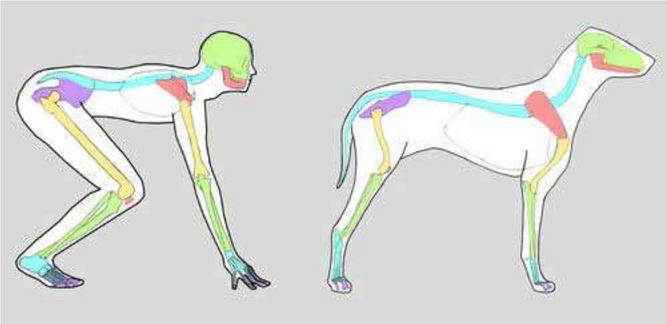
Comparative Medicine: Similarities Between Domestic Animals and Humans – Do these Help in Translational Medicine?

Although appearances can be deceptive, there are considerable biological similarities between humans and animals. At the physiological and anatomical level, the similarities are remarkable. Animals ranging from mice to monkeys have the same organ systems, which function in a very similar manner to those of people. This means that many human and animal diseases are also highly similar. For this reason, about 90% of veterinary medicines are the same, or very similar, to those used in human patients. On the whole, while there are obviously differences, the similarities between humans and animals far outstrip the differences in physiological and biochemical function. To a large extent this is not surprising, bearing in mind evolutionary linkages. It is, for example, well known that humans share over 90% of their DNA with other mammals. The study of comparative genomics helps to understand how species have evolved and what genes regulate species specific traits. Where differences between animals (including humans) exist, these can, in fact, also give powerful insights into mammalian physiology and disease resistance and may even suggest novel targets for drug treatments. By way of an example, type 2 diabetes is common in people and cats that are obese, whereas obese dogs rarely suffer from type 2 diabetes. If we understood why obesity in dogs does not predispose them to type 2 diabetes, this might help us to find new ways of preventing this problem from occurring in overweight people and cats.

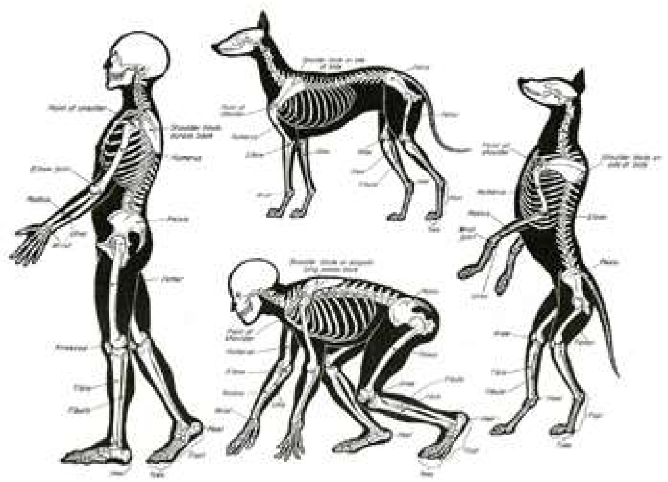
Following a good basic understanding of a human disease process *in vitro*, it is still necessary to test hypotheses and ideas in a living animal model where all the physiological systems interact. At the present time, a test tube environment cannot provide the dynamics and interactions of a live animal system. While not perfect, animal models allow a much closer approximation than *in vitro* studies of how a medical intervention is likely to work in people. As discussed above, there are differences between species and between individuals within a species, which must be considered when extrapolating results to humans. Knowledge of comparative physiology is important to determine which species is the most appropriate model to undertake a proof of concept study for a particular treatment. Therefore, for the purpose of human therapeutic development, it is a question of identifying which animals have physiological and biochemical systems of interest, that are sufficiently similar to human. Rodent models of some diseases have not proved successful in predicting the likelihood of success of treatments for some human diseases. For example, cancers are difficult to model in laboratory animals, whereas some naturally occurring cancers in dogs are very similar to those in people, and those dogs with currently untreatable disease might benefit from the use of developmental treatments. Their response to treatment would, in turn, benefit medical science and help in deciding which drugs should go into human clinical trials. In summary, greater cooperation between human clinicians, veterinarians and the biomedical scientists who generate the new knowledge



which underpins both disciplines would be highly beneficial for both professions.

An historical perspective on the relationship between human and animal medicine is revealing, especially the work undertaken by the veterinarian and historian, Abigail Woods (2017). Traditionally, historians have propagated the view that human and veterinary medicine have always operated as separate domains. Woods' research gives a novel commentary on the evolving relationship between human and veterinary medicine following the creation of the Royal Veterinary College (RVC) in 1791. It is generally acknowledged that it was the founding of the RVC that gave birth to the veterinary profession in Britain. Woods coherently argues that when the RVC was set up, the study of veterinary medicine was considered continuous with its human counterpart, not separate from it. However, within the first 40 years of the creation of the RVC, veterinary and human medicine evolved into two separate fields having different institutions, professional bodies and teaching curricula, and their relationship became much more fluid.

