



CALGB Focuses on Cancer in the Elderly

by Hyman B. Muss, M.D. and Harvey J. Cohen, M.D.

Cancer is mainly a disease of aging with an increase in incidence that almost parallels increasing age. As the population ages, cancer will ultimately overtake heart disease as the major cause of death in America. The older patient with cancer poses unique problems. Coincident with the increased risk of cancer in the elderly is an increased incidence of other major illnesses (comorbidity). Such illness frequently has profound effects on patient management, including the type of cancer treatment offered and the potential for increased toxicity of treatment. Moreover, access to care, transportation, cost, and reimbursement concerns are quite often major barriers to cancer care in this group. Older patients are also more likely to have inferior insurance coverage than their younger counterparts, and lower income as well. Dr. B.J. Kennedy recently reviewed this experience in (*Cancer Control*, Vol. 17, March/April 1995).

Historically, the CALGB has been very interested in cancer in the elderly. In response to a request by several Group members for the CALGB to expand its research programs for older patients, the Working Group on Cancer in the Elderly was established, and its first meeting was held in November 1995. The charge of the Working Group is to provide a forum for CALGB members interested in cancer in the elderly to share ideas; to transform the most promising and innovative ideas into concepts and, ultimately, protocols; and to provide input to other CALGB committees about opportunities for developing clinical trials focused on cancer in the elderly.

Committee members were selected

based upon their interest in cancer in older individuals. Dr. Schilsky appointed Drs. Harvey Cohen and Hyman Muss to Co-Chair this Working Group. Other members include: Alice Kornblith, Ph.D., Drs. Stuart Lichtman, Merrill Egorin, Margaret Kemeny, and Richard Stone. CALGB staff members appointed to the Working Group are: Gini Fleming, M.D., Executive Officer, Bercedis Peterson, Ph.D., Statistician, Judith Wheeler, Data Coordinator, and Michael Kelly, Protocol Editor.

Three meetings have taken place since the Working Group's inception, each characterized by lively discussions from a diverse group of CALGB members, including patient advocates. Several concepts have been presented and are in the protocol development process. These include a PET Committee study of paclitaxel pharmacology in older patients, a phase III lymphoma trial evaluating the role of a unique antitumor antibody when added to chemotherapy and growth factors in patients 65 years and over, and a trial exploring the barriers to entry into clinical trials of older women with both early- and late-stage breast cancer. The latter study has received supplemental funding from the National Institutes of Aging (NIA) and will gather information from both patients and their physicians concerning major obstacles to trial participation. The data obtained will be used to develop focused interventions to overcome these obstacles. A concept has also been submitted to examine data from previously completed

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Articles should be sent to:

*Barbara Hower, Newsletter Editor
Cancer and Leukemia Group B
208 South LaSalle Street, Suite 2000
Chicago, IL 60604-1104*

(312) 702-9479 FAX (312) 345-0117

e-mail: bhower@midway.uchicago.edu

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Message from the Group Statistician...

It is clear from some of the discussions surrounding the revelations of deliberate entry of some ineligible patients by an NSABP investigator that there are misunderstandings concerning the typical causes of ineligibility, the types of ineligible patients, and the implications of entering such patients on clinical trials. In a previous *Cal Gab* article (Vol 4, No. 3), I presented the arguments for broadening patient eligibility requirements for Phase III clinical trials. These comments were expanded and published in the *Journal of Clinical Oncology* ("Reducing patient eligibility criteria in cancer clinical trials," *JCO*, 14 (1996), 1364-1370). One outcome of this discussion is that the eligibility requirements for all new CALGB Phase III clinical trials are being carefully reviewed so as to eliminate unnecessary ones. At the Plenary Session of the Spring Group Meeting, I presented some further thoughts on broadening patient eligibility. Although I will not repeat the arguments for broadening eligibility requirements here, there are some additional points concerning the handling of ineligible patients in the statistical analyses and the follow-up of such patients that are worth further comments.

