The Pathology Committee of the Cancer and Leukemia Group B (CALGB) was initiated in 1977 and for many years had a limited role within the Group, primarily central review of hematopathology cases for diagnostic confirmation. The scope of committee activities has expanded considerably since that time, especially in the last 8 years, and the Committee is now integral to all clinical, scientific, and administrative functions of the Group. The Pathology Committee is composed of seven cadres of expert pathologists with specific clinical and scientific expertise in the disease areas studied by the CALGB. The Pathology Committee is committed to providing expert pathologic central review and quality control for all tissue-based correlative science studies in the Group, a role that is anticipated to expand with CALGB's expanding scientific activities. In collaboration with the Correlative Science Steering Committee, it will continue to strengthen and expand the central specimen banking and processing services of the Pathology Coordinating Office (PCO), the primary tissue repository for CALGB. The committee also is focused on the initiation, development, execution, and publication of innovative pathology-driven scientific studies. In all of these roles, the members of the Pathology Committee now serve the CALGB, broadly and deeply, as clinical consultants, scientific contributors, quality monitors, administrators, and overseers of critical scientific infrastructure and look forward to the continued evolution of all these functions in the years to come.

The CALGB Pathology Committee is a cross-cutting modality committee that is broadly integrated into CALGB structure and function. Its members participate directly in every relevant clinical, scientific, and administrative activity of the group. Pathologists serve as full members of the disease committees, surgery subcommittees, and correlative science working groups and also serve on the CALGB Executive Committee and Board of Directors. Conversely, the Pathology Committee receives input from its liaison members representing the Correlative Science working groups, the Statistical Center, the Central Office, and the patient advocacy groups of CALGB. The Pathology Committee shares responsibility for oversight of the CALGB PCO at the Ohio State University, the central specimen banking, and processing facility, with the Correlative Science Steering Committee.
For the last 8 years, since it was consolidated into a single committee from separate surgical pathology and hematopathology components, Dr. Carolyn Compton has served as its chair. Drs. Ann Thor and Saul Suster have served as vice-chairs, with Dr. Suster providing on-site administrative oversight of the PCO until recently. Dr. Scott Jewell, also at the Ohio State University, has served as the PCO Laboratory Director, coordinating its day-to-day functioning and has recently assumed responsibilities as Principle Investigator for the PCO. The Committee itself is organized into seven cadres (as shown above) that mirror the disease committee and correlating science structure of the CALGB. Each cadre is lead by and composed of nationally and internationally recognized academic surgical and hematopathologists who are subspecialty experts, widely recognized for their diagnostic and scientific expertise in their respective areas. Members of the Pathology Committee provide leadership in tissue banking within the National Cancer Institute–sponsored clinical trials mechanism and chair three of the five subcommittees of the Group Banking Committee of the National Cancer Institute.

The primary mission of the Pathology Committee is to ensure the highest possible quality of all tissue-based correlative science in CALGB. In addition to the quality control and quality assurance related to the PCO, the Pathology Committee provides quality control for all morphology-based correlative science analyses, such as immunohistochemistry studies, through the auditing of a statistically determined proportion of cases to assess interobserver variability. In lymphoma, leukemia, and melanoma protocols, for which confirmation of disease diagnosis is critical, central review is done. Lastly, to minimize variation at the site of origin of the specimen, the Pathology Committee provides guidelines, which are approved by the College of American Pathologists, for the handling, interpretation, and reporting of tumor specimens within institutional pathology departments. A second mission of the Committee, integrally related to the first, is to provide high-quality tissue banking and centralized morphology-based support services for all relevant CALGB activities throughout the entire organization.

Figure 1 illustrates the method by which the Pathology Committee and the PCO achieve their mission of prospective quality control for every specimen sent to every investigator from the PCO central facility. As an integral part of every tissue-based correlative science study, a plan for paraffin block sectioning at the PCO, like the one shown, is developed. Blocks are sectioned to provide adequate sample for each of the planned analyses, and a “top,” “middle,” and “bottom” section is stained for pathologic quality control. These sections are reviewed by the assigned cadre pathologist who reports back to PCO as to the accuracy of the diagnosis and the adequacy of the tissue sample on each of the three levels. This guarantees the quality of the unstained samples in between, which then are released to investigators. Thus, investigators can be completely confident of the nature and the quality of the samples they receive.