At its inception in the UK, veterinary education existed as a 'branch' of human medicine and was grounded in the study of man. The veterinary arena was also partially populated with human surgeons, with veterinary and medical educations considerably integrated. It is also interesting to note that many medics were strong supporters of the creation of the RVC, including the prominent surgeon, John Hunter, who was its Vice President in the early days of the College. Many others were on the board of the RVC. Those human clinicians connected with the RVC were not necessarily concerned with practising the



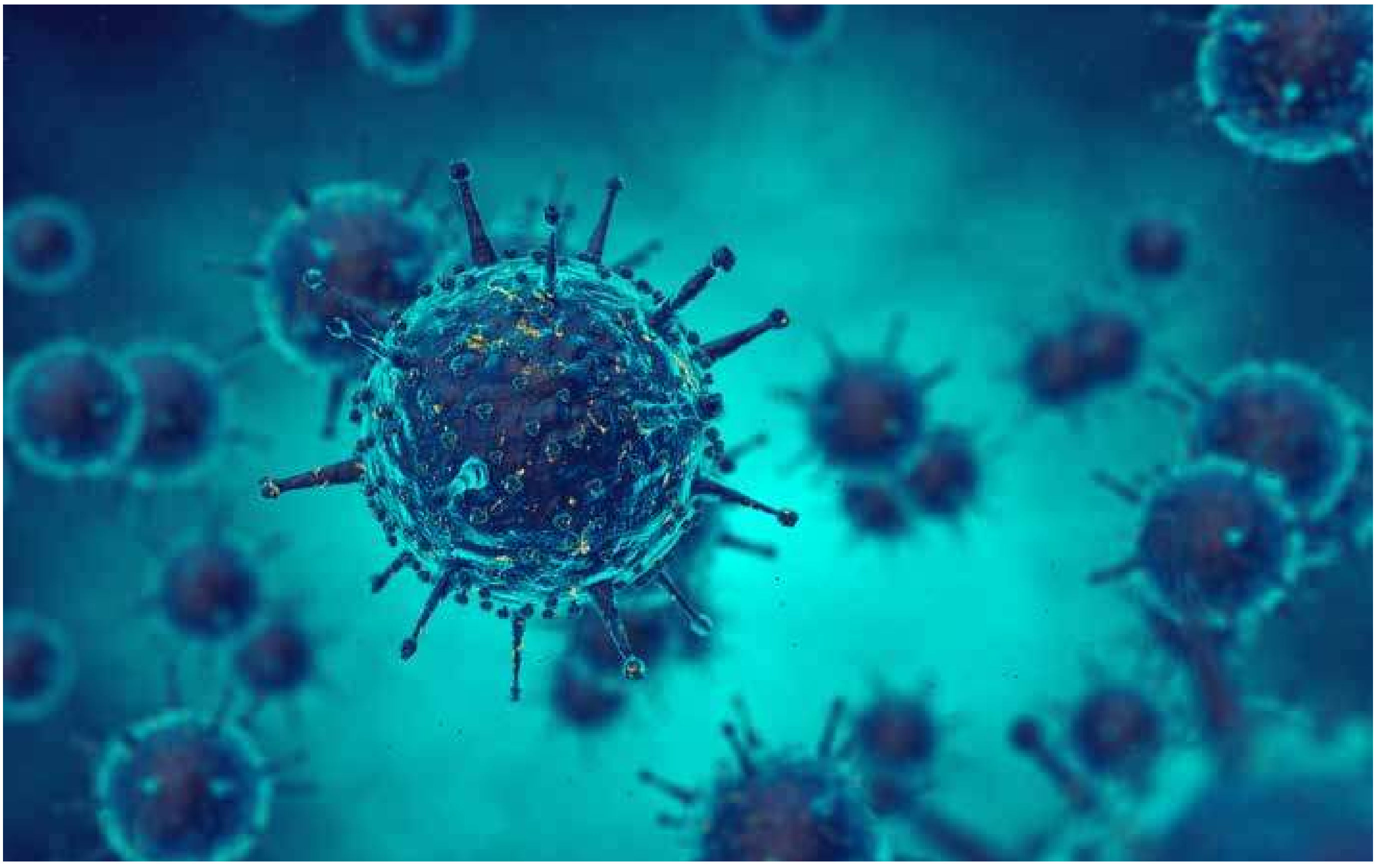
veterinary art themselves, but a key driver for them was using animals for the improvement of human surgery. The medical community at that time were driven by the principle that human and animal medicine shared the same fundamental biological laws. They sought to understand diseases, such as rabies and glanders, which were transmitted between them, to better differentiate species similarities and differences through comparative anatomy as well as to advance physiological understanding via animal experimentation. They very much advanced the One Medicine concept.

This situation largely existed until the 1830s, by which time many veterinarian reformers were voicing concerns about what actual contribution the medical community had made to veterinary medicine. These reformers, including many human surgeons amongst their number, concluded that veterinary medicine had benefited little from its association with its human counterparts – the benefits had all seemed to have gone the other way. The ambition of the reformers was to establish veterinary medicine as an independent discipline, rather than a sub-category of human medicine. In this way One Medicine became Two.