Causes of Ineligibility and Types of Ineligible Patients

The entry of an ineligible patient on a clinical trial is certainly something to be avoided, but it is not generally of much scientific or medical importance. With respect to scientific importance, the procedures that are in place to verify eligibility result in a very low percentage of ineligible patients on most CALGB studies. Also, one of the powerful advantages of a randomized trial is the elimination of potential bias caused by a severe imbalance in the treatment assignments to the ineligible patients. With respect to medical significance, the primary concern is whether or not the treatment given to an ineligible patient is appropriate and safe. Although it is certainly possible that a treatment may not be appropriate, this is a very rare occurrence. Nearly all ineligible patients are declared so because of minor deviations from overly strict criteria that have nothing to do with appropriateness of treatment or patient safety. The primary reasons for ineligibility are: minor technicalities, e.g., age or a lab value just above or below an arbitrary cut-off point; ex post facto reviews - e.g., central pathology review; and vague criteria, e.g., "unresolved infection."

All of these reasons may be classified as "honest errors" or, in another interpretation, may not be considered errors at all. A scientific argument can be made for dropping the label "ineligible" for patients who were thought to be eligible, in good faith, by the registering physician. In this pragmatic approach, a patient thought to be eligible at the time of registration is, in fact, eligible by definition. This is, after all, most reflective of actual medical practice. However, it must be pointed out that this argument is not widely accepted at present.

The previous arguments are not excuses for sloppiness and, of course, there can be no excuse for consciously entering patients who clearly violate stated eligibility criteria. However, a relaxation of the eligibility criteria would eliminate many of the causes of ineligibility and save considerable effort on the part of investigators, clinical research associates, data coordina-

tors, auditors, and others responsible for verifying eligibility.

Implications of Entering Ineligible Patients

Once a registered patient is declared ineligible, what are the implications? There are at least four areas that are worth comments: institutional evaluations, statistical analysis, continuation of therapy, and follow-up.

One of the areas that causes the most concern among institutions is the institutional "report card." Eligibility criteria are checked for patients selected in institutional audits and a high percentage of ineligible patients can result in an unfavorable audit report. Three points are relevant here. First, because of the inevitable but innocuous reasons for ineligibility, a non-zero background percentage of ineligible patients would be expected for most institutions. Unless the institutional percentage is unusually high, there is no cause for concern. Second, the percentages of ineligible patients are a minor part of the overall evaluation. And third, as long as the reasons for the ineligible patients are not gross carelessness or a deliberate intention to enter ineligible patients, there is little or no harm.

The use of ineligible patients in the statistical analysis is often misunderstood. Fundamental principles of clinical trials design and analysis call for the inclusion of ineligible patients in as many analyses as possible. Such an inclusion is related to, but not identical with, the intent-to-treat principle in randomized trials. As an example, the toxicity analysis of ineligible patients provides obviously usable information. Although it is not widely recognized, the same principle applies to all other endpoints, including response rates, disease-free survival, and survival. The number and type of ineligible patients should be reported clearly, but not otherwise excluded from the analysis. An erroneous assumption is often made that such patients will be (and should be) excluded from all analyses. Ineligible patients should be followed for the primary outcome(s) of the trial exactly as eligible patients. Otherwise, it will not be possible to carry out the proper analyses. This principle is quite broad and applies to all patients. That is, the primary outcome variables for a clinical trial are needed for all patients, regardless of eligibility status, treatment received, intervening events, or other factors. Another erroneous assumption is that if a patient is found to be ineligible during treatment, then he or she must be (or should be) taken off the protocol-specified therapy. In fact, such action should be taken only if there is a medical reason (e.g., the therapy is unsafe or no longer appropriate). Otherwise, the therapy should be completed exactly as for an eligible patient.

