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One medicine, one pathology, and the one health concept

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In a recent article in the *Journal of the American Veterinary Medical Association*,¹ a “One Health” concept to integrate principles and discoveries in both veterinary and human medicine for the mutual benefit of all the species involved was outlined. This article was a summary of a report² created by a task force of veterinarians and physicians that is trying to coordinate efforts and knowledge dealing primarily with infectious diseases. The purpose of the One Health Initiative Task Force (OHITF) was to lay the groundwork for a “campaign to facilitate collaboration and cooperation among health science professions, academic institutions, governmental agencies, and industries to help with the assessment, treatment, and prevention of cross-species disease transmission and mutually prevalent, but non-transmitted, human and animal diseases, and medical conditions.”¹

Although this endeavor was aimed at coordinating efforts within the United States and especially within the veterinary community, we would like to highlight and develop the OHITF report’s brief mention of one of the most important paradigms of biomedical research—animal models of human diseases. Historically, these have been of central importance to the study of human diseases and treatments, and are based on the premise of evolutionarily conserved pathogenetic mechanisms. There are profound challenges in relating disease processes in humans and other animals, which are generally exemplified by a critical lack of the expertise in comparative pathology. Many such challenges are being faced head-on by those working with mouse models of human diseases, specifically with regard to inbred strains of laboratory mice.³ Robert Koch’s exhortation, “Gentlemen, never forget that mice are not human beings,”⁴ reminds us that although use animal models of human diseases can be extremely valuable, knowledge of comparative anatomy, pathology, and pharmacology are needed to bridge the species gap.

Formal bridging of the divide between the pathobiology of humans and a key model organism, the mouse, is attracting serious international attention at the highest level. In December 2008, the second Coordination And Sustainability of International Mouse Informatics Resources (CASIMIR) meeting was held at the Nobel Forum, Stockholm, Sweden. The meeting was focused on the topic of One Medicine, One Pathology, a concept developed more than a century ago by Rudolf Virchow and later articulated by his pupil, Sir William Osler. As stated by Virchow, “Between animal and human medicine there is no dividing line – nor should there be. The object is different but the experience obtained constitutes the basis of all medicine,”⁵ a point that has been championed more recently by others.⁶ Although the laboratory mouse has, without doubt, become the premier mammalian model for human diseases, it also serves as a tool for understanding the pathobiology of diseases in many different species.

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Two of the greatest advocates of this One Medicine, One Pathology concept in recent times were Drs. Thomas Carlyle Jones and George Migaki, veterinary pathologists who managed the Armed Forces Registry of Comparative Pathology for decades. Their legacy was the *Animal Models of Human Diseases Fascicle Series*.⁷ Many of us, both veterinarians and physicians, studied these fascicles in great detail while preparing for board-certification examinations in anatomic pathology, and these fascicles have served as the prototype for many of the books subsequently published on this topic.

As mentioned in the OHITF report, the most obvious means of pathologic convergence between species, especially domestic species and humans, are the infectious diseases. This point was most clearly made by a physician named Jenner who, before the time of Virchow and Osler, was greatly criticized for his work that, in retrospect, was probably one of the all-time greatest contributions to the relief of suffering and death in humans and other animals. Jenner used infection with cowpox virus, or what some now believe was horsepox virus, to prevent infection with smallpox virus in humans.⁸ As a result, the word that we still use today for this procedure, vaccination, was derived from the Latin word *vaccinus*, which means relating to cows.⁹ Yet another major milestone was the discovery of Smith and Kilborne regarding the spread of diseases by ticks.¹⁰ These types of discoveries and breakthroughs that are based on domestic animal research continue today. For example, a collaborative effort that involved dogs treated with a recombinant vaccine that prevented oral papillomavirus infection provided the proof of concept that resulted in development of the recombinant human cervical cancer vaccine, which undoubtedly will prove to be a major cancer prevention breakthrough.^{11,12} This medical advancement was acknowledged when Harald Zur Hausen was awarded the 2008 Nobel Prize in Medicine for being one of the pioneers in the field of cancer-causing viral infections, a field that relies heavily on animal models of human disease for its success. Such attempts to bring together basic and clinical research approaches are representative of translational research. These and other breakthroughs and plans for the future are summarized in *Critical Needs for Research in Veterinary Science*,¹³ a document that was created by a panel of veterinarians for the National Academy of Science and that addresses the fifth recommendation of the OHITF.²

We and many others have been trying to reconcile pathology nomenclature for laboratory mice with that for humans to deal with the reality of a one medicine-one pathology-one health concept.¹⁴ Development of a common framework to describe diseases (phenotypes) of humans and other animals (more specifically mice) will allow for seamless integration of the huge amount of genetic association data that are being generated from clinical genetic studies and from the analyses of mutant animals. The key to unifying the understanding of mouse and human diseases has been the realization that there are common underlying pathobiologic processes, which is the true underpinning of the one medicine-one pathology-one health concept and the basis of the model organism approach to human disease research.^{3,15,16} As we begin to understand the specific genetic and environmental effects associated with each disease, we can more accurately compare the diseases between species. This is the legacy of the monumental breakthrough in reverse genetics for which Martin Evans, Mario Capecchi, and Oliver Smithies won the Nobel Prize in Medicine in 2007. Those researchers were responsible for the development of embryonic stem cells from laboratory mice and for subsequent advances in genome manipulation that resulted in genetically engineered mice and ultimately promoted genetic engineering in other domestic mammalian species. Genetic and physiologic similarities between humans and mice,¹⁷ indeed between humans and many other mammals, means that the close phenotypic similarity between cognate sporadic diseases of humans and other mammals certainly exceeds the 60% of shared infectious diseases listed in the OHITF report.^{1,2} These similarities range from single-gene disorders that follow simple Mendelian patterns of inheritance, to the complex polygenic diseases with which veterinarians and physicians are

much more familiar in clinical practice, cause the lion's share of morbidity and mortality, but are not generally perceived of as *genetic* diseases.¹⁸

To truly generate One Health, we need to break down the historical separation of humans and other animals and embrace the development of comparative medicine; this will require a new generation of experimental pathologists and physicians who are trained to think across species. The development of such researchers is a direct challenge to our veterinary and human medical schools.

Although we may disagree with the use of the words One Medicine versus One Pathology versus One Health, or any combination of these, the basic issue is that these concepts will never gain real favor in the international biomedical research and clinical communities until we acknowledge the obvious truth, that humans are mammals¹⁹ and therefore animals. Until we stop referring to humans and animals in separatist terms, these goals will never be achieved.

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