

PERSPECTIVE

'One medicine—one pathology': are veterinary and human pathology prepared?

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The American Medical Association and the American Veterinary Medical Association have recently approved resolutions supporting 'One Medicine' or 'One Health' that bridge the two professions. The concept is far from novel. Rudolf Virchow, the Father of Modern Pathology, and Sir William Osler, the Father of Modern Medicine, were outspoken advocates of the concept. The concept in its modern iteration was re-articulated in the 1984 edition of Calvin Schwabe's 'Veterinary Medicine and Human Health.' The veterinary and medical pathology professions are steeped in a rich history of 'One Medicine,' but they have paradoxically parted ways, leaving the discipline of pathology poorly positioned to contribute to contemporary science. The time has come for not only scientists but also all pathologists to recognize the value in comparative pathology, the consequences of ignoring the opportunity and, most importantly, the necessity of preparing future generations to meet the challenge inherent in the renewed momentum for 'One Medicine.' The impending glut of new genetically engineered mice creates an urgent need for prepared investigators and pathologists.

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THE ORIGINS OF ONE MEDICINE

The German physician and statesman Rudolf Virchow (Figure 1) is universally recognized as the Founder of Modern Medicine. The son of a butcher, Virchow noted the link between diseases of humans and animals and coined the term 'zoonosis' to indicate the infectious disease links between animal and human health. The concept was not uniformly appreciated during Virchow's lifetime. His interests evolved from a period of parallel human and animal microbial pathogen discovery by many others, including Koch and Pasteur during the early to mid-1800s. Indeed, creation of the discipline of pathology has been attributed to the microbe.¹ Among Virchow's many interests was helminthology, and he described the life cycle of *Trichinella spiralis* in swine and its zoonotic consequences (trichinosis).² In addition to being a clinician and insatiable comparative pathologist, he served in the German parliament as an outspoken advocate for public health. Several historical biographies of Virchow relate a possibly apocryphal anecdote in which he opposed Bismarck's excessive military budget, which angered Bismarck sufficiently to challenge Virchow to a duel. Virchow, being entitled to select the weapons, chose two pork sausages: a

cooked sausage for himself and an uncooked one, loaded with *Trichinella*, for Bismarck.^{3–5}

William Osler (Figure 2), a Canadian physician who briefly studied in Germany with Virchow, is given credit for coining the phrase 'One Medicine' in the English language literature.⁶ Osler is widely recognized as the 'Father of Modern Medicine' and, similar to Virchow, was also a passionate comparative pathologist, and he is considered the founder of the discipline of veterinary pathology.^{7,8} Indicative of the rift that has arisen between human and veterinary medicine, various biographies of Osler tend to be parochially focused on his contributions to one profession or the other, but seldom recognize his inestimable contributions to One Medicine. Osler's first academic appointment was a lectureship in the Medical Faculty of McGill University in Montreal. He lectured to not only medical students but also veterinary students from the Montreal Veterinary College, which soon became affiliated with McGill. He demonstrated anatomy and pathology on a daily basis to the veterinary students. As an active participant in comparative pathology, he became vice president and later president of the Veterinary Medical Association. When the Veterinary School failed after several

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Figure 1 Rudolph Virchow, founder of modern cellular pathology with his dictum ‘*omnis cellula e cellula*,’ was an advocate of one medicine. The son of a butcher, Virchow discovered the cause of trichinosis. His early research laboratory was provided by the School Of Veterinary Medicine where he taught veterinary students. A vociferous public health advocate, he became a major political figure in the late 1800s. His distracters were challenged to eat raw pork sausages, and at least one of whom became seriously ill upon accepting the challenge.⁵ (Courtesy of The Blocker History of Medicine Collections, University Texas Medical Branch, Galveston).

years, he continued within a Division of Comparative Medicine. His influence was felt in subsequent faculty appointments in Philadelphia, and then Baltimore. The Johns Hopkins Medical School Dean, William Welsh, who himself was a pathologist influenced by Osler and his veterinary contacts, suggested a study of mice to Livingood, a pathology fellow, that resulted in the most accurate description of mouse mammary tumors and their metastases available at that time (1896).⁹

Other luminaries of One Medicine, among many, included Daniel Salmon, a veterinary pathologist who was a leader in the field of public health,¹⁰ and his colleague Theobald Smith, a medical pathologist, who distinguished himself with