Although the CALGB is attempting to broaden the eligibility criteria on its Phase III clinical trials, it is still important to avoid entering ineligible patients. Except for those extremely rare cases in which the reason for ineligibility results in an inappropriate treatment for a patient, all ineligible patients should continue to be treated and followed for the primary outcome measures.

Stephen L. George, Ph.D.

Cancer in the Elderly

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CALGB trials concerning differences in chemotherapy toxicity in older and younger patients.

At present, the CALGB has two active protocols written specifically for older patients. CALGB 9343 is a randomized trial exploring the role of breast radiation in women 70 years and older who have had lumpectomy and been placed on tamoxifen. (A companion study, which will assess biologic and molecular marker expression in these patients, has also been developed and is pending activation.) CALGB 9420 is a phase I trial studying biochemical modulation of the multidrug resistance protein and interleukin-2 maintenance therapy in patients 60 years and older with acute myelogenous leukemia.

The Working Group encourages input from all CALGB members concerning issues related to cancer in the elderly. Concepts for cancer control, treatment, and epidemiologic studies are all sought. We welcome your participation in our Working Group.

New Chair for Cancer Control Committee

At the Spring 1996 Group Meeting in Miami Beach, Electra Paskett, Ph.D., was named the new Chair of the Cancer Control Committee. She replaces Vincent Vinciguerra, M.D., who has been Chair of the Committee since it was initiated in 1987.

A member of the Comprehensive Cancer Center (Cancer Control Program) at the Bowman Gray School of Medicine (BGSM), Dr. Paskett is also an Associate Professor in the BGSM Department of Public Health Sciences (Epidemiology). She has lectured widely in epidemiology, preventive medicine, research methodology, and in clinical trials management.

Dr. Paskett has received many grants to investigate such issues as cancer screening, smoking cessation, cancer prevention, and barriers to cancer treatment. She also awaits approval for support of a phase II trial that will study the effects of dietary soy supplements on the prevention of prostate cancer.

The origins of the CALGB's Cancer Control Committee can be traced to

1987 when a new modality, the Cancer Control Science Committee, was formed. The Committee was established to implement clinical research trials in conjunction with the National Cancer Institute's Community Clinical Oncology Program (CCOP). Subcommittees within the Committee included screening and prevention, smoking cessation, supportive care, and minority population affairs.

Cancer control is defined as the reduction of cancer incidence, morbidity, and mortality by application of an orderly sequence of activities, ranging from research on interventions and their impact on defined populations to broad, systematic applications of the research results.

Research goals of the Cancer Control Science Committee were:

- To develop strong scientific concepts and protocols in cancer control that blend basic scientific and clinical relevance in practice;
- To involve a new cadre of medical professionals and Community Clinical Oncology Programs in the development and implementation of cancer control clinical trials that meet the accrual needs of CCOPs;
- To interact with other Modality and Disease committees in CALGB in the development of cancer control protocols;
- To develop new initiatives in smoking cessation in an attempt to decrease morbidity and mortality from smoking-related cancers;
- To participate in protocols that study new methods of cancer screening and prevention of colorectal, prostate, ovarian, and lung cancers;
- To explore supportive care research emphasizing areas such as cancer pain, nutrition, antiemetic therapy, and psychosocial support;
- To emphasize cancer control research that recognizes the special needs of minority and elderly populations; and
- To foster and promote educational workshops on cancer control topics for the benefit of the CALGB membership.

As the newly appointed Cancer Control Committee Chair, Dr. Paskett has outlined her focus for the Committee. Under Dr. Paskett, the Cancer Control Committee will focus mainly on primary prevention and palliative care, targeting cancer patients, their families, and high-risk populations. Research projects will need to be scientifically sound and feasible within

the cooperative group setting, including CCOPs. The Cancer Control Committee will also focus on integrating studies with the Psycho-Oncology Committee, the Clinical Economics Committee, and the Epidemiology Working Group. Several new individuals will be added to the Committee to increase its depth in these areas.