The separation of the two professions has not necessarily benefited them and was certainly not based on biological differences between their patients, as development of treatments can be remarkably similar between humans and animals. Today there are many advocates of Comparative Medicine (One Health or One Medicine), particularly from the veterinary profession.

The opportunities for translating new treatments between animals and humans are many. Finding more ways of working together to make such translation happen more effectively would be enormously beneficial to both veterinary and human patients. Just by way of some examples, below are outlined some interesting cases currently being undertaken at the RVC that have important implications for translational medicine:

- Dogs with idiopathic epilepsy have been shown to benefit from inclusion of medium-chain triglycerides (MCT) in their diets. This has been shown to improve seizure control, if used as a supplement to drug therapy. This is something that had been also been demonstrated in human patients. The canine work at the RVC has led to the launch of Purina's Pro Plan Veterinary Diet that includes MCTs for dogs with epilepsy.
- A study known as EPIC has found that administration of pimobendan to dogs with myxomatous mitral valve disease, results in prolongation of the preclinical period by about 15 months. This provides a substantial clinical benefit and interest has been expressed by cardiologists for use in human patients. Pimobendan is a drug which was initially developed for human medicine, designed to sensitise the calcium binding protein in cardiac muscle to



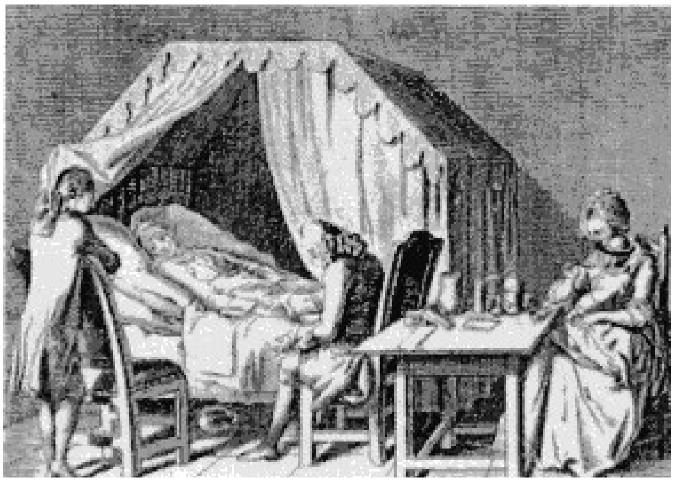
calcium. This should mean it would increase the force of contraction of heart muscle without a rise in intracellular calcium and increase in energy expenditure required for the heart muscle to relax, both of which are problems of other positive inotropic drugs. This drug was abandoned after very early clinical trials in selected human patients. The remarkable effects the drug has in dogs on cardiac remodelling in the early stages of mitral valve disease have made medical cardiologists think this drug should be re-examined more thoroughly in human medicine. The question remains as to how it is working in dogs – calcium sensitisation is not its only action.

- Treatment for recurrent laryngeal neuropathy in horses using functional electrical stimulation (FES). This has been shown to be highly effective in opening airways in horses with this condition. A collaboration is currently underway with human clinicians as a potential treatment for vocal cord paralysis.

- One in four diabetic cats has been found to be suffering from hypersomatropism-induced (HST) diabetic mellitus. It has been found that if HST is diagnosed (screening with IGF-1) and surgically treated, most of these cats have diabetic remission. If the HST remains undiagnosed, the diabetic cat tends to be very difficult to control since growth hormone is an insulin antagonist. Further work suggests not only a genetic link to acromegaly, but also one relating to environmental organohalogenated contaminants. The research further demonstrates that feline HST, phenotypically and genetically resembles that in humans. HST studies in people are currently being progressed, based on this underlying research in cats.

- Considerable work has been undertaken on biomarkers for the early detection of chronic kidney disease (CKD). One aspect of this research in cats identifies FGF-23, which is elevated in the pre-azotemic stage of CKD, as the most sensitive and earliest indicator of bone and mineral disturbances in CKD. This is a diagnostic test that is also applicable to humans.

A number of other areas of such translational research could be highlighted, including, for example, the parallels between feline cardiomyopathy and the similar condition in man. Or the use of animal models that may eventually lead to a treatment for an equivalent human disease. The list of possible opportunities for veterinarians and human clinicians to work together towards comparative medicine goals is extensive. Transfer of knowledge between veterinary and human medicine



is important for advances in both disciplines. In particular, this applies to chronic diseases of ageing (arthritis, cancer, chronic kidney disease and neurodegenerative diseases). Most laboratory animal models of these diseases are acute models and poorly mimic the chronic and slowly progressive pathology seen in diseases associated with ageing. Dogs and cats age much faster than humans, yet the pathology of these chronic diseases is very similar. Species differences and comparative genomics provide further insights. By working together, it is likely that new treatments will emerge to the benefit of people and our companion animals.

In summary, for the benefit of their patients, it is highly important to find ways that enable animal and human clinicians to work together more effectively, especially if the One Health objectives are to be met.

Acknowledgements to the following for their valuable contribution to this article: Professor Jonathan Elliott, Vice-Principal Research and Innovation, Royal Veterinary College Elizabeth Hawes, who studied Modern History at Keble College, University of Oxford and has a special interest in the history of science and medicine

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