Validation: The New Challenge for Pathology

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ABSTRACT

Modern pathologists have been challenged to “validate” mouse models of human cancer. Validation requires matching of morphological attributes of the model to human disease. Computers can assist in the validation process. However, adequate controlled, computer-readable vocabularies that can match terms do not currently exist in mouse pathology. Further, current standard diagnostic terminologies do not include the new concepts discussed here such as pathway pathology and mammary intraepithelial neoplasia. The terminologies must be revised and improved to meet the challenge. Human medicine has traditionally used “guilt-by-association” to validate interpretations of disease. Experimental pathology uses experimental verification exemplified by “test-by-transplantation.” Genetically Engineered Mice (GEM) develop unique tumor phenotypes bringing new structural-functional insights and reevaluation of concepts. Novel GEM-related tumors appear in all organ systems but mouse models of human breast cancer are prototypes. For example, mammary tumors induced by Mouse Mammary Tumor Virus (MMTV), chemical, radiation or other carcinogenic stimuli have limited phenotypes. These “spontaneous” or induced mammary tumors have never resembled human breast cancers. GEM tumors created with genes associated with human cancer are strikingly different. GEM tumors have unique histological phenotypes. Depending on the genes, the tumors may: 1) resemble MMTV-induced tumors, 2) display “signature” phenotypes, and 3) mimic human breast cancers. The phenotypes can be placed into structural and functional clusters with shared characteristics leading to the concepts of Pathway Pathology: tumor phenotype reflects the genotype.

Keywords. Pathology; informatics; mouse models; breast cancer; genetically engineered mice; validation; vocabulary.

INTRODUCTION

Pathologists have traditionally been the final arbiter in human and veterinary medicine. Accustomed to this role, we have lived a charmed existence sheltered by our authority. With the advent of genetically engineered mice (GEM), Pathology has been asked to assume a new role in the scientific dialog. The scientific community is no longer content for the verification that a tumor or another disease exists. Rather, they are asking for the pathologist to “validate” their creation as a model of a specific human disease. The future of the GEM and the investigator research program hinges on the pathologist’s “validation.” Papers, grants, programs, and careers hinge on the pathologist’s judgment. So, the pathologists need to be very clear about what is meant by validation in this context and how to go about validating.

Here, we discuss the formal meaning and implication of validation in the context of GEM modeling of human breast cancers. We will compare and contrast the approaches to these cancers in medical1 and veterinary pathology. Furthermore, we propose the use of a formal terminology to classify these neoplastic entities. By formal terminology, we mean terminological systems as defined by Rector and colleagues—“an on-
Then:

4. A scientist studies phenomena by observing their characteristics using techniques described in standard protocols, classified by a formal terminology and documented by images.

5. The characteristics are documented by images obtained using technical protocols and described using terminology.

Given that:

6. Model Validation is the process of delineating the attributes (characteristics) of an experimental system that accurately match the attributes (characteristics) of human disease. Where,

Modeling is the process of developing an experimental system that has one or more attributes of a human disease.

Attributes are qualities or quantities that are possessed by the system. An attribute may possess one or more components, depending on the level of organization described.

Characterization is a process that lists and describes the attributes of a diseased organ.

Validation is the process of delineating the attributes of an experimental system that accurately match the attributes of human disease. Where, Accuracy of a model is determined by the number and/or types of attributes that are shared by the model and human disease. Precision of “fit” is judged by the extent those attributes are shared.