QARC FELLOWSHIP AVAILABLE

The Quality Assurance Review Center (QARC) has established a Quality Assurance Review Center Research and Educational Trust Fund to subsidize Senior Trainees and Junior Staff Personnel from institutions participating in cooperative group trials. Fellows will receive experience with cooperative group clinical research, including protocol development, performance assessment, and outcome analyses in relation to adherence to protocol requirements. Two or three candidates will be funded each year for this special program.

QARC monitors more than 70 protocols being carried out in more than 500 U.S. institutions under the aegis of CALGB, POG, and IRSG. In its files are the case records and x-ray films of more than 22,000 patients treated on 187 protocols during the last 20 years.

Institutions participating in cooperative group trials can nominate individuals to spend two months in residence at QARC. Candidates may come from any of the oncologic specialties. In addition to review sessions and on-treatment reviews, each Fellow will become familiar with protocols that are currently under investigation and review all new protocols in development to better understand the scientific questions being addressed and the technical requirements for the delivery of therapy.

Each Fellow will undertake a research project designed to use some aspects of the QARC program. A stipend of \$3,500 will be awarded to cover travel and living expenses for the two-month period.

Applications for the Fellowship will be available in Summer 1996. For information, contact:

Dr. Arvin S. Glicksman, M.D.,
 Director, Quality Assurance Review
 Center, 825 Chalkstone Avenue,
 Providence, RI 02908-4735. Telephone:
 (401) 456-6500; FAX: (401) 456-6550.

CALGB Pathology Committee Restructured

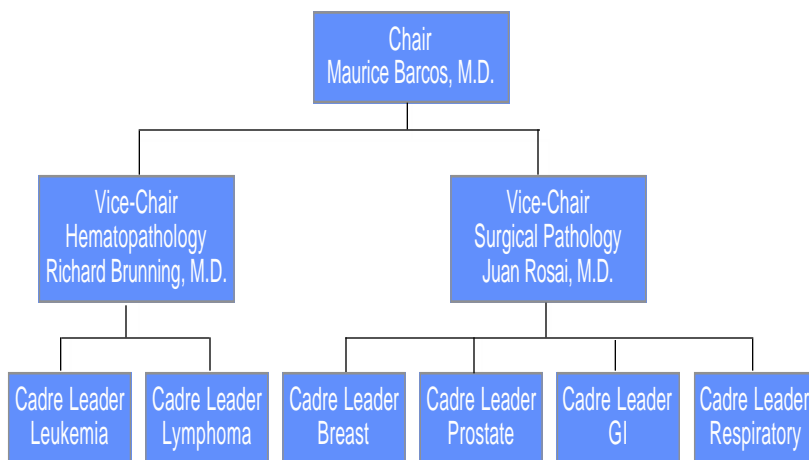
Realizing the importance of involving CALGB pathologists in the CALGB and recognizing that the Group relies heavily upon the expertise of the pathology community to contribute to CALGB correlative sciences studies and on institutional pathologists to supply tissue samples from patients, the Executive Committee has approved restructuring the Pathology Committee into specialty areas (see chart at right). Maurice Barcos, M.D., will continue as Chair and Director of the Pathology Coordination Office and Laboratory at Roswell Park Cancer Institute (RPCI). Drs. Richard Brunning, University of Minnesota, and Juan Rosai, Memorial Sloan Kettering Cancer Center, have been appointed Vice-Chairs for Hematopathology and Surgical Pathology, respectively. The following disease-specific cadre leaders have also been selected: Dr. James Vardiman, University of Chicago, for leukemia; Drs. Nancy Harris, University of Massachusetts, and Dennis Weisenburger, University of Nebraska, for lymphomas; Dr. Steven Silverberg, University of Maryland, for breast cancer; Dr. Anna-Louise Katzenstein, Syracuse, for lung cancer and mesotheliomas; and Dr. Victor Reuter, Memorial Sloan Kettering, for prostate cancer. The cadre leader for gastrointestinal cancers will be appointed shortly. More than 30 pathologists have also been nominated by Principal Investigators for membership in the Pathology Committee. The Central Office has obtained travel funds for pathologists to attend Group Meetings, and the Pathology Committee will work closely with the Disease and Modality chairs to expand the role of pathologists beyond quality control into the development and implementation of clinical and correlative sciences research protocols.

