Making comparative medicine more so

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In an intellectual context, comparative medicine is historically the name given that arena of biomedical research pertaining to the discovery and characterization of animal models for human disease.1 Such conditions may consist of spontaneous diseases, such as viral leukemia in cats or inherited coagulopathies in dogs. Alternatively, an animal model can represent an induced condition that does not naturally occur in nature. Examples of the latter include feeding pigs or rabbits a high-cholesterol diet to create atherosclerosis or modifying the genome of a mouse to create Alzheimer’s disease-like lesions in its brain. These scientific endeavors almost always compare the pathologic features in the test animal (animal model) to those in humans with the condition being studied, but they seldom address comparisons in medicine, that is, treating the illness. The only situation where the comparative efficacy of a drug or medical device between species is a primary objective is in preclinical testing. This involves use of an animal disease model for regulatory assessment of a new product in vivo before human clinical trials are permitted.

In a political context, comparative medicine is a name occasionally taken by a department that provides laboratory animal husbandry and veterinary services to its parent institution, such as a medical school, university, or pharmaceutical company. This name is usually adopted to provide a more sophisticated image for the department to investigators and administrators or to mask its daily activities from the public or from animal rights activists. This is unfortunate because tending to laboratory animals is an honorable and critical mission and should not require such embellishment or disguise.

More recently, comparative medicine has also been used in veterinary academic circles as a unifying term to highlight similarities in diseases and treatments. But these initiatives are usually limited to domesticated animal species and often confined within a professional specialty, such as comparative dermatology or comparative ophthalmology.

These and other similarly narrow uses of the term obscure substantial benefits when comparative medicine is considered in its most literal and universal sense. By comparing how a larger variety of species are treated for a given disease, we may learn more quickly about better treatments for any of those groups of patients. In this respect, there can be no difference between human and nonhuman animals as potential sources of knowledge. In fact, a medication originally developed for use by a physician is usually just as appropriate for a veterinarian to prescribe (regulatory and litigious realities of the marketplace preclude the inverse of this situation). Nor must there always exist only the conventional, unidirectional flow of knowledge from animal models to human patients. Indeed, the vast human medical literature can provide excellent models for veterinary situations. And since more pet owners are willing to pay for sophisticated veterinary care today, it behooves our profession to expand its thinking in this regard.

At the MGH, we have launched several programs with this extended concept of comparative medicine in mind. One of these initiatives is briefly described here as an example of how opportunities may emerge when all medicine is appreciated as truly comparative.

We are working with the MGH departments of molecular pathology and neurogenetics to establish a tissue and information exchange with veterinary teaching hospitals, noted canine geneticists, and the Comparative Oncology Program at the National Cancer Institute.2 The resultant organization has been recently launched as the CCOGC. The biomedical impetus is a need for additional animal models in cancer research to augment mice and rats used in or bred for laboratory testing. Larger species (compared with rodents) traditionally have not been used because spontaneous cancer takes too long to develop, and it is neither ethical nor cost-effective to induce cancer in companion animal species unless under compelling circumstances.

But thousands of spontaneous cancers are detected in dogs and cats every month. Since many of these diagnoses are confirmed histologically and followed by some level of therapeutic intervention, why not consider them for their latent value to biomedical research? With the advent of genomics and more informative tumor cell markers, it is now possible to query this medical population in ways never imagined.

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This essay was inspired by Drs. Leo K. Bustad, James G. Fox, John R. Gorham, and Franklin M. Loew, four veterinarians who have practiced comparative medicine to its fullest extent.

CCOGC Canine Comparative Oncology and Genomics Consortium

MGH Massachusetts General Hospital

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example, gene expression profiling microarrays (gene chips) may be able to identify which genes are actively turned on or suppressed during the course of chemotherapy of osteosarcoma in giant dog breeds or lymphoma in cats. It has already been demonstrated that genomic analyses of tumors have enabled more accurate prognoses for some human patients. And dogs and humans likely share genes that influence tumor aggressiveness or response to therapy because the genome sequences of dogs and people are roughly 80% identical. Thus, the other participant in the CCOGC will be the Broad Institute (Cambridge, Mass), which completed a seven-fold sequencing of the dog genome in 2004. Our initial efforts at MGH will focus on canine tumors of neural origin for genomic interrogation, whereas other CCOGC participants are interested in osteosarcoma, lymphoma, and melanoma. This consortium will also include physicians to communicate human cancer genomic discoveries to veterinarians so animal patients may benefit sooner. In the context of comparative medicine, humans can sometimes provide the best disease model for other species.

Many other ways exist to apply an expanded, literal approach to comparative medicine. Some of these already exist but should be expanded as follows:

- Veterinary schools and veterinary associations can host physician organizations to demonstrate how conditions in nonhuman patients are diagnosed and how affected animals are treated. For example, we recently participated in a continuing education symposium in comparative oncology sponsored by the Massachusetts Veterinary Medical Association and the Massachusetts Society for Medical Research. At this symposium, advances in cancer genomics were described for canine and human applications.

- Departments of laboratory animal care in large medical research centers can serve as a portal through which veterinary clinical specialists learn about recent human medicine developments from their physician counterparts. As an example, a new physiologic monitoring device can digitally record breathing patterns, posture, and cardiovascular parameters, without involving any surgically implanted sensors or connections to laboratory equipment. It is being used as an ambulatory patient monitor to better characterize sleep disorders, pulmonary disease, and autism as well as physical conditioning in jobs involving extreme exertion. We are evaluating this product in larger laboratory animal species as a noninvasive and, therefore, more humane means to monitor recovery from anesthesia or effectiveness of analgesics and for treating behavioral disorders.

- Traditional postdoctoral training programs in laboratory animal medicine that combine clinical residencies with independent research can serve as a template for other veterinary specialties within the biomedical milieu. Disciplines in which much more research is merited for laboratory animal species include anesthesia and analgesia, radiology, critical care, clinical nutrition, and behavior.

- A number of human teaching hospitals now have newer and more powerful imaging equipment that is used on human patients and research animal subjects. Such equipment is frequently not accessible to veterinary practitioners but could be useful for particularly vexing small animal cases. Such an arrangement could be even more attractive to the hospital if the affected animal’s condition resembled a human clinical situation. We recently collaborated with another human teaching hospital in which a 3.0-T magnetic resonance scanner was used for a young dog with progressive paresis and ataxia that defied diagnosis. It is hoped that this is merely the first of many imaging sessions for companion animals in partnership with local veterinary teaching hospitals and specialty practices.

The variety of possible scenarios in which comparative medicine may be expanded is limited only by one’s imagination. The central tenet remains that comparative medicine can be much more than currently practiced, to the benefit of many.

References