Then:

Figure 1.—An ontology based on the Rosse Foundational Model of Anatomy (Rosse and Mejino, 2003) that illustrates the relationship between the structure, the data sources, and the diagnostic terminology. The ontology provides an organ-based hierarchy that uses levels of anatomic organization to describe structure (Columns B1, B2). The left hand ontology emphasizes normal relationships (Columns A, B1). The center demonstrates the relationship between the levels of organization and diagnostic nomenclature (Column C). In this scheme, the diagnosis (Column C) is based on the data collected by the pathologist from a number of different disciplines (Column D) that specialize in collecting data from different levels of organization (Column B2). The pathologist’s interpretation of the structural changes ideally, and traditionally, integrates all of the clinical, functional and structural information (Column D). The column on the far right indicates the level of information that is used to decide on different clinical features of tumors in human medicine (Column E). The connecting lines indicate the relations and flow of information (Data) that is used for the “diagnosis.” In this scheme, the “diagnosis” is primarily descriptive and adheres to standard nomenclature. However, as pathologists integrate more sophisticated data sources, the data should be recorded as “diagnostic modifiers.” If pathologists and scientists will adhere to this, or a similar, ontology, computer and informatics to enable the scientific community to organize their data sets and recognize the relationships (“map”) across species. The pathologists will need to recognize and understand their central role in the organizational scheme as the ultimate integrative biologists. This is our challenge and our responsibility.
the Foundational Anatomy by Cornelius Rosse (Rosse and Mejino, 2003), is in a hierarchical form that acknowledges levels of organization. The levels of organization can be related to clinical disciplines. The data from each discipline is organized into the diagnosis. Each level of organization then becomes a node within the server architecture, as either a single server in a server farm or as a portion of a server in a farm.

When considering the Rosse ontology, it is clear that the pathologist’s diagnostic vocabulary is primarily restricted to the level of tissue and cell. Most organized schemata for diagnostic terminology require disease process and organ or tissue for a “diagnosis.” For example, carcinoma, breast. Diagnostic terminology used by most pathologists also includes the putative cell of origin or the types of differentiation in the tumor. For example, mucinous adenocarcinoma, breast.

Such vocabularies are based on Aristotelian hierarchical structures and have served Pathology quite well. However, the new demands on Pathology came from the NCI Director’s Challenge asking for a molecular-based diagnostic terminology. While the intent is salutary, purely molecular taxonomies can be as misleading as purely morphological classifications. The two approaches need to be merged into a single system; one which describes entities using both molecular and morphologic parameters. Further, if this system is based on formal knowledge representation formalisms such as description logic, the resulting ontology can support limited automated reasoning.

In order to begin the process, the MMHCC pathologists have explored various classification schemes. The schemes have corrected some of the difficulties at the upper levels of the hierarchies but have failed to develop consistent systems for the molecular levels. Further, the pathology community responsible for creating the diagnostic vocabularies has become increasingly frustrated because the existing veterinary and human classification schemes are not sufficiently detailed, or “granular” in computer terms, to describe the phenomena that are being observed. As a further complication, the diagnostic and anatomic terms in veterinary pathology for some organ systems do not correspond to those in the human terminologies. The terminology developed by toxicological pathology is serviceable but is not yet completely defined electronically. Most authors have simply ignored the situation and applied the human terminology to the mouse. This may assist grantsmanship but it also promises to hopelessly confuse the field with many examples of inappropriate use of terms.

**TERMINOLOGIES**

The central dilemma is one of understanding what is meant when the pathologist uses a specific term. Preserving what the pathologist meant at the time he/she applied the diagnosis is of great importance if others are to use the information at a later time. It is not uncommon to encounter situations among surgical (medical) and veterinary pathologists where the same word is used to mean different things (polysemy), or where different words are used to mean the same thing (synonymy), leaving each other confused. For example, is a keratoacanthoma a mammary tumor (veterinary pathology) or a skin tumor (human dermatopathology)? If humans are unable to understand each other, one can imagine how difficult it is for the computer to interpret the words used by humans. This tendency for individuals to use different terms to describe the same concept is well established and not unique to biomedicine and is often referred to as “the vocabulary problem” (Chen, 1994). The solution to the problem is to insist on a controlled terminology.

