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VIEWPOINT

Our time is now – how companion animal veterinarians can transform biomedical science

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Over the past decade, there has been growing interest in the "One Health" agenda, defined by the One Health Initiative to be "a worldwide strategy for expanding interdisciplinary collaborations and communications in all aspects of health care for humans, animals and the environment." The concept has spawned numerous conferences, under- and post-graduate courses and has been the topic of dozens of articles that have discussed how medical doctors, scientists and veterinarians can work together to improve the health of both animals and humans. Although there is widespread agreement about the potential benefits of medical doctors and veterinarians working more closely together, this is far from routine practice for most companion animal veterinarians. This article reflects on why the topic of "One Health" is attracting such interest at the moment and discusses some of the reasons why the "One Health" agenda offers companion animal veterinarians a chance to be centre stage in the global drive to improve the health of both animals and humans.

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HISTORY OF "ONE HEALTH"

Medics and veterinarians have a long history of working closely together on diseases of mutual interest that can be traced backed to the late 18th century (Woods & Bresalier 2014). The increasing awareness of zoonotic diseases in the 19th century resulted in numerous collaborative initiatives. However, despite the history of collaboration, there has been growing concern about the development of "stubborn silos" where interdisciplinary interactions between medics and veterinarians is the exception rather than the rule (Christopher 2015). The "One Health" movement has emerged out of these concerns and embraces a cross-disciplinary, collaborative approach between medics, veterinarians and scientists to address diseases of importance to both scientific communities (Gibbs 2014).

Over recent years, the emergence of important zoonotic diseases has been a key driver in the development of collaborations as the wider biomedical community attempts to develop management approaches for diseases such as severe acute respiratory syndrome (SARS) and H5N1 influenza. These diseases, which have caused significant global morbidity and mortality, highlighted the need to understand disease biology in one species in order to develop rational therapeutic and preventive approaches for another. The merits of a "One Health" approach continue to be a made for many other zoonotic diseases in which infections in one species can subsequently impose a heavy disease burden on another. For example, over 50,000 people a year die from rabies and almost all victims contract the disease following a bite from a dog infected with rabies (Hampson *et al.* 2015). However, it is well established that if over 70% of the canine population were vaccinated, both humans and canine rabies could be eliminated (Cleaveland *et al.* 2003). The challenge is now for veterinarians, medics, community leaders, scientists and funding agencies to come together to roll out vaccination, education and public health programmes that have the capacity to reduce the prevalence of one of the distressing diseases to infect both humans and animals (Cleaveland *et al.* 2014). There are numerous other examples beyond zoonotic diseases where an integrated, multi-discipline "One Heath" approach has been strongly advocated from topics as diverse as antibiotic resistance to the biology of obesity (Sandoe *et al.* 2014, Travis *et al.* 2014).

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THE NEED FOR BETTER MODELS OF HUMAN DISEASES

Aside from the need to control zoonotic diseases, another major driver of the "One Health" agenda is the lack of progress which has been made on understanding, and subsequently developing novel therapies for, many human disorders. The numerous recent medical advances in these fields have frequently only allowed for more effective palliation of the clinical signs and, often, complete resolution of the underlying disease is not achieved. This failure has promoted reflection among scientists as to whether new approaches are required to make clinically relevant advances in patient care. Although lack of funding for scientific research is frequently cited as a major barrier in the drive to develop novel therapies, the failure to make significant, step-change advances in the treatment of many diseases has occurred despite an expansion of global biomedical research (Kaiser 2015, Moses *et al.* 2015).

This paucity of major advances in clinical treatments has, in part, driven a large increase in the number of animals, particularly mice and rats, which are used in experimental models of human diseases. While absolute figures are difficult to obtain because of the lack of recorded data on animal use in many countries, there is considerable evidence to suggest that the number of rats and mice used in experimental studies has continued to increase over the past decade. A study on the top institutional recipients of National Institute of Health research funds reported a 73% increase in the use of vertebrate animals between 1997 and 2012 (Goodman *et al.* 2015). The number of scientific procedures performed under a Home Office License in the UK increased by 52% between 1995 and 2013. In large part, this was driven by an increase in the production of genetically modified mice (Anon 2014). The expansion in the number and range of murine models has allowed scientists to undertake more studies in which the biology of disease can be mechanistically probed and new treatments tested prior to the initiation of phase 1 trials in humans.