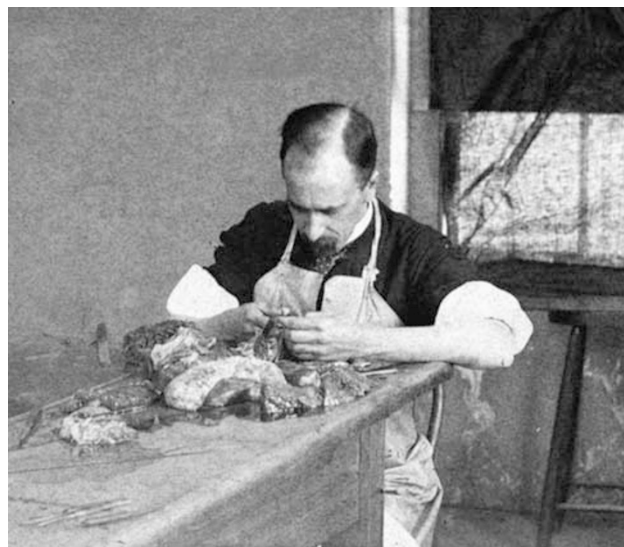


Figure 2 Sir William Osler, the founder of modern medicine and of veterinary pathology, photographed while at the autopsy table. Osler is credited with coining the term ‘One Medicine.’ Osler began his scientific training with a veterinarian, spent 3 months with Virchow, and founded the McGill School of Veterinary Medicine. Osler autopsied his own patients. Note the lack of gloves, mask and gown. (Photo credit: 044/1 Osler Library Photography Collection, Osler Library of the History of Medicine, McGill University, Montreal, QC, Canada).

seminal discoveries in veterinary and zoonotic diseases, as well as anaphylaxis (long referred to as ‘Theobald Smith’s phenomenon’).^{10,11}

One Medicine was alive and well at the beginning of the last century, but, despite its promise, it began to decline in the early 1900s. Calvin Schwabe (Figure 3), an epidemiologist at the University of California, Davis School of Veterinary Medicine, provided a historical analysis that decried the waning of Virchow’s concept and the subsequent loss of interest by the veterinary community.¹² He ascribed this loss to the replacement of horses and oxen with the combustion engine. During the early 1900s, many Colleges of Veterinary Medicine closed and the emphasis in the remaining schools turned to agriculture. Ironically, as the concept of One Medicine was waning, the inbred laboratory mouse was born in 1907, just as the automobile was replacing the horse and buggy.

Calvin Schwabe was the modern advocate of One Medicine. He held numerous national and international positions and his studies in Africa and the Middle East (Lebanon) led to appreciation of the role of animals in human health. His concepts of One Medicine were based on the close relationship between humans, domestic animals and public health. Schwabe proposed a unified human and veterinary approach to zoonoses in the 1964 edition of his monograph ‘Veterinary Medicine and Human Health’ and subsequently formalized the One Medicine concept in the third edition that appeared in 1984.^{12–14}