Bone marrow specimens on patients with leukemias, myelodysplastic syndromes, and multiple myelomas should continue to be sent to the Bone Marrow Laboratory in Syracuse until September 30, 1996. Beginning October 1, 1996, they should be addressed to: Dr. James Vardiman, Department of Pathology, University of Chicago Medical Center, 5841 S. Maryland Avenue, MC 0008, Chicago, IL 60637-1470; telephone: (312) 702-6196; FAX: (312) 702-9082.

All paraffin blocks on Solid Tumor Correlative Sciences studies should continue to be sent to the CALGB Pathology Coordinating Office at RPCI in Buffalo, NY, for storage and processing. By agreement with SWOG and ECOG, paraffin blocks will be retained for processing at the originating cooperative group. The CALGB has recently submitted requests to the NCI for supplemental funds to support the repository of paraffin blocks at RPCI, a Leukemia Tissue Bank at RPCI, and a Tumor DNA Bank at the University of North Carolina. We anticipate that these supplemental funds will ensure the success of our tissue banking efforts.

If you are interested in joining the Pathology Committee or if you know of a pathology colleague at your institution who might want to participate, please contact Dr. Barcos; telephone: (716) 845-4443; e-mail: calgbpath@sc3102.med.buffalo.edu.

Pathology Committee



CHAMPUS Support of NCI-Sponsored Trials

If you are a CALGB investigator wishing to request CHAMPUS support for a patient entered on an NCI-sponsored trial, you should:

1. Contact Rita Maultsby, R.N., Nurse Case Manager for the CHAMPUS Program at 1-800-779-3060.
2. Ms. Maultsby will obtain pertinent information regarding patient background and a description of the trial to which you wish to enter your patient.
3. After reviewing the information, Ms. Maultsby will either approve or deny your request to enter the patient on the trial and notify you of her decision.

Note: CHAMPUS only supports phase II and III trials.

Highlights of 1996 Study Chair Workshop

Many factors are involved in being a Study Chair. The Study Chair assumes many responsibilities connected with the design, conduct, analysis, and reporting of CALGB studies. Every year, at the Spring Group Meeting, a Study Chair workshop is held, which all new Study Chairs are required to attend. Complete details on the duties of a Study Chair can be found in Section 6.3 of the *CALGB Policies and Procedures (P&P)* manual. Following are brief highlights of what was discussed at this year's workshop.

Dr. Richard Schilsky began the workshop with comments on a Study Chair's responsibilities, followed by information provided by members of the CALGB Central Office, Statistical Center, and Data Management Center on protocol development, statistical considerations, and data coordination.

Briefly, some of the basic responsibilities of Study Chairs are:

- Ethical conduct of research. Study Chairs must sign and submit a Conflict of Interest Form (see Chapter 3 in the *P&P* manual for more information);
- Protocol development;
- Protocol monitoring, including toxicities and Adverse Event Reports, accrual, and outcome. The phase III Study Chair should attend all open sessions of the Data and Safety Monitoring Board when his or her study is being reviewed, as the input of the Study Chair is very important;
- Protocol analysis, i.e., case evaluations and collaboration with the Statistician; and
- Publications. When phase III study data are released, the Study Chair should consult with the study's Statistician to develop a timeline for publishing the study in a timely manner (see Section 10 in the *P&P* manual for more details).

