to address these concerns.

As with any recent field, however, core generalizations derived from a relatively small set of case studies may not fully encompass nuances (Magliocca et al. 2018). Thus, there is a need to continue to visit the topic of dog–wildlife interactions to discern gaps in our understanding of not just how dogs interact with wildlife, but also whether these interactions are always important. For example, there have been several case studies revealing that dogs may act as reservoirs for pathogens of concern to native carnivore populations (e.g., Belsare et al. 2014). However, surveys of the pathogens shared by dogs and native carnivore species often assume that the pathogens of native wildlife populations are derived from (initial invasion of the pathogen) and maintained by (through repeated cross-species transmission) the dog population. Such assumptions fail to recognize that native carnivore communities, even in the absence of dogs, are often above the critical community size necessary to support a pathogen (e.g., Almberg et al. 2010), or that antibody-based serologic assessments may be insufficient to discriminate among multiple co-circulating strains in populations and communities (e.g., Wostenberg et al. 2018). In such cases, the removal of dogs may fail to reduce the incidence of pathogens in the broader wildlife community. Similarly, recognition of concurrent pathogen occurrence in dogs and wildlife sometimes results in calls for increasing vaccination efforts. However, the resources that go into these vaccination efforts may be for naught if most of the dogs are already immune due to early-age exposure and recovery. In such cases, vaccination efforts may contribute little to herd immunity, which in turn reduces the likelihood of dog vaccination approaches contributing substantively to a reduced impact of the pathogens to wildlife (Belsare and Gompper 2015). Such findings suggest a need for additional attention to the context-dependent role of dogs when considering wildlife health.

An additional consideration is also likely necessary for assessing the importance of other dog-wildlife interactions. For example, the role of dogs as real or perceived predators of, or competitors with, wildlife is based on numerous studies of the diets of free-ranging dogs, and focal studies of the response of some wildlife to the presences of dogs (e.g., Ritchie et al. 2014; Vanak et al. 2014). However, wildlife may not always see dogs as a risk (Parsons et al. 2016),

and indeed, play is often as common as agonistic behavior in interactions between dogs and some native carnivores (Boydston et al. 2018). The idea that dogs may act as prey for large(r) carnivores and thus underpin human–wildlife conflict, or that dogs used to mediate one conflict may enhance another, is also based on studies in very specific settings (Butler et al. 2014; Sepúlveda et al. 2014). But on a broader spatial scale, the likelihood of such interactions is typically minor. Finally, the suggestion that dogs commonly represent a hybridization risk to populations of native *Canis* species is based on a wide variety of observed recent or historic introgression events (Leonard et al. 2014). However, while such cases may be locally or regionally important in areas where native canids lack mating opportunities, in most regions where dogs overlap with native *Canis* populations, hybridization is of little apparent consequence. Thus, there is a need to recognize spatial and temporal nuance in the quantity, quality, mechanism and basis of dog-wildlife interactions (see Gompper 2021).

Ecology of dogs in human communities

Ecological anthropologists study the ways that humans adapt to their environments. Adopting a cost–benefit approach that is common to behavioral ecology more generally, anthropologists view dogs as part of the suite of adaptations that humans may use to subsist in a particular socioecological setting (Koster 2009). It is fairly easy to consider possible uses for dogs in subsistence-oriented societies: as hunting assistants, watchdogs, herding or flock guardians, cargo-pulling dogs, and sources of food in some cases. However, dogs also impose costs: they require food, they spread pathogens, and they may attack and harm humans and other animals. Unlike other tools, they can die suddenly, and replacements (i.e., adult dogs) may be difficult to obtain. Currently, anthropologists are engaged with assessing these costs and benefits while investigating variation in the importance of dogs across time and space. Anthropologists are also mindful that the dogs themselves are under selective pressures in anthropogenic environments, and the extent to which this socio-ecological variation can explain the evolution of dogs is an emerging source of research attention, too.

Often working in small-scale communities where most humans are engaged with subsistence tasks (foraging, farming, herding, etc.), ecological anthropologists employ observational methods to study dogs. For example, Koster (2008) followed hunters and their dogs on excursions into the Nicaraguan

forest, which led him to advance an extension to the optimal foraging model that is often used to study prey choice by foragers. The primary value of dogs in Nicaragua is that they increase hunters' encounters with elusive prey (agoutis, pacas, armadillos, etc.), but in other settings, dogs provide value by increasing the speed and success of catching animals that have already been encountered (Lupo 2011). Building on these insights, archaeologists attempt to explain the prominence of hunting dogs in past societies by considering their potential value relative to hunting strategies that do not include dogs. This approach requires careful consideration of the extent to which dogs would be useful for hunting each of the respective species in a given environment. There is an evidence that hunting dogs surged in importance among foragers in temperate Holocene forests, then declined in importance as foraging societies turned toward alternative subsistence strategies, such as horticulture (Perri 2016). Dogs can serve alternative roles in such societies (e.g., herding dogs), but such roles are understudied and somewhat undertheorized.