To facilitate its primary mission, the Pathology Committee and the PCO have introduced new and cutting edge technologies, including tissue microarray, for all newly initiated studies and selected ongoing and closed studies, electronic tracking of all specimens, and, uniquely within the clinical trials mechanism, a web-based pathology quality control system. All top, middle, and bottom slides are scanned in a digital virtual microscopy system, and study pathologists review and annotate the images via the web and designate areas for coring for tissue microarray production. For selected studies, central diagnostic review of cases and analysis of immunostains are also done using this web-based image transmission system. To facilitate use of this new system, the PCO created a web-based educational service for the committee pathologists.

The CALGB Pathology Committee has two additional goals. One is to provide input during clinical and scientific protocol development to assure that all relevant pathologic issues are addressed prospectively. To accomplish this, a study pathologist from the relevant cadre is assigned to each protocol to address pathologic issues on an ongoing basis. In addition, the committee is committed to developing innovative pathology-driven research. The thematic basis of this research can be classified as either disease related or process related, relevant to the PCO and quality control activities. The following are selected scientific accomplishments of the CALGB Pathology Committee by cadre (1–21):

**Breast Cadre**
- CALGB 9342: In metastatic breast cancer, HER-2-positive tumors less responsive to paclitaxel than HER-2- tumors; p53 and mutational analysis not predictive of response.
- CALGB 8591: Fluorescence in situ hybridization and immunohistochemistry analysis of Her2 both reliably predictive in adjuvant doxorubicin-based therapy.

**Genitourinary Cadre**
- CALGB150005: Serum hepatocyte growth factor is prognostic in metastatic hormone-refractory prostate cancer.
- CALGB 9181 and 9182: Serum hemoglobin increases prognostic value of prostate-specific antigen in hormone-refractory prostate cancer.

**Respiratory Cadre**
- CALGB 9761: In stage I non–small cell lung cancer, immunohistochemistry detects twice as many positive regional lymph nodes as routine histopathology.
- CALGB 30101: Gefitinib treatment does not improve disease-free survival in mesothelioma that overexpresses epidermal growth factor receptor.
Gastrointestinal Cadre
- CALGB 9865: Somatic alterations in DNA repair genes in high-risk microsatellite unstable colorectal cancer include hypermethylation of the MLH1 promoter, hypermethylation of the PTEN promoter, and epigenetic inactivation of RunX3.
- CALGB 9865: Adenomatous polyposis coli promoter hypermethylation contributes to the loss of adenomatous polyposis coli function in colorectal cancer with allelic loss of 5q.
- CALGB 80001: Sentinel lymph node analysis in colorectal cancer does not improve risk stratification colorectal cancer. Leukemia Cadre
- CALGB 9720: Morphology predicts inv(16) and t(8;21) alterations in acute myelogenous leukemia.
- CALGB 9621/9720: Two subtypes of acute myelogenous leukemia without differentiation (FAB M1) can be differentiated morphologically and genetically.
- Central and institutional immunophenotyping is highly concordant for acute myelogenous leukemia versus acute lymphoblastic leukemia and T-cell versus B-cell acute lymphoblastic leukemia.

Over the past 8 years, the Pathology Committee has evolved rapidly in response to the growing multidisciplinary activities and needs of the CALGB. In the last 3 years, 15 new committee members have been recruited. The Lymphoma Cadre has been entirely rebuilt with new leadership and new membership. The Committee has done quality control/central review of >7,000 cases in 22 studies, involving the review of >38,000 slides. The Committee has published 23 articles and numerous abstracts. It has initiated 21 new pathology-driven scientific projects with a pathologist serving as the principal investigator in each. In >22 additional, newly initiated scientific studies, a pathologist is serving as a coinvestigator.

The committee members perform a prodigious amount of work on behalf of the group. Table 1 summarizes the workload that is the joint effort of the PCO and the Pathology Committee in supporting CALGB correlative science. As is evident from the table, the Pathology Committee has shown outstanding commitment to and achievement of its mission of insuring the quality of analytes in all tissue-based correlative science. This work underscores the importance of multidisciplinary teamwork within CALGB that is essential to achieve the overall Group mission of high-quality performance. Table 1 also shows the need for diagnostic review in particular cancer types. For example, in the six lymphoma studies listed, 558 slides were reviewed for diagnosis in >300 cases. Of these, there was an 88% acceptance rate. The percentage accepted are those in which the slide read by the cadre pathologist agrees with the institutional pathology report: that the tissue meets the study protocol criteria, and that the slide shows the specified pathology. These data substantiate the need for the complex quality control and processing methods carried out, particularly in this disease.