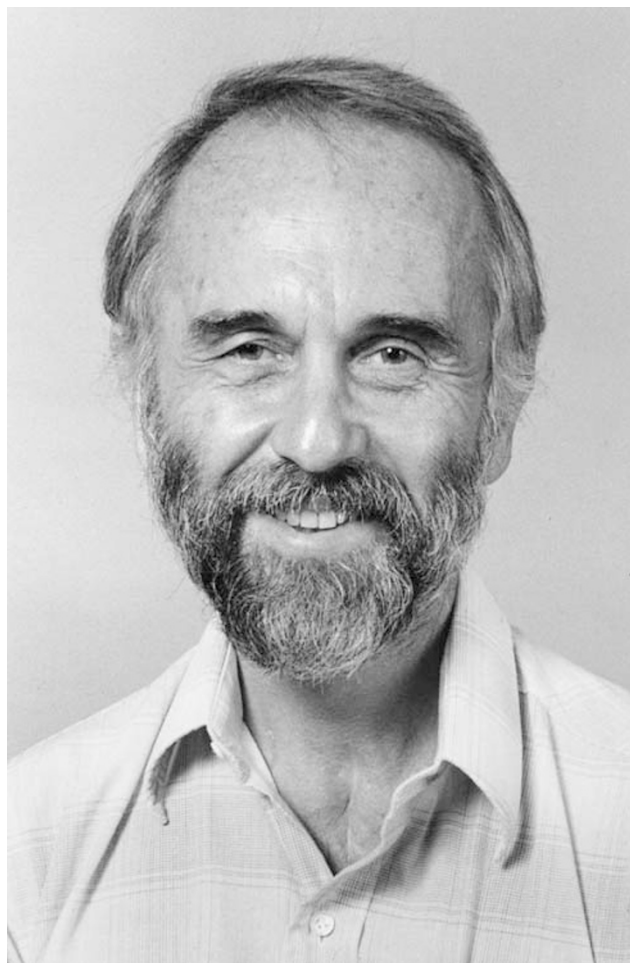


Figure 3 Calvin W Schwabe, DVM epidemiologist, is credited for the rebirth of the modern One Medicine movement. An equally colorful person, he also wrote about the close association between religions, animals and cultures and published a gourmet cookbook describing the exotic meals he enjoyed from around the world. (Courtesy of the School of Veterinary Medicine, University of California, Davis).

The growth of funding for biomedical research in the US and the emergence of the laboratory animal as an essential component of that effort led to the primacy of medical and biological scientists, many of whom did not feel the need for, or appreciate the value of, veterinary colleagues. Schwabe and others chronicle the increasingly arrogant, proprietary attitude of medical investigators who often expressed open disrespect for veterinarians.¹² Inadvertently, much of this attitude was stimulated by the veterinary profession itself. Public sentiment for laboratory animal welfare built momentum in the 1960s, with the passage of the Animal Welfare Act in 1966. This act was intended to protect pet dogs and cats from theft, sale, or use in research or experimentation, and initiated standards for the humane treatment of dogs, cats and other animals by animal dealers and research facilities. As social pressure continued, the Animal Welfare Act was amended in 1970, 1976, 1985, 1990 and 2002. The *Public*

Health Service Policy on Humane Care and Use of Laboratory Animals issued its own set of more rigorous standards and subscribed to compliance with the *Guide for the Care and Use of Laboratory Animals* published by the National Research Council of the National Academies in 1963, with subsequent revisions. Even higher voluntary standards were established by the Association for Assessment and Accreditation of Laboratory Animal Care (AAALAC) International. The veterinary profession has been, and continues to be, intimately involved in developing these policies. This involvement, albeit appropriate, placed the veterinarian in the unenviable position as ‘welfare police,’ with resentment by scientists who naively wanted no restrictions on their research.

These events took place during a time of transition within the veterinary profession that was evolving toward the end of Schwabe’s career. The emphasis of veterinary medicine changed increasingly from serving society and public health to companion animal medicine, with rising emphasis on the ‘human–animal bond.’ Rather than seizing a rich opportunity for One Medicine through biomedical research and the laboratory animal, veterinary schools tended to ignore specialization in laboratory animals, and the research that they foster, as irrelevant. Most schools did not even offer courses involving laboratory animals, unless within the context of ‘pocket pets.’ Specialized training in laboratory animal medicine and biomedical research generally took place in departments of Comparative Medicine in medical schools rather than in veterinary schools. However, laboratory animal welfare regulations increasingly diverted the efforts of veterinarians to service and support roles. The rising regulatory burden in animal-related research thus drained what little veterinary biomedical scientific manpower remained, with little left over for science. The result of these trends has been a generation lost among veterinary biomedical research scientists, consumption of veterinary talent for regulatory activity and relatively low value placed on research within the profession, except for research involving domestic animals. These trends are well documented in a 2004 National Academies report, *National Need and Priorities for Veterinarians in Biomedical Research*, in a 2005 report, *Critical Needs for Research in Veterinary Science* and other publications.^{15,16}

Comparative pathology would seem to be common ground for professional interaction, but it, too, has atrophied. Within the veterinary profession, pathology residency training has become strongly oriented toward achieving board certification in The American College of Veterinary Pathologists (ACVP). The enormous growth of information that must be assimilated by today’s pathology residents has diluted the historic emphasis on experimental pathology training. Residency training is increasingly detached from research training, and in many cases, when the two are linked, both are diluted. Most veterinary pathology residency programs are embedded within veterinary schools, with all of the prejudices and negative trends reflected on the

discipline of pathology. In the mid-1960s, for example, the majority of articles published in the ACVP official journal, *Veterinary Pathology*, involved experimental pathology of animals of agricultural importance. Today, the majority of articles in *Veterinary Pathology* are case reports, documenting esoterica of companion and exotic animals. Most veterinary pathology residents eschew laboratory animal pathology for the more glamorous or relatively comfortable appeal of companion animal and wildlife diagnostic pathology. At the same time, medical pathology training is increasingly focused on high throughput surgical pathology.