Consistent with Rector and colleagues, we prefer to think of terminologies as ontologies with linguistic labels (Rector and Nowlan, 1994). The discipline of ontology has its roots in philosophy and is described by Guarino as the study of the organization and the nature of the world (Guarino, 1995). An ontology is a recorded conceptualization of such a world. Today ontologies exist primarily as hierarchies of concepts in domains of knowledge such as medicine (Figure 1). Terminologies are a combination of ontology and vocabulary such that ontological concepts have linguistic labels. For example, the concept known as “a malignant neoplastic process originating from mammary epithelium” is labeled “carcinoma of the breast.”

Terminologies today often include multiple terms for each concept, with one term being a preferred term. In addition, since terms are attributes of concepts, more than one term can be stored for each concept. As a result, these systems have no difficulty supporting two concepts with the same name (synonymy) as well as the same name for two different concepts (polysemy). This makes them candidates for resolving the vocabulary problem previously described. A controlled terminology is a special situation in which the terms used by a user to record the occurrence or presence of a particular concept must be drawn from a particular terminology. In this regard, it is somewhat of a misnomer in that what is being controlled is not the terminology but rather the available terms the end-user can utilize, for example, when recording diagnoses on a case.

Terminological systems have been the focus of considerable research in the medical informatics community for over two decades. Most recently, description logic has emerged as a strategy for creating terminologies that not only deal with the synonymy issue but also have logic based formalisms for the ontology. This benefits the effort by improving consistency in the creation and use of the terminology as well as providing limited automated reasoning capabilities (Baader et al., 2003). Systems that today use description logic frameworks include the Systematized Nomenclature of Human and Veterinary Medicine—Clinical Terms (SNOMED CT) (Spackman et al., 1997) and the European Union’s GALEN effort (Rector and Nowlan, 1994).

The use of logic constructs for attributes is a fundamental core of description logic and enables a system to infer knowledge if it does not explicitly contain. For example, if Female-has-uterus is a definitive statement in the terminology as is uterine-cancer-occurs-in-uterus, the system can infer that uterine-cancer-occurs-in-females. This statement is represented in formal logic notation as seen in Figure 2. This inferencing can be used to aid in the classification of new entities as well as aggregation of entities under larger (parent) classes based on the sharing of attributes. These formats for controlled vocabularies are used every day by pathologist but the rules are seldom recognized as a formal vocabulary until the pathologists are required to develop such systems for computers. Our general lack of understanding often leads to confusing and contradictory
FIGURE 2.—This figure illustrates the type of formal logical notation that goes on “behind the scenes” to assure that the pathologist’s statements can be understood and interpreted by the computer with the correct inferences. The formal logic notation for “Woman with uterine malignant neoplasm” derived from Woman is a Female. Female-has-uterus is a definitional statement in the terminology as is uterine-cancer-occurs-in-uterus, the system can infer that uterine-cancer-occurs-in-females using the AL description logic.

\[
\begin{align*}
\text{Woman} & \equiv \text{Person} \cap \text{Female} \\
\text{Woman with Uterus} & \equiv \text{Woman} \cap \exists \text{hasOrgan.Uterus} \\
\text{UterineNeoplasm} & \equiv \text{Uterus} \cap \exists \text{hasLesion.MalignantNeoplasm} \\
\text{Woman with UterineNeoplasm} & \equiv \text{Woman} \cap \text{UterineNeoplasm} \\
\text{Alternatively,} \\
\text{Woman with UterineNeoplasm} & \equiv ((\text{Person} \cap \text{Female}) \cap \exists \text{hasOrgan.Uterus}) \cap (\text{Uterus} \cap \exists \text{hasLesion.MalignantNeoplasm})
\end{align*}
\]

\(\cap\) = Intersection

\(\exists\) = Existential quantification

statements in our pathology literature. The situation has been further confused as nonpathologists publish descriptions of pathologic phenomena. Strict adherence to the rules is, however, essential for machines.