Protocol Development

A Concept Sheet, which is a brief summary of a proposed protocol, is prepared for discussion at a Disease or Modality Core Meeting. The concept should also be discussed with the CALGB Statistician assigned to the committee from which the protocol will originate and should consider such matters as study size, duration, and patient availability. A Concept Sheet should include:

- Title;
- Study Chair/Co-Chairs;
- Rationale;
- Objectives;
- Eligibility criteria;
- Statistical considerations;
- Treatment plan; and
- Funding options.

After passing through a network of reviews and revisions, the Study Chair receives a new Study Chair package from the CALGB Central Office if the concept is approved by the Executive Committee. Contained within this package are:

- Model protocol hard copy;
- Model protocol on diskette;
- Study Chair guidelines;
- Conflict of Interest Disclosure form;

- Study Chair agreement; and
- Names of the protocol team, i.e., Protocol Editor, Data Coordinator, and Statistician assigned to the study.

The assigned Protocol Editor formats and edits the protocol that the Study Chair has written and then readies it for a series of reviews. Subsequently, a revised draft is submitted to the NCI and to the entire Group through the monthly mailing from the Central Office. After receipt of a written review from the NCI, the Study Chair drafts a response to the NCI, which is then forwarded to the Central Office along with a revised protocol that reflects the NCI-suggested changes and recommendations. Once written NCI approval is received, the protocol is activated in the next monthly protocol mailing.

Following are some troubleshooting tips on protocol development.

- E-mail is the most effective means of communicating with your protocol team;
- Don't concentrate on the format of your protocol. The Protocol Editor will apply the style used for all CALGB protocols to your document. Nevertheless, using the model protocol as the basis of the document will hasten development;
- Communicate frequently with the Protocol Editor, Data Coordinator, and Statistician to ensure that protocol and forms development are in sync; and
- Once you've submitted the disk version of the protocol, don't submit new versions either on diskette or in hard copy. Make any changes on the Central Office hard copy version of the protocol.

Statistical Considerations

The Faculty Statistician's primary responsibility is the statistical aspects of the protocol, and he/she is assisted by Staff Statisticians. The role of the Statistician during protocol development is to clarify study objectives and aspects of study design, including eligibility; to determine sample size for the study; and to write the statistical section for the concept sheet and protocol. The Statistician will also determine data collection needs and, if necessary, develop new forms. Points to consider about data collection include:

- Minimize the amount of data collected;
- Avoid retrospective data collection; and
- Understand what data will be computerized.

Data Collection

It is also important for new Study Chairs to establish a working relationship with the assigned Data Coordinator. The Data Coordinator is responsible for the data management of assigned protocols; edits and receives all data forms; performs quality control on collected data; contacts institutions for clarification or to request missing data; and prepares data for

Study Chair Workshop

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analysis. The Data Coordinator corresponds with the Study Chair to ensure completion of eligibility and case evaluation forms, responds to questions from the institutions about the data submission, and serves as a primary contact with the Statistician and Study Chair on the status of the database for the study. Briefly, here are some Study Chair "Do's and Don'ts" regarding data collection:

DO

- Communicate regularly with the protocol team;
- Review data regularly;
- Keep the team apprised of your schedule;
- Keep up with your eligibility and case evaluations and return them to the Data Coordinator within 60 days of receipt.

DON'T

- Override eligibility;
- Send queries to institutions (send them to the Data Coordinator);
- Ask the Data Coordinator for reports (request them from the Statistician);
- Keep your own database (only the Data Management Center database may be used to generate reports).

Please remember that Study Chairs for all new studies or studies in development must attend the Study Chair Workshop. If you are unable to do so, you must view a videotaped version of a Study Chair Workshop. To obtain the video, contact the Protocol Editor to whom you have been assigned.

NCI Cooperative Group Data Monitoring Committee

Changes are under way that will affect the Data Monitoring Committees of all cooperative groups. The National Institutes of Health (NIH) has urged the Cancer Therapy Evaluation Program (CTEP) to change the current membership requirements of the Cooperative Group Data Monitoring Committees (DMC) so that a majority of voting members come from outside of the Group.