Lastly, the Committee conducts CALGB-wide symposia on pathology topics critical to current and future CALGB initiatives. Recent examples include a symposium on the use of tissue microarrays in clinical trials featuring pathology leaders in this field and a state of the science symposium on defining pathology response following neoadjuvant therapy in various cancer sites. This is a timely topic given the nearly universal lack of uniformity in defining this critical end point, which is becoming more and more widely employed in CALGB and intergroup trials.

### Table 1. Work product of the CALGB pathology committee (2003-2005): quality control/central review of >6,000 cases in 22 studies

<table>
<thead>
<tr>
<th>Disease</th>
<th>Cases in PCO</th>
<th>Blocks received</th>
<th>Slides received</th>
<th>Slides cut</th>
<th>Studies reviewed</th>
<th>Cases reviewed</th>
<th>H&amp;E slides reviewed</th>
</tr>
</thead>
<tbody>
<tr>
<td>Breast</td>
<td>9,614</td>
<td>11,560</td>
<td>29,172</td>
<td>67,644</td>
<td>7</td>
<td>3,468</td>
<td>5,063</td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td>3,521</td>
<td>5,883</td>
<td>27,697</td>
<td>112,514</td>
<td>5</td>
<td>1,625</td>
<td>11,157</td>
</tr>
<tr>
<td>Genitourinary</td>
<td>673</td>
<td>716</td>
<td>3,592</td>
<td>986</td>
<td>1</td>
<td>29</td>
<td>93</td>
</tr>
<tr>
<td>Leukemia</td>
<td>117</td>
<td>108</td>
<td>377</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Lymphoma</td>
<td>1,200</td>
<td>567</td>
<td>9,350</td>
<td>3,192</td>
<td>5</td>
<td>282</td>
<td>448</td>
</tr>
<tr>
<td>Melanoma</td>
<td>101</td>
<td>364</td>
<td>1,461</td>
<td>1,370</td>
<td>1</td>
<td>90</td>
<td>198</td>
</tr>
<tr>
<td>Respiratory</td>
<td>785</td>
<td>702</td>
<td>3,062</td>
<td>8,687</td>
<td>2</td>
<td>242</td>
<td>300</td>
</tr>
<tr>
<td>Transplant</td>
<td>20</td>
<td>4</td>
<td>185</td>
<td>0</td>
<td>1</td>
<td>23</td>
<td>23</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>16,031</strong></td>
<td><strong>19,904</strong></td>
<td><strong>74,896</strong></td>
<td><strong>194,393</strong></td>
<td><strong>22</strong></td>
<td><strong>5,759</strong></td>
<td><strong>17,282</strong></td>
</tr>
</tbody>
</table>

The CALGB Pathology Committee at 50

The cross-disciplinary strength and diversity of the CALGB Pathology Committee has evolved and matured dramatically over the years. During its early years, the CALGB operated without any formal input from pathologists for two decades. As the need for diagnostic confirmation of disease before entry onto CALGB trials became recognized, the Pathology Committee of the CALGB was organized in 1977 with Dr. Louis Dehner, then at the University of Minnesota, as its chair. In 1979, Dr. Maurice Barcos of Roswell Park Cancer Institute was named the Pathology Committee Chair, and a CALGB PCO was established there. Just as it does today, the PCO of the CALGB served as a central repository for the majority of the diagnostic patient specimens (glass slides and paraffin blocks) collected in association with CALGB clinical trials and as a central processing facility for specimen preparations used by CALGB investigators in correlative scientific studies, but its activities were limited in number and type.