APPLICATION

The validation exercise requires consideration of vocabulary, as discussed in the preceding section. As important is the consideration of the differences in how data is collected and analyzed in experimental pathology as compared to human medical pathology. There are significant differences in the types of data that are accepted as “proof” in experimental and clinical pathology. The differences are illustrated by the intraepithelial (in situ) or premalignant lesions of the mammary glands (Figure 3). In clinical medicine, proof by association is sufficient. However, in experimental

FIGURE 3.—Validation is one of the major challenges of modern comparative pathology. This panel exemplifies the dilemma with comparisons from several premalignant mammary intraepithelial neoplasms (MIN) of human (A to C) and mouse (D to F) that are associated with progression to invasive carcinoma. Human associations are based on clinical studies. The mouse associations are based on experimental transplantation criteria. The MIN in both species are associated with heterogeneous morphological patterns. The human lesions (A to C) are associated with more dense connective tissue. All of the lesions meet the criteria of MIN in their respective species. Figure A illustrates a cribriform pattern, Figure B a comedo-type pattern, and Figure C is “cancerization” of a lobule. The lower set of images are from polyoma virus middle T mice with mammary intraepithelial neoplastic outgrowths showing cribriform (D), cystic (E), and glandular (F) patterns.
medicine, biological proof by transplantation is considered more rigorous.

Further, if the biologist is to integrate structure and function, the tenants of description logic must be used. The “controlled” vocabulary should assist the pathologist in describing new phenomenon to distinguish between closely related but distinct phenomena. The use of differentia and genera with description logic is illustrated by the ability to distinguish between the wnt and erbB signal transduction pathways in pathway pathology (Figure 4).

**PREMALIGANCY VS. CARCINOMA IN SITU**

The type of evidence accepted as support of a concept in human medicine is frequently different in experimental pathology. These evidentiary differences lead to different terminologies based on different assumptions and illustrate some of the difficulties in indiscriminant application the vocabulary from one species to another. The concepts and proofs of premalignancy in the human and mouse mammary gland show the differences between demography-based as compared to experimental-based concepts.

As the name (term) implies, ductal carcinoma in situ of the human breast (DCIS) is considered “malignant,” with the capacity for invasion and metastasis. Accordingly, carcinoma in situ is sometimes referred to as carcinoma of the “early stage,” with the stage denoted as “Tis” (Tumor-in-situ) in the TNM staging systems (Greene, 2002). The evidence that these morphologically defined patterns are malignant is based on extensive demographic and epidemiological evidence gathered by the analysis of immense populations over long periods.
and correlating the clinical outcome with the morphology of the breast lesion (Page et al., 1982; Page, 1991; Lenington et al., 1994; Page and Lagios, 1994). The atypical lesions identified in the human breast are heterogeneous (Figure 3 A–D). However, all HuDCIS patterns are defined on the basis of an increased risk for subsequent invasive carcinoma adjacent to the site of the biopsy.

Since the biopsy sample was surgically removed from the patient, the sample did not cause the subsequent breast cancer. Several alternate hypotheses have been invoked; The first hypothesis assumes that HuDCIS is a neoplasm in which populations of malignant (premalignant) epithelial cells expand in continuity within the duct system. The biopsy of such a lesion may sample a portion of these clonally related (identical) HuDCIS cells, without removing the entire population. The possibility of adjacent contiguous disease is used to provide a basis for therapeutic decisions. Complete excision of HuDCIS, excising involved ducts and branches to a point not involved by the cells of HuDCIS, is considered complete and adequate therapy. The degree of certainty that all of the premalignant cells have been removed defines the need for additional therapy (wider excision or radiation therapy).

Alternatively, HuDCIS is a multifocal disease within a given breast. The most compelling evidence for multifocal disease comes from subgross studies of entire mammary glands that demonstrate widely dispersed, focal lesions in at-risk human breasts (Wellings et al., 1975). HuDCIS can sometimes be documented as discontinuous, multifocal disease. A single focus found by biopsy may then be an indicator of increased risk of additional HuDCIS an related (or unrelated) invasive carcinoma elsewhere in breast (Warnberg et al., 2001). The evidence for this hypothesis is indirect, essentially guilt-by-association, involving static observations at few points in time, rather than direct observation of evolution over time.

