

Peer Review in Toxicologic Pathology: Some Recommendations

THE SOCIETY OF TOXICOLOGIC PATHOLOGISTS

P.O. Box 368, Lawrence, Kansas 66044

PREFACE

The paper, "Peer Review in Toxicologic Pathology: Some Recommendations" was prepared at the direction of the Council of the Society of Toxicologic Pathologists. The Council wished to support the concept of the "Peer Review Process" and, at the same time, document the benefits, potential problems, and methods of problem resolution that are associated with it. The paper represents the efforts and reflects the experiences of a committee of toxicologic pathologists who, under the leadership of Dr. Curt Barthel, assembled and refined many early drafts before one was agreed upon; this draft was then released for further review and critique outside the Committee. The paper outlines a process that is both constructive and workable. It describes a procedure that assures everyone who must make a decision based upon the final report for a toxicology study that the changes described in the pathology report are accurate and fully document the lesions that were present.

The Council wishes to express its appreciation to each individual who contributed his/her time, ideas, and experiences to the preparation of this paper.

Hugh E. Black, D.V.M., Ph.D.
Past-President,
Society of Toxicologic Pathologists

INTRODUCTION

Since the inception of the Good Laboratory Practice regulations, numeric toxicologic data produced in the course of consumer product, chemical, and pharmaceutical safety assessment have come under increased scrutiny. This scrutiny has generally taken the form of formal audits performed by individuals unconnected with the conduct of the study(ies) in question. Thus, the Quality Assurance Unit was born. As a result, many administrators have come to realize the need for documented accuracy in various aspects of research. Because of the non-numeric nature of pathologic diagnoses, these data do not readily lend themselves to the same type of audit as numeric data. Also, concern over the possibility of bias (intentional or otherwise) in the practice of pathology has been occasionally voiced. Hence, to assure the accuracy of pathology data, many laboratories have instituted a process called "pathology peer review," in which the findings of the original pathologist are reviewed by a second pathologist. The following recommendations are an effort by the Society of Toxicologic Pathologists to offer a constructive approach to the conduct of these reviews. It is not the intent of these recommendations to dictate how, or if, institutions should conduct peer

reviews, but rather to suggest some principles of conduct should the peer review be performed.

A "pathology peer review" should not be confused with "audit" since the confirmation of raw data (i.e., the tracking of microscopic diagnoses with gross findings, numbers of animals dead vs numbers examined, etc.) is within the purview of a quality assurance group. Nor should the peer review process be viewed as a modality for evaluating the competence of a pathologist. More specifically, these suggestions are given to guide administrators and organizations requesting such reviews, as well as the peer review pathologist. The ultimate goal of the process should be to assure the development of accurate pathology data which clearly and cogently support the scientific conclusions.

PURPOSE AND IMPLEMENTATION OF A PATHOLOGY PEER REVIEW

In larger laboratories, where a number of pathologists are available, experienced pathologists may be available internally for the peer review process, whereas in smaller laboratories, or because of time constraints, it may be necessary to engage an experienced outside pathologist for this purpose. Regardless, it is especially important that the review

be handled in such a manner that the most correct scientific data and interpretations are established, and that the process be constructive for all of the pathologists involved.

The methods employed may vary depending on the purpose of the peer review:

Routine Peer Review. For a routine peer review, tissues from a sufficient number of treated animals need to be evaluated to assure that significant lesions were not missed, and that a "no effect level" can be verified. All target tissues (tissues suspected of having a treatment-related change) and, in carcinogenicity studies, most proliferative lesions would be included in the review.

Peer Review for Confirmation of Unexpected Findings. For confirmation of unanticipated toxicity findings, a review of at least all target tissues in controls and treated animals down to and including the "no-effect" dose level would be appropriate. In some circumstances, it may be better to conduct this review in a "blinded" fashion.

Peer Review to Confirm Subtle Quantitative or Qualitative Differences. The review in this instance should probably be coordinated by a second person and be conducted on a "modified blinded" basis. Since it is beyond the scope of this paper to discuss the "blinded" slide evaluation in detail, only a few brief comments will be made here. To make the process productive, the reviewing pathologist should have access to slides of all target tissues from all groups, including controls, and a "dictionary" or listing of all diagnostic terms plus the grading scale utilized in the original evaluation. Microscopic slides should be coded so that the reviewing pathologist is unaware of dose groups. Pertinent in-life and post-mortem data on each animal should be similarly coded. Upon completion of the microscopic evaluation by the reviewing pathologist, a copy of the coded findings should be forwarded to the coordinator of the blinded review so that the results can be collated by that individual. Subsequently, the coordinator should submit to the reviewing pathologist a copy of the results of his/her diagnoses and any relevant comments or additional data that might facilitate further interpretation. If the reviewing pathologist should want to change a slide description, diagnosis, or interpretation after receipt of the decoded data, he/she should explain/justify this action.