Meanwhile, medical pathology training faces its own challenges, whereby time for training in experimental pathology is difficult to come by. Medical pathology training involves diminishing exposure to autopsies, and strong emphasis on surgical pathology and the breadth of laboratory medicine.¹⁷ Pathology, literally defined as 'the study of disease,' is therefore at risk of deteriorating into pattern recognition and diagnosis in both professions. In addition, the training pipeline of experimental pathologists within both professions is inadequate to fill demand, with experimental veterinary pathologists in particular vanishingly scarce.

The legendary giants of medical and veterinary pathology are rapidly aging and fading away. These individuals flourished and evolved on the shoulders of their prestigious predecessors during the One Medicine era. The opportunities for scientific discovery and contributions came in large leaps for these individuals, with high impact on public health and comparative medical science, whereas their successors must now focus their research questions in an increasingly reductionist manner, often at the molecular level, to foster their careers. Thus, the niche for the 'big picture' pathologist, who is engaged at the whole organism level (be it human or animal), tends not to exist in biomedical research arenas. Pathologists were once at the forefront of discovery, but they now suffer from the fate of the elephant, 'everybody likes them, but nobody wants to own one.' In some institutions, however, the flame of One Medicine continues to flicker between medical and veterinary faculty.

REBIRTH OF ONE MEDICINE

As technology progressed beyond the combustion engine to the jet engine, the world has continued to shrink. Travel that previously took months now features overnight flights for the jet set. As the world has shrunk and ecosystems are increasingly perturbed by expanding human populations, we have experienced the emergence of a number of zoonotic diseases, including AIDS, Ebola, West Nile virus, avian influenza, bovine spongiform encephalopathy and SARS. This in turn has spawned an increasing need for scientists who appreciate the complex links between emerging diseases and the relationships between humans and their animals.¹⁸

The major human and veterinary medical associations have recently enthusiastically embraced and endorsed the

concept of One Medicine.¹⁹ The July 2007 American Medical Association (AMA) resolution resolved to promote collaboration between human and veterinary medicines, joint educational programs, efforts in clinical care, cross-species disease surveillance and control and new diagnostic methods, medicines and vaccines¹⁹ (<http://www.ama-assn.org/ama/pub/upload/mm/467/530.doc>). The American Veterinary Medical Association (AVMA) passed a similar resolution at their July 2007 meeting.²⁰ One can only hope that these initiatives are not lost in the proverbial subcommittee and will lead to definitive action. Other learned societies have endorsed the concept (<http://www.socropvetmed.org/>). Numerous supportive essays have appeared.^{18,21–23}

In short, the current medical and veterinary communities are re-discovering and endorsing the concepts espoused by Virchow, Osler and Schwabe. The AVMA and AMA resolutions are resurrecting One Medicine on the traditional foundations of ecosystem health, food safety and emerging infectious disease. There is a need to expand One Medicine to other areas of medicine. For example, the United Kingdom has established the Comparative Clinical Science Foundation to fund comparative studies in cancer, aging and genetic disorders (<http://www.onemedicine.org.uk/>). Perhaps, the chasm between human and veterinary medicine will be effectively bridged, but if that is to happen, it must also be within the context of modern experimental biology.

ONE MEDICINE AND CONVERGENCE WITH GENOMIC BIOLOGY

Although One Medicine foundered, molecular scientists, oblivious of Schwabe's concepts, were independently creating their own version of One Medicine. In the early 1980s, molecular biologists were developing the technologies that would provide unequivocal proof of his credo at a genomic level. Comparative sequence analyses demonstrate extensive genetic homologies among species.²⁴ The technologies led to the most convincing line of evidence: mutations of one gene in one species cause a similar disease in other species.²⁵ As the genes and diseases are the same, the medicine will be the same: the genetic version of One Medicine.