The more recent investigation of molecular genotypic markers has supported the hypothesis of clonal evolution from HuDCIS to invasive mammary carcinoma. Markers such as microsatellite instability (MSI) and losses of heterozygosity (LOH) may accumulate progressively in clonal and derivative subclonal cell populations (Díaz-Cano et al., 2001). Thus, the presence of a set of these markers in both a HuDCIS lesion and an associated invasive mammary carcinoma is evidence of clonal progression from HuDCIS to the invasive mammary carcinoma. This evidence has, so far, supported the clonal hypothesis (Fujii et al., 1996; Buckhaults et al., 2003; Ma et al., 2003). Nevertheless, it remains circumstantial. If these markers were simply identification badges, like our fingerprints, the evidence might be conclusive. Instead, different patients with similar morphological lesions share these markers. Again, this is not much more than guilt-by-association.

In contrast to the vagaries of guilt-by-association, the mouse, with the potential of direct experimental observation, has been a model of the biology of premalignant lesions in the mammary gland. The original observations of premalignant mammary lesions in mice also involved correlation of focal lesions that stood out from the background, hyperplastic alveolar nodules (HAN), with the probability that the mouse would develop mammary cancer. The credit for first recognizing the biological potential is generally given to Halaand in 1911 (Nandi and McGrath, 1973). The HAN were subsequently associated with the Mouse Mammary Tumor Virus (MMTV), adding additional dimensions (Cardiff, 1984). Mice infected with MMTV that had HAN were at risk of developing mammary cancer (Nandi and McGrath, 1973).

The correlation between the presence of HAN and risk of mammary cancer was formally proven experimentally by the gland-cleared fat pad transplantation system developed by DeOme and his colleagues (Cardiff et al., 2002; Daniel et al., 1968; Faulkin and DeOme, 1960). These experiments led to formal proof that HANs are premalignant and an operational definition of premalignancy in the mammary gland. By the operational definition, premalignant mammary lesions are 1) atypical foci that 2) can be serially transplanted in the gland cleared fat pad but 3) will not grow when transplanted in ectopic sites and 4) have a high risk of undergoing malignant transformation (Cardiff et al., 2001). Several morphological examples are illustrated in Figure 3. In contrast, a malignant mammary tumor is a neoplasm that does grow when transplanted into ectopic sites (Cardiff et al., 2000).

In formal terminologies, a premalignant mammary lesion is a neoplasm characterized by focal atypia of the mammary epithelium that can be serially transplanted in gland cleared fat pads but not in subcutaneous tissue and is a tissue with a high risk of malignant transformation (Cardiff et al., 2000). The premalignant lesions in the GEM models are frequently morphologically different than the classical MMTV-induced HAN and have been designated with a broader term, Mammary Intraepithelial Neoplasia (MIN) (Cardiff et al., 2000).

Many investigators using GEM of human breast cancer have been content to use the morphological definition of human DCIS in their publication (Cardiff et al., 2001). That is, any focal area of mammary atypia. This less-than-rigorous use of terminology has been applied indiscriminately to many model systems (Cardiff et al., 2001). Even more confusing, some investigators have used the term “adenoma” as a synonym for premalignant lesions of the mouse mammary gland. Since the biology of the lesions is not known, the use of these terms is frequently misleading when applied to mouse MIN. Thus, the Annapolis Pathology Panel recommended test-by-transplantation (Cardiff et al., 2000). Fortunately, several groups have begun to test the postulated biology using classical test-by-transplantation for MIN (Maglione et al., 2001; Aldaz et al., 2002).

In summary, in-situ, non-invasive mammary lesions demonstrate the differences in admissible evidence and interpretation of a key concept in human and murine breast cancers. Thus, “validation” of mouse models of HuDCIS requires the operational biological proof by “test-by-transplantation” (Cardiff et al., 2000, 2001). Since similar techniques are not available for human disease, certification of the model will have to be based on a detailed structural and functional comparison of the characteristics of disease in both species. In this case, the experimental insights of the mouse models may lead to new definitions of the human disease.