Paradoxically, it is the increasing reliance on murine models that has been implicated as one of the reasons why so many treatments fail in human trials. Firstly, there are concerns that mouse physiology is so different from humans that it is unreasonable to assume that humans and mice will respond in a similar fashion to the same physiological challenge or novel therapy. For example, a recent study in *Proceedings of the National Academy of Sciences* titled "Genomic responses in mouse models poorly mimic human inflammatory disorders" revealed that acute inflammatory stresses from different aetiologies result in highly similar genomic responses in humans, yet the responses in corresponding mouse models correlated poorly with the human conditions (Seok *et al.* 2013). While alternative analyses have argued that their conclusion is overstated (Takao & Miyakawa 2015, Warren *et al.* 2015), this work resulted in major scientific journals cautioning against the heavy reliance of murine models in human translational medical research. Indeed, *Nature Medicine* ran an editorial titled "Of men, not mice" highlighting that "the findings of this study has provoked renewed discussion of the validity of animal models in translational research" (Anon 2013).

Secondly, there are increasing concerns that murine models do not accurately mimic human disease. In neuroscience, the process of reflection on the merits of widely used animal models has been largely driven by the failure of many positive findings in trials of new drugs in experimental murine models to be replicated in human studies (Howells *et al.* 2014, Perrin 2014). A striking example is stroke. A meta-analysis of all published experimental studies of stroke found that 912 candidate stroke treatments had been tested in animal models with many giving promising therapeutic responses (O'Collins *et al.* 2006). However, only one, tissue plasminogen activator, has been demonstrated to be effective in both animal and human clinical trials (Howells *et al.* 2014). Potential reasons for the spectacular failure to translate these positive results from mouse into man were not difficult to identify. For instance, many experimental treatments were given before the disease was induced rather than following the development of clinical signs, publication bias (the greater likelihood of publication of reports indicating a "significant" benefit of the novel therapy) and that the underlying biology of the murine model was vastly different from the pathophysiology of the human condition (Sena *et al.* 2010). Furthermore, concerns were identified about the robustness of the experimental design of many of the experiments involving murine experimental models (Sena *et al.* 2010).

Stroke models are not alone in attracting criticism for their lack of similarity with the human diseases they are attempting to mimic. Experimental autoimmune encephalomyelitis (EAE) is one of the most widely used models of the human disease multiple sclerosis (MS). However, numerous authors have questioned whether EAE is a good model of MS (Vesterinen *et al.* 2010, Baker *et al.* 2011, Constantinescu *et al.* 2011, Behan & Chaudhuri 2014). For example, numerous EAE models involve only a short, monophasic course of disease rather than a relapsing-remitting disease course that is the clinical pattern for many MS patients. In many EAE models, there is little evidence of demyelination, again in marked contrast to MS in which demyelination is a key pathological feature of the disease process. Furthermore, many EAE models require immunisation with myelin proteins and adjuvant or the transfer of ex vivo-activated T cells that is far removed from the human clinical scenario (Baker *et al.* 2011, Behan & Chaudhuri 2014). Even the spontaneous models of human diseases such as the non-obese diabetic mouse have many disease features that are markedly different from the human disease they are modelling, in this case type 1 diabetes (In't Veld 2014, Reed & Herold 2015).

There are also continuing concerns among the public about the morality of inducing disease in healthy animals. Although activity by antivivisection groups is lower now than two decades ago (Holder 2014), there is clear evidence that a significant proportion of the population are uncomfortable with the use of animals in experimentation. A recent poll by the IPOS MORI of nearly 1000 adults in the UK found that almost a quarter of respondents believed that the UK Government should ban the use of animals for any form of research (Leaman *et al.* 2014). Even though two thirds of respondents believe that the use of animals in scientific research is acceptable, they only considered

it acceptable if "there is no alternative." Such concerns about the use of healthy animals in experimentation have driven an expansion of activity and funding opportunities for research, which aims to replace, reduce or refine animals in experimentation. There are numerous examples of the replacement of in vivo with in vitro models of disease and refinement of experimental protocols to reduce the welfare impact on the mice involved (Fleetwood *et al.* 2015). However, these initiatives have not been effective at reducing the number of animals used in experimentation in many countries (Goodman *et al.* 2015).

CAN A "ONE HEALTH" APPROACH IMPROVE THE HEALTH OF COMPANION ANIMALS AND HUMANS?