This modern genetic version of One Medicine had its origins within the era of traditional One Medicine. For example, the virus discovered to cause sarcomas in chickens by Peyton Rous and others 100 years ago harbors the gene associated with cancers in rats, mice and human. Rous's study of chicken sarcomas netted him a Nobel Prize and Varmus and Bishop's subsequent molecular studies of Rous's sarcomas also netted them a Nobel prize. The Abelson murine leukemia virus oncogene is the same as the gene in human chronic myelogenous leukemia and the basis for the Philadelphia chromosome in human leukemia. Both can be treated with the same receptor tyrosine kinase inhibitors: One Medicine.²⁶ In a like manner, promyelocytic leukemia associated with mutational RAR α can be controlled by all-*trans* retinoic acid in both species.²⁷ Extensive similarities

in the gene profiles are shared by human and mouse tumors of leukemia, liver, lung and breast,^{28–31} giving hope that One Medicine will be operational in other types of cancer.

The transgenesis and genetic manipulation technologies applied to the mouse genome led to the 2007 Nobel Prize for Capecchi, Smithies and Evans and have provided experimental proof that diseases in all species share a common genomic source. The insertion or deletion of defective genes into the mouse genome provided the ‘Koch’s Postulates’ of modern biology.^{32,33} Isolation and cloning of a gene associated with human disease, when inserted into and expressed by the mouse genome, recapitulates the disease in the mouse. Clearly, one gene can cause the same disease in another species.^{32,33} By implication, the same disease caused by the same gene can be treated by the same medicine. Because of our ability to manipulate the genome of the laboratory mouse, the mouse has become the surrogate for human disease.²⁵

Modern biological science is dominated by molecular biology. In many research areas, the discoverers of new molecules or new molecular relationships cannot obtain the next grant without testing their hypothesis in a genetically engineered mouse (GEM). Driven by funding agencies, molecular biologists have created an abundance of GEM models of human disease. Genomics has given rise to the subdisciplines of phenomics, proteomics, phosphoproteomics, physiomics, metabolomics, dramonomics, toxicogenomics, pharmacogenomics, glycomics, lipidomics, neuromics, urinomics, morphomics, transcriptomics, interactomics, epigenomics, panomics, kineomics, immunopeptidomics, nutriphenomics, among others.³⁴ A journal, ‘OMICS,’ has been created to accommodate this trend.

Scientific advisory boards and study sections are populated by molecular biologists who have sought models to prove their hypotheses. The emphasis on this form of ‘hypothesis driven’ research has led to a generation of scientists who are poorly informed of normal biology and naturally occurring disease processes in the context of the whole organism. The insights of previous generations of natural historians of disease have been lost. In one sense, we have succeeded in learning more and more about less and less. Therefore, few molecular biologists have had enough exposure to the discipline of pathology to appreciate the phenotypes and biology of the disease. As science becomes increasingly reductionist, biomedical research is at a juncture in which there is a growing emphasis on translational research, with the realization that much of the scientific progress at the bench is no longer reaching the bedside. Where are the pathologists needed to fill the void?³⁵

THE RISE OF DO-IT-YOURSELF PATHOLOGY

All investigators using mice for biomedical research should collaborate with a pathologist with appropriate mouse expertise to provide the interpretation of lesions in their mice. However, pathologists with the requisite experience

remain scarce and geographically dispersed.^{35,36} Therefore, many investigators are forced to rely on their own ‘Do-it-Yourself’ (DIY) pathology or on local, albeit inexperienced, pathologists. As a result, the scientific literature is replete with erroneous interpretation of phenotype by DIY pathologists lacking expertise in mouse pathology. The cottage industry of DIY pathology has led to embarrassing and egregious errors. These are not trivial misinterpretations. Some, as discussed below, have had expensive consequences.

Microscopic Interpretation and Diagnoses

GEM often develop lesions not seen previously in mice.³⁷ These unique lesions can be especially difficult to interpret and should be evaluated by pathologists. A number of excellent reference books are now available to guide the advanced student of pathology and the beginner.^{38–43} Unfortunately, many publications on the pathology in GEM mice do not have input of any pathologist much less pathologists experienced in mouse pathology.^{44,45} This situation leads to the publication of unsubstantiated lesions, erroneous phenotypes and poor illustration of normal or abnormal tissues and cells. Of course, it may be difficult to prove that the lesion is not what the publication contends.