PATHWAY PATHOLOGY

The need for validation rather than simple verification requires that the pathologist observes and records more of the details of the disease process. The detail (“granularity”) required for this analysis is not encoded in our current lexicons.
If the pathologist’s task is to simply record a general diagnosis, such as adenocarcinoma, verification is complete. However, if the pathologist’s role, as suggested, is to provide more detailed interpretations, a new terminology will have to be developed. The challenge of recognizing and encoding new phenomena can be illustrated by the newly emergent pathway pathology that recognizes the similarities and differences between genes and between different signal transduction pathways (Cardiff et al., 2000, 2001; Rosner et al., 2002).

Specifically developing tumors in GEM are microscopically different from those arising spontaneously in mice (Cardiff et al., 2000). Many tumors are so morphologically distinct that they are signature phenotypes of the genotype (Cardiff et al., 1991, 2000). This principle extends into entire signal transduction pathways (Rosner et al., 2002). The experienced pathologist can identify the genes involved in tumorigenesis by examining the microscopic slide. How are these new differences going to be incorporated into our diagnostic terminology? The challenge is illustrated by comparing the wnt and the erbB signal transduction pathways (Figure 2).

The ERBB2 signal transduction pathway stimulates growth and differentiation. The Breast Epidermal Growth Factor Receptor-2 (HER-2) (synonym: ERBB2) is amplified and overexpressed in 14% to 30% of human breast cancers (Slamon et al., 1989; van de Vijver et al., 1988) and in up to 100% of ductal carcinoma in situ (DCIS) of the comedo-type (van de Vijver et al., 1988). Other molecules in the pathway such as src (Webster et al., 1995), grb 2 (Dankort et al., 2001), Pten, Akt1, Ilk1, and vHras have been associated with tumorigenesis. The highly potent polyoma virus middle T (PyV-mT) is a surrogate for the ERBB2 receptor molecule and, like erbB2, induces metastatic diseases (Guy et al., 1992; Muthuswamy and Muller, 1994; Rauh et al., 1999; Webster et al., 1998).

ERBB2 pathway tumors tend to produce solid nodular tumor masses with solid sheets of uniformly uniform cells. The cells have uniform nuclei and relatively abundant pink cytoplasm. The ERBB2 pathway members induce tumors with close resemblance to some human breast cancers especially the comedo-type lesions (Cardiff, et al., 2000). The larger tumors tend to organize into zones that appear to have functional significance (DiGiovanna et al., 1998).

In contrast, the Wnt signal transduction pathway governs differentiation and cell fate decisions in early development. It includes numerous molecules associated with carcinogenesis such as Fibroblast Growth Factor-2 (FGF-2), adenomatous polyposis coli (APC) (Mosser et al., 1993), β-catenin (CTNNB1) (Michaelson and Leder, 2001), glycogen synthase kinase-3B (GSK 3B), casein kinase II (CK2) (Landesman-Bollag et al., 2001) and cyclin D1 (CCND1) (Wang et al., 1994). The Wnt pathway is best known in human oncology for its association with colon cancer (Kinzler and Vogelstein, 1996). However, the Wnt pathway may also have a role in rare subsets of human breast cancer (Karayiannakis et al., 2001; Katoh, 2001; Lejeune et al., 1995; Sawyer et al., 2002).

In the mouse mammary gland, the WNT pathway is the major target for MMTV and, in most strains, activated in almost all “spontaneous” MMTV-induced mammary tumors (Nusse et al., 1990). It is interesting to note that most MMTV-induced mammary tumors have little or no morphological resemblance to human breast cancer. It is also satisfying to know that the tumors in transgenic mice induced by members of the wnt pathway resemble the MMTV-induced tumors and not human tumors. Again, genotype is predicted by the phenotype.