Initially, the Pathology Committee was responsible primarily for the central review of lymphoma cases for diagnostic
confirmation. In addition, the Committee assumed responsibility for review of diagnostic specimens associated with CALGB lung cancer and mesothelioma trials. When the French-American-British Cooperative Group criteria for leukemia classification were developed, the Pathology Committee assumed responsibility for leukemia specimen review from the Leukemia Committee. By 1987, the work of the Committee had expanded beyond the central review of routine histopathologic materials to include special studies, such as flow cytometry for leukemia protocols and immunohistochemistry for breast and lung studies. Scientific studies requiring microdissection of paraffin blocks also required the expertise of CALGB pathologists. Thus, the scientific output of the Pathology Committee was focused on correlative scientific studies of hematologic malignancies and breast cancer done in collaboration with investigators from the respective disease committees and on studies related to technical issues in histopathology relevant to the tissues being studied (17, 22–59).

During these early years, the Pathology Committee received excellent ratings for its quality control functions and overall compliance with submission of specimens was excellent, but the committee was criticized for being poorly integrated into other CALGB activities. It was not actively contributing to the development of new protocols nor taking an active role in scientific decision-making. The CALGB leadership realized that the contributions of all modality committees, including the Pathology Committee, would be most effective in an interdisciplinary context, and greater integration into the disease committee structure and greater participation in protocol design were promoted. Involvement of the Pathology Committee in group-wide educational activities also increased significantly. From 1988 to 1992, the Pathology Committee sponsored 23 educational seminars of broad interest to the group and made a number of important scientific contributions (17, 22–59).

However, during this period, the primary function of the pathologists in CALGB was the central morphologic review for patient eligibility in various clinical protocols of the CALGB and the quality of control of tissue sections used in the various biological assays of the Correlative Science Working Groups. By 1992, with the development of separate correlative sciences in leukemia/lymphoma and solid tumors, the CALGB Pathology Committee had ceased to meet as a separate modality. Participation by pathologists then dwindled to a few individuals with specific responsibilities for central diagnostic review of the leukemias/lymphomas and mesotheliomas or for the quality control, grading, and assessment of immunohistochemical assays in one breast cancer companion study. At that time, factors contributing to the low pathology participation included the preponderance of advanced-stage disease protocols for solid tumors in the CALGB and the lack of institutional funds for travel by pathologists to Group meetings.

Following Dr. Schilsky’s election as Group Chair, all institutional Principal Investigators were approached personally and asked to nominate pathologists to revitalize the Pathology Committee. In 1996, the Pathology Committee was restructured into Hematopathology and Surgical Pathology divisions. Dr. Richard Bruning was appointed Vice-Chair for Hematopathology, and Dr. Carolyn Compton was appointed Vice-Chair for Surgical Pathology under the overall leadership of Dr. Maurice Barcos. Dr. James Vardiman was appointed cadre leader for leukemia, and Drs. Nancy Harris and Dennis Weisenburger were cadre leaders for lymphoma. Two years later, the committee was reorganized and assumed its present structure.

Reorganization, improvement, and expansion of the CALGB PCO began in 1999 with the move of the PCO to the Ohio State University. At that time, archiving of all CALGB specimens was completed, and full conversion to electronic record keeping was achieved. Installation and implementation of CALGB’s LabTrak system for specimen tracking was completed, and the technical ability to establish tissue microarrays of CALGB specimen collections was achieved and perfected.

Conclusion

The Pathology Committee of CALGB has shown extraordinary growth, maturation, and growing accomplishments over the past 30 years. The superb contributions of the Pathology Committee are essential to and an integral part of the success of CALGB correlative science. The pathologists in CALGB contribute on every level to the multidisciplinary approach with which CALGB clinical trials are planned, carried out, analyzed, and reported. The activities of the Pathology Committee provide assurance for the entire Group that patient diagnoses are correct and that the quality of the analytes for all tissue-based correlative science within CALGB is as high as possible.

References

The Cancer and Leukemia Group B Pathology Committee at 50

Carolyn Compton

Updated version
Access the most recent version of this article at:
http://clincancerres.aacrjournals.org/content/12/11/3617s

Cited articles
This article cites 59 articles, 29 of which you can access for free at:
http://clincancerres.aacrjournals.org/content/12/11/3617s.full.html#ref-list-1

E-mail alerts
Sign up to receive free email-alerts related to this article or journal.

Reprints and Subscriptions
To order reprints of this article or to subscribe to the journal, contact the AACR Publications Department at pubs@aacr.org.

Permissions
To request permission to re-use all or part of this article, contact the AACR Publications Department at permissions@aacr.org.