Misidentification of Normal Organs

Proper diagnosis of a lesion requires experience in pathology and the species studied. Each species may have unique anatomical or histological features.⁴⁶ For example, the sexual dimorphisms in mouse salivary glands or kidneys have been misinterpreted. The mouse preputial and clitoral glands that humans and other species do not possess are another prominent example.⁴⁶ The observer should assume by their bilateral location and shape that they may be normal mouse tissues. If observers are not familiar with mouse anatomy, misinterpretation is possible. For example, misinterpretations have led to three publications, in which preputial glands were reported as ‘teratomas in the skin,’ ‘skin tumors with cysts and sebocytes’ and ‘squamous cell carcinomas.’^{47–49} The pathologist in one publication was not familiar with mouse pathology⁴⁷ and no pathologists were involved in the other two publications. Another publication has images of ‘perimammary papilloma’ with a lactiferous duct in the center, suggesting the ‘papilloma’ is actually a nipple.⁵⁰

Misinterpretation of Tumors and Related Biological Processes

Tumors and preneoplastic/precancerous lesions are the most common and perhaps most difficult lesions to interpret accurately in GEM.⁵¹ Investigators often feel pressured to produce positive and desired results, which in the case of GEM are often tumors. Many publications claim to illustrate neoplasms found in a new mutant mouse line. The illustrations have often shown hyperplasias, dysplasias, cystic lesions, lesions without invasion and apparent non-neoplastic lesions, for example, diverticulosis in the GI tract⁵⁴ or

other non-neoplastic lesions.⁵³ One recurrent debate remains the gastrointestinal hyperplasias associated with *Helicobacter* sp. infections in immunologically impaired mice.^{52,54–56} Ample evidence has been published that these gastrointestinal lesions, including crypt herniation through the smooth muscle, disappear with antibiotic treatment.^{54,57} However, some authors have persisted in naming these dysplasias of repair as ‘non-metastatic carcinomas’.⁵⁵

Enthusiastic, but premature, reports of ‘simultaneous transformation’ of mammary epithelium induced by oncogenes is another example that led investigators to assume that the ‘tumors’ were malignant.⁵⁸ However, the test-by-transportation proved the ‘tumors’ to be premalignant.⁵⁹

Other examples of mistakes resulting from ‘pathobiology’ in the absence of a qualified pathologist include published descriptions of GEM that lack details of necropsies.^{60–62} For example, runting, often attributed to ‘developmental genes,’ can be caused by malocclusion of the teeth, resulting in starvation.^{46,63} The malocclusion can be detected by simple examination of the mouth.⁶⁴

Too many publications combine sexes and have too few mice available for meaningful comparisons.⁶⁵ Many publications have no statistical evaluations of tumor incidences at all. For example, most background strains of mice (C57BL/6, 129, FVB) used in GEM studies develop age-related tumors, which are often the major cause of illness and death.⁴⁰ Yet, the so-called aging phenotypes, including lifespan measurements, seldom include awareness of the tumors or other age and environmental related disorders (such as amyloidosis) that affect specific mouse strains.^{43,46}

Misuse of diagnostic terminology and mouse nomenclature has become an issue.⁶⁶ The National Cancer Institute’s Bioinformatics Division and the Mouse Models of Human Cancers Consortium (MMHCC) have developed frequently ignored classifications and controlled vocabularies for the major murine cancers.^{54,67–71} Several MMHCC consensus reports provide diagnostic criteria for precancer and invasive cancer for specific organ systems. The criteria are most thoroughly presented in the reviews on precancer,⁵¹ prostate^{67,72} and breast.^{51,73}

ETIOLOGY OF PUBLICATIONS WITH MISINTERPRETATION OF MOUSE PATHOLOGY

The publication of normal tissue as lesions or misinterpretation of legitimate lesions is often exacerbated by the journals themselves. Reports on GEM are generally found in molecular biology journals (Figure 4). The reviewers are often gene experts and not pathologists or even biologists.^{44,45}