The tumors from the Wnt pathway are heterogeneous. They are, however, associated with a strange, difficult to identify branching ductal dysmorphogenesis (Rosner et al., 2002). These abnormal radiating ducts may have papillary proliferations and terminate in clusters of cells that are composed of microacini, basolaid nests, solid cords, or squamous metaplasia. The tumors may have combinations of all 4 patterns or may be composed of one pattern (Rosner et al., 2002). Some transgenic or mutant lines associated with the APC/beta-catenin axis produce tumors that resemble cutaneous tri-choeitheliomas and actually produce hair proteins (Miyoshi et al., 2002; Rosner et al., 2002). In the mammary gland, a skin appendix, the Wnt/beta-catenin pathway promotes both epidermal transdifferentiation and pilar tumors (Miyoshi et al., 2002). Phenotype predicts genotype.

Other transgenes such as MYC also have signature tumor phenotypes (Cardiff et al., 1991, 2000). Clearly, we are learning how the genotype effects phenotype. However, these new variations in tumor types are not encoded in our existing veterinary or medical lexicons. If, as pathologists, we had simply verified the presence of malignant neoplasms and adhered to the accepted standard terminology, the opportunity to correlate structure with function would have been lost. However, the process of validation that requires recognition and documentation of the characteristics led to the recognition of these very important correlations between genotype and phenotype.

These new phenomena illustrate the new challenges of validation for the pathologist. How do we tell the computer that these tumors do or do not resemble human cancer? How do we record the structural effect of the genetic manipulations? The Annapolis Panel laid the foundation for a new expandable terminology by which the well accepted diagnostic terms, such as adenocarcinoma, can be modified by structural descriptors, such as papillary or solid (Cardiff et al., 2000). The proposed ontology also allows for the introduction of modifying terms that are association with specific and known molecular lesions, such as myc-induced or erbB2-type. Although these recommended modifications have not been rigorously tested in other organ systems, they represent one means of remaining within the proposed ontology without drastically changing current concepts.

**DISCUSSION**

There is one biology. The diseases of all animals merge, in the principles, but diverge in the particulars of each species. The laboratory mouse, originally established by C.C. Little to study the genetics of cancer, has emerged as the primary animal model of human disease. With the completion of the sequences of the human and the mouse genomes and the emergence of genetic engineering of the mouse, the mouse’s role as the primary model for human cancers has been enhanced.

The mouse modelers have impressive tools for the exploration of genetic functions. However, they rarely have the
training, or the experience, to evaluate the structural consequences of their genetic manipulations. They have, therefore, called upon the pathology community to validate their model systems.

The call for validation has created new and interesting challenges for the pathologist. While the role of the pathologist as the interpreter of abnormalities of structure and function is newly appreciated, we are faced with daunting challenges that go far beyond simple verification of disease entities. In the information age, we are called upon to provide vocabulary for images, detailed descriptions of the characteristics of disease entities and certification that the characteristics are similar to, or the same as, those found in the human. When the characteristics are different, we are expected to not only recognize and document the differences but to explain their basis.

In order to meet the challenge, the modern pathologist must be conversant with anatomy, histology, physiology, pathology, demography, and, now, the language of computer science. This is not new to our discipline. Pathology, when correctly practiced, is integrative biology. We are the content experts who have been called upon to integrate human and mouse disease.

Two examples from a specific disease process, neoplastic progression in the mammary gland have been presented for illustration and discussion. Premalignancy, or in situ carcinomas, illustrates the need for precise definition and pathway pathology illustrates the need for a more detailed description logic.

The emerging understanding of the ways that the genotype affects the phenotype is based on our increasing ability to understand the consequence of gene function on tumor phenotype. Pathway pathology demonstrates how careful attention to the detailed characteristics of mammary tumors in GEM has led to a new appreciation of how genetic changes can be detected and understood at a structural level. Pathology integrates structure and function. Pathologist must now also pay attention to the details of their vocabulary.

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