POTENTIAL PROBLEMS AND SUGGESTED SOLUTIONS

Unrealistic Expectations of the Peer Review Process

A potential problem for the reviewing pathologist may occur if the initiator is not satisfied with the

extent, conduct or results, possibly due to a lack of direction in the review process. To avoid this problem the objective of the review must be clearly identified, and an approach "plan" developed before the review is begun. The plan should be sufficiently detailed to clearly define the limitations and potential benefits of the particular review. The plan should also include a detailed listing of any materials needed by the reviewing pathologist to meet the objectives of the review.

Bias of the Reviewing Pathologist

Peer review is often requested because of unanticipated findings for which the initiator seeks confirmation. The microscopic findings in question may be very subtle; they may reflect variations in incidence of lesions; they may be related to the differentiation of neoplasia from non-neoplastic changes, or the differentiation of benign from malignant neoplasia. When these situations arise, the reviewer probably should be given the original report or very specific information about the issue in question (i.e., the target tissue(s), specific diagnoses, etc.). Although supplying this information may be necessary, it may immediately bias the reviewer. This possibility should be considered and addressed jointly by both the reviewing pathologist and the initiator of the review prior to beginning the process. Again, the detailed objective and plan of the review should be clearly understood by both parties before the review has begun.

Differences: Real or Apparent

Differences in diagnoses, terminology, incidence, etc. may be generated by the peer review process as it is unlikely that the results of a reviewing pathologist will duplicate exactly the results of the initial pathologist. Synonymous terms exist for many lesions, and individual pathologists may have preferences for different terms or grading scales based upon their training and experience.

In some cases, such as a "blinded" evaluation, the reviewer may have no choice but to describe all variations in a given tissue in great detail, since he/she may not know the critical questions being addressed by the review. Consequently, some of the findings described by the reviewing pathologist may be toxicologically insignificant background changes or variations of normal. One possible solution to this problem of describing background changes might be to institute an initial "unblinded" review of all or a portion of the tissues from control groups in order to establish the proper background information before the actual blinded review is initiated.

Most importantly, any or all of the above mentioned factors may result in 2 quite different sets of

histomorphologic data. To a non-pathologist, the additional diagnoses or variations from the original data may be interpreted as discrepancies between the 2 pathologists' conclusions when, in fact, there may be none. As a result, there could be unwarranted confusion and misunderstanding by the non-pathologist who initiated the process concerning the toxicologic significance of the diagnoses. Therefore, it is important that the original plan for the review process include a joint review by the initial and reviewing pathologist of the 2 sets of results to explain or resolve apparent differences, should they occur.

THE PEER REVIEW REPORT AND EVALUATION

This section applies to external peer reviews and how the review will be summarized and documented; *not* to in-house peer reviews which may be documented less formally, or not at all, since the results are discussed "face-to-face" and any differences resolved.

It is the responsibility of the individuals involved in the review process (initiator and/or pathologists) to decide how the data from the review will be summarized. Some documentation is necessary, however, and the report should at the very least include: a) objective and/or method of review; b) name of person doing review; and c) summary of results.

If the results are consistent between the 2 pathologists, a succinct statement to that effect may be all that is needed in the original report.

For all of the reasons previously discussed, it is possible that the reviewing pathologist's results may differ noticeably from those of the original pathologist; however, if both pathologists maintain their objectivity, these differences should be resolvable. If such differences cannot be resolved through a joint review of the data, then separate reports may be needed and the problem may have to be referred to

a "pathology working group" or to expert consultants for resolution.

The Pathology Working Group (PWG) should be composed of individuals having expertise both in the pathology of the test species and with the specific lesion in question. The PWG may include both the original and the reviewing pathologist but the diagnoses of both the original and the reviewing pathologist should not be known to the other PWG members. Prior to beginning work, the focus of the PWG must be clearly defined, i.e., the question is proliferative follicular cell lesions of the thyroid gland and specifically, differentiation of hyperplasia from adenoma. The PWG must agree upon and document prior to beginning the slide review the criteria to be used to make the diagnoses of the lesions in question. Following slide examination by the PWG in a blinded fashion and tabulation of the results, the findings of the PWG are compared to those of the study pathologist. When the consensus of the PWG is clearly different from that of the study pathologist, the diagnosis for an individual lesion should be changed. When there is a close split on a vote on a diagnosis, however, the diagnosis of the study pathologist should be allowed to stand. The records of the PWG should indicate the final diagnoses for each lesion and the degree of certainty (split of votes) of the diagnoses.

CONCLUSIONS

Regardless of its exact form, the peer review process should encourage direct interaction between the original and the reviewing pathologist and should result in the production of a single, scientifically sound pathology report that appropriately and accurately summarizes the results. The process should be constructive, meet the needs and objectives of the review, and have built into it a procedure for resolving differences, should they arise.