Frequently, no pathologist or a co-author reviews the paper, nor is any pathologist acknowledged for consultation (Figure 4). Figures in journals that are intended to depict pathology phenotypes are often so small that they cannot be interpreted (postage stamp pathology). Moreover, pathologists are frequently missing from grant applications, and reviewers

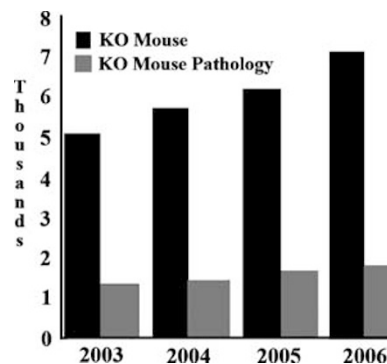


Figure 4 A graph depicting the increase of PubMed publications involving knockout mice relative to the number of publications associated with knockout mice and pathologists.

often fail to recognize the need for pathologists in such applications.

The Impending Catastrophe

The success of testing molecular hypotheses in GEM has encouraged the development of massive new mouse projects designed to test every mammalian gene.⁷⁴ With laboratory mouse colonies straining the housing capacity of research institutions, and the number of mice outnumbering the entire university workforce and student body, the growth of mouse populations nevertheless remains unabated. Following several large-scale mouse mutagenesis programs and considerable growth in GEM created by individual laboratories, the National Institutes of Health (NIH) has now started a huge ‘Knock Out Mouse Project (KOMP),’ with the goal of knocking out every functional gene in the mouse genome.⁷⁵ Similar large-scale efforts have been launched in Canada (NorCOMM: North American Conditional Mouse Mutagenesis Project), Europe (EUCOMM: European Conditional Mouse Mutagenesis Programme) and Asia. These programs, now combined in the ‘International Mouse Knockout Consortium,’ are going to create a critical, but currently unmet, need for expert comparative pathologists. The US KOMP aims at developing 8500 new mouse strains by 2010. Some experts have estimated that 200,000 new strains will be available by 2015. Another consortium, the ‘Complex Traits’ Consortium, is developing even more mouse strains. The molecular geneticists are going wild. One can only guess at the scientific catastrophe that will result without enough adequately prepared pathologists.³⁵ There are no proposals for pathology support of these massive studies.

The recent Nature editorial, ‘Mutant mice galore: A new consortium will fulfill a genomics dream—provided it gets the support it deserves’⁷⁵ highlights the need for phenotyping but neglects the discipline of pathology that is required for the phenotyping of the disease states created in these mice. The scientific community lacks sufficient manpower and

expertise in comparative pathology to effectively characterize and validate these model animals. Several recent articles call attention to the problems that arise from the pending crisis.^{35,36} Basically, we currently have a shortage of pathologists qualified to examine this glut of mice. This creates a problem, a challenge and an opportunity.

The Beginnings of Pathology for Genomic Biology

A small number of comparative pathologists have persisted and provided unique insights. They recognized that ‘spontaneous’ diseases in mutant laboratory mice frequently resembled human disease. These comparative pathologists had the skill to correlate genomic change with microscopic appearances, in other words, function with structure. As the genetic details became known, it became increasingly clear that the diseases in mice were associated with the same genes as the comparable diseases in humans.²⁵ With the advent of genetic modification producing cancer models, they recognized that tumors produced in GEM are different from the spontaneous tumors of mice. When genes associated with human cancers were inserted into the mouse, many resulting tumors are remarkable phenotypic copies of their human counterparts.³⁷ Subsequently, many genes were recognized to produce ‘signature’ tumor phenotypes^{76,77} which are reproducibly unique to the gene. These observations were the beginnings of what we refer to here as genomic pathology, that is, a new discipline of pathology concerned with comparative pathology involving specific genetic changes associated with disease including cancer in humans and animals especially mice.

Pathology in the genomic era requires knowledge in integration of structure, function, natural history, etiology and clinical context. Without this information, pathology is useless. Armed with this information, pathology provides integrative biology. Therefore, the genomic pathologists need to work with the creators of mouse models to understand the molecular biology.