In addition to research questions about the roles of dogs in human societies, anthropologists also contribute to applied research. In terms of wildlife conservation, for instance, dogs entail pros and cons (Koster and Noss 2014; Gompper 2021). In some cases, dogs are largely useless for hunting certain kinds of species, such as endangered arboreal primates. In certain settings, natural resource managers and conservationists might consider permitting the use of dogs for hunting, but not firearms. In other settings, however, those recommendations might be reversed depending on the specific relationships that dogs have with the respective wildlife species. And conservationists must be mindful that dogs can impact wildlife not just via hunting harvests, but also via disease transmission, particularly to imperiled species (Fiorello et al. 2006).

For canine science more generally, anthropologists may challenge assumptions about the roles of dogs in human societies (Gray and Young 2011). Canine scientists benefit from working with owned dogs in industrialized nations, but as discussed, such dogs occupy a relatively narrow sliver of the global dog population. Overall, relatively few dogs on the planet receive regular veterinary care and special diets. Not all dogs maintain affectionate relationships with humans. In some ways, subsistence-oriented societies provide better analogs for the kinds of settings in which dogs first evolved (see Koster 2021). The logistics of sampling dogs in such contexts are nontrivial, but these challenges are arguably outweighed by the chance for a more holistic picture of dogs as biological organisms that are adapted to human environments.

Dogs aiding conservation efforts

Despite numerous and wide-spread adverse effects of dogs on wildlife communities, canines can play valuable roles in nature conservation efforts. Conservation detection dogs (hereafter, CDD) have been partners to conservationists since at least the 1890s, when a fox terrier in New Zealand sniffed-out hundreds of kakapo (*Strigops habroptilus*), a parrot species, that were subsequently relocated to safety. In North America and Europe, field biologists have employed hunting dogs since the mid-20th century to find wildlife, primarily birds of interest (Dahlgren et al. 2012). The late 1990s saw the inception of organizations dedicated to the training and fielding of CDD teams consisting of dogs of various breeds motivated by a toy or food reward. This change in motivation allowed for diversification of targets to an increasingly wide array of species of plants, animals, animal scat, insects, mollusks, and other genera to which no dog is bred to hunt (Beebe et al. 2016).

The latter type of CDDs began to appear in the scientific literature in the early 2000s. Reports ranged from descriptive "first-ever" accounts of dogs trained to find scat from a single species of interest (Smith et al. 2003) to methodological comparisons between CDDs and other survey methods (Long et al. 2007). Species' monitoring standard protocols are starting to include the use of CDDs (e.g., Northeast Eastern Box Turtle Working Group 2020), affording opportunities to improve study design, modeling, and analysis based on detection by scent.

While researchers and managers generate the demand for CDDs, dog trainers have the responsibility to prepare dog-handler teams to work effectively and safely, often close to highly imperiled species. Teams may be professionals for hire, biologists, or managers paired by CDD experts with a canine co-worker and trained as a team. There is growing interest among the public to be citizen scientists and there are opportunities in the CDD field to do so. Invasive species (e.g., devil weed) detection, where there is inherently less concern about ensuring the safety of the target itself, or laboratory-based work where dogs select target scent from an indoor line-up, are especially well-suited realms of CDDs for citizen science.

Most CDD programs utilize dogs from the canine rescue community. Working with dogs in need of homes, rather than intentionally breeding more

dogs, is a value that complements conservation agendas and is likely to continue to dominate the field. To successfully identify dogs that are likely to excel, the CDD field would benefit from implementing standardized evaluation criteria for cognitive capacity (e.g., MacLean and Hare [2018] for explosives and assistance dogs) and behavioral assessments (e.g., Wilsson and Sinn [2012] for military working dogs). Moreover, handler attributes are important (Jamieson et al. 2018), but ensuring appropriate candidates and adequate training is largely unexplored. While current CDD operational paradigms have contributed substantially to wildlife conservation efforts, careful honing of the selection and training processes will improve efficiency and afford the broader application of canine detection dogs to conservation challenges around the world.

Conclusion

As the world's most ubiquitous, phenotypically variable carnivore (Fig. 1) and the first domesticated animal, dogs have evolved alongside humans for millennia, transforming the environments we co-inhabit. The resulting intimate and enduring human–dog relationship consists of not only reciprocal benefits to both species, but challenges acting across multiple biological and spatial scales globally (reviewed here and in Sykes et al. 2020). Collectively, our growing understanding of the multifaceted nuances of the human–dog relationship has produced a unique multidisciplinary field of research: canine science.

Dogs have now risen to, and in some ways exceeded, the bars set by other biological models. The dog is ready to take its rightful place as a model organism capable of making unique and powerful contributions to our understanding of biological development, disease, behavior, and nuanced ecological interactions. Our aim in this symposium-generated issue of *Integrative and Comparative Biology* is to demonstrate that the more we discover about canines, the more indispensable they become as a model spanning major biological lines of inquiry. As such, this issue is dedicated not only to summarizing our current knowledge across diverse biological subdisciplines of canine research, but also to suggesting future avenues of interdisciplinary study with the potential to transform how and what we learn about dogs, and in-so-doing, ourselves.

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Conflict of interest

The authors declare no conflict of interest in this work.

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