How can a "One Health" approach involving companion animal veterinarians address these problems and provide a framework to further understanding of human and animal diseases? Arguably, companion animal veterinarians are now uniquely placed to help overcome these challenges and, at the same time, allow a deeper understanding of common canine and feline disorders to emerge. There is an expanding evidence base that the biology of many spontaneous disorders in companion animals closely mimic human disorders including a wide range of developmental, autoimmune, degenerative and neoplastic conditions (Ranieri *et al.* 2013, Switonski 2014). The similarity between numerous spontaneous disorders in cats and dogs and their human counterparts is, in many cases, striking. For example, features of the pathophysiology of canine diabetes are similar to human type 1 diabetes (Catchpole *et al.* 2005). A number of genes, linked with susceptibility to diabetes mellitus in humans, are associated with an increased risk of diabetes mellitus in dogs (Catchpole *et al.* 2013). Dystrophin-deficient muscular dystrophy in the cavalier King Charles spaniel has emerged as a powerful model of the human disorder (Walmsley *et al.* 2010). Other naturally occurring inherited diseases in dogs such as protein-losing nephropathies, haemophilia B and narcolepsy have been highly informative from a comparative genomic perspective (Tsai *et al.* 2007).

Companion animals also develop diseases that are almost analogous to the experimental models that are created in healthy animals. For example, congenital portosystemic shunts (cPSS) is one of the most common congenital abnormalities diagnosed in dogs-in which an anomalous vessel connects the portal vasculature to the systemic circulation (Tobias & Rohrbach 2003). This abnormality is very similar to the widely used surgical portocaval models of hepatic encephalopathy (HE) in which healthy animals have their portal and systemic circulations connected via a surgical anastomosis (Butterworth *et al.* 2009). There is growing evidence that the same metabolic derangements occur in dogs with cPSS and HE also occur in humans, indicating that dogs with cPSS could act as a spontaneous, naturally occurring model of human HE (Shawcross *et al.* 2007, Tivers *et al.* 2014).

There are numerous other reasons as to why there has never been a better time for multi-disciplinary research involving wider collaboration between medics, veterinarians and basic scientists to become more commonplace. There are now increasing numbers of longitudinal cohorts and consortiums of academic institutes and primary care practices involving large number of patients meaning that the risk factors involved in disease development can be explored with a degree of rigour that was not possible until very recently (Clements *et al.* 2013, Jones *et al.* 2014, O'Neill *et al.* 2014). The dramatic advances in companion animal genomics afford opportunities to understand the role of genotype on the development of diseases in both highly inbred breeds and more genetically diverse crossbreed populations (Mellanby *et al.* 2013, Schoenebeck & Ostrander 2014). In addition, the more widespread availability of advanced diagnostic imaging equipment such as MRI and CT has greatly enhanced the ability of companion animal veterinarians to precisely phenotype diseases. There has also been an increase in diagnostic reagents that have facilitated the detailed phenotyping of diseased tissues. Together, these advances have enabled veterinarians to routinely phenotype companion animal diseases with great precision. Several UK veterinary schools now have pan-hospital Home Office licenses, which provides the necessary regulatory framework around which high-quality science can be performed on client-owned animals. There is now an expanding pool of research-literate clinicians who are emerging from training programmes such as Wellcome Trust fellowship schemes or institute-focussed schemes such as ECAT-V that will help address shortages in staff who have the prerequisite skill sets needed to develop comparative medicine research programmes (Argyle *et al.* 2013).

SUMMARY

In summary, the collective forces involving the need to reduce experimentation on healthy animals, the limitation of murine models to effectively model human disorders, together with the availability of the necessary technology, infrastructure and personnel provide the veterinary profession with a unique opportunity to advance the understanding of diseases of companion animals and potentially improve the health of humans at the same time. Arguably the least formidable yet the most stubbornly intractable challenge is for the medical, veterinarian and basic scientist communities alongside funding bodies and industry to come together to embrace the unique opportunities which are offered by spontaneous disorders in companion animals. The shift towards a more inter-disciplinary approach may not be a natural one, particularly as many research programmes become increasingly focussed on ever more refined study questions. However, if the veterinary community is able to persuade the wider biomedical community of the merits of "One Health" approach, then the potential benefits for both humans and companion animals will be considerable.

Conflict of interest

None of the authors of this article has a financial or personal relationship with other people or organisations that could inappropriately influence or bias the content of the paper.

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