The National Cancer Institute, in organizing the MMHCC grant program in 2000, recognized the need for pathology and required that each grant have a designated pathologist. The MMHCC Steering Committee assigned their Pathology Committee the tasks of reviewing the status of each organ system, of validating the models, and of recommending terminology. The Pathology Committee produced consensus reports for each organ system that included terminology and image archives.^{54,67–71,78} The committee was also able to identify and recruit a cadre of young pathologists thereby expanding the supply of genomic pathologists.

Current Educational Opportunities

Effective modern mouse pathology requires a global understanding of mouse biology, euphemistically termed ‘Muromics’ (for a more thorough discussion of Muromics, see reference Barthold³⁴). The critical shortage of human and veterinary pathologists with expertise in the mouse has been

emphasized in recent reports of the National Academies, which estimate 150 positions in veterinary pathology are currently open in industry.^{15,16}

The majority of Human and Veterinary Pathology Training programs are led by a generation of pathologists whose expertise is not focused in genomic pathology. Although they prepare the trainee for board certification, the faculties are not qualified to teach genomic pathology. Medical pathology residencies rarely provide training in murine pathology. Colleges with both human and veterinary schools rarely have joint conferences. As a result, resident trainees are not exposed to the pathology of genetically engineered mice, genomic pathology.

Several organizations, notably The Jackson Laboratory, Johns Hopkins University, the CL Davis Foundation, and the Armed Forces, periodically offer courses in mouse pathology that are very well attended by eager trainees and pathologists who want more mouse pathology expertise.⁷⁹ However, they do not offer the opportunity for the repetition and feedback that is essential for educational progression.

NIH recognizes the lack of appropriately trained comparative pathologists, but is attempting to address this shortage with only a minimal investment of resources. The NCRR awarded only two K26 grants this year, which are research grants and will hardly meet the stated need for mouse pathologists. Ironically, the majority of the current awardees are not board-certified pathologists. Moreover, NIH funding mechanisms allow for scientific training and research, but not discipline training, such as genomic pathology.^{15,80}

Financial austerity of the NIH budget does not bode well for solving the problem. Partnership and investment by industry, which waits at the doors of academic institutions to hire the few pathologists who are being trained, are critically needed. Where are the mouse pathologists of the future and who is going to train them?

Solutions: Pathology is still the Integrative Discipline

Although we can decry, as did Schwabe in 1984¹² and Barthold in 2005,⁸¹ the shortcomings of our educational systems, assigning blame does little to solve the current dilemma. The systems have not produced a generation of comparative pathologists prepared for the current demands of One Medicine and Genomic Pathology. Because of the shortage of qualified individuals, no existing faculties are capable of training and inspiring the future generations. The usual funding sources for education, such as academia, NIH or NSF, require years to organize and convince.

Can Pathology rise to the challenges inherent in the new world of One Medicine? For over a century and a half of modern Pathology, we have possessed a unique technology, the microscope.⁸² We possess a unique skill, microscopic interpretation. Expressed phenotypes in both humans and animals are immutable, and we possess the skill to perceive them. As we have documented, attempts to compensate for

the pathologist shortage, with instrumentation or DIY pathology, have led to documented disasters. Genomic Pathologists have a unique training, an irreplaceable technology and a long tradition of being the scientists who can integrate structure and function of disease. We are the one discipline who can bridge the gap because we, often alone, are the integrative biologists.

The traditional academic departmental or divisional structure will prove ineffective because the few interested, capable pathologists are geographically dispersed. With the impending glut of mice and the current shortage of pathologists, we need to take action in a prompt and effective manner without depending on institutional support. An alternate solution involves the development of a 'virtual academy' of interested genomic pathologists who will use their collective knowledge to support and spread the new Genomic Pathology. An Academy of Genomic Pathology can be responsible for the accumulation and integration of information regarding genetically engineered animals and comparative pathology. They can develop educational opportunities using the new tools of distant education. The model can include the traditional apprenticeship training of pathology over a microscope. Instead of a face-to-face meeting using a multi-headed microscope, the faculty and trainees can meet virtually using interactive programs and whole slide images.

The good news is that an Academy of Genomic Pathology has been organized with a membership largely based on the interested pathologists identified in the context of the MMHCC and Infectious Diseases. The bad news is that we have not had the opportunity to identify all of the like-minded pathologists with expertise and enthusiasm to share. We invite you, our pathology colleagues from the veterinary and medical professions, to join our efforts to address the future.

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