An important and distinguishing feature of a clinical trial is that it must be monitored as it is being conducted. Each cooperative group has in place a

Data and Safety Monitoring Board (DSMB) or a Data Monitoring Committee, which monitors the safety and well-being of patients entered on a phase III clinical trial, i.e., that they are not subjected either to unacceptable toxicity or to inferior therapy. These Data Monitoring Committees also consider the economic and scientific need for obtaining definitive trial results in a timely manner for the benefit of medical practices and for future patients.

Following are highlights of the Cooperative Group DMC policy changes. Of the changes, two in particular may affect members of the CALGB.

(1) A majority of the DMC voting members must come from outside the Group. The Committee will consist of physicians and statisticians both from within and outside of the Group. Their selections will be based upon experience, reputation for objectivity, absence of conflicts of interest, and knowledge of good clinical trial methodology. The Committee will also include: a consumer representative and a voting statistician from outside the Group, and a CTEP physician and statistician who will be nonvoting members free to attend all sessions of the DMC. Group members who are members of the DMC are primarily responsible for representing patient interests and not Group or Group Chair interests and must maintain strict confidentiality in regard to all deliberations; and

(2) The routine sharing of confidential trial data, e.g., the statistician's report on the interim trial results, with the Study Chair and the Disease Committee Chair is forbidden until accrual has ceased and all patients have concluded their randomized treatment. At this point, the DMC may approve the release of outcome data on a confidential basis to individuals who are planning future trials, and may consider special requests for information from a Disease Committee Chair prior to accrual cessation.

To reflect the updated policy, three new members have been named to the CALGB's DSMB. They are: Eli Glatstein, M.D., Vice-Chairman, Department of Radiation Oncology, University of Pennsylvania Comprehensive Cancer Center; Steven Piantadosi, M.D., of Johns Hopkins Oncology Center; and Bliss Packer, of Chicago, a consumer representative.

Clinical Research Associate Update

At the CALGB Group Meeting in Miami Beach, Debbie Sawyer of the CALGB Data Management Center reinforced some of the changes in follow-up data submission for Clinical Research Associates. Those changes include:

1) The new five-year follow-up policy (CALGB Policy and Procedures manual section 8.3.3). This policy reads "During the first 5 years after the end of protocol therapy, updates of clinical status must be based on physical examination by a physician. After 5 years, updates can be based on contact with the patient or a patient's relative."

2) Guidelines for follow-up for studies opened before and during 1980. The only required data is the survival status, occurrence of secondary malignancy, and notification of death. Exceptions to these guidelines are CALGB 7951 and 7581. The follow-up schedules stated in the protocol should still be followed for these two studies.

3) Guidelines for follow-up forms (CALGB Policy and Procedures manual section 8.1.1.3.A.2). As an example, if follow-up forms are to be submitted after every two cycles of treatment, the first form should cover the period from day one of treatment though the day on which cycle 3 begins. The next follow-up form "from" date would be the same as the "to" date on the previously submitted form. In essence, this is an overlapping of dates. This procedure ensures the complete capture of toxicity data for an entire two-cycle time period. A copy of the previous flow sheet may be used to continue entering the current follow-up form documentation. In addition, a new follow-up form should be submitted when a patient enters a different phase of the study or begins a different regimen.

4) The new C-300 Off-Treatment Notification form. This form is being utilized in newer CALGB studies. Submit C-300 only if required by the protocol.

Ms. Sawyer reminded everyone that SWOG had expanded its race/ethnicity codes. When registering to SWOG-coordinated studies, their race/ethnicity coding must be used. These were distributed in the 4/15/96 Central Office Mailing. Finally, Ms. Sawyer stated that radiation therapy materials (films, photos, etc.) should not be sent to the CALGB Data Management Center, which is listed incorrectly in several CALGB Intergroup protocols as the location to which these materials should be sent. Resolutions to this problem are being discussed with the cooperative groups coordinating the involved studies.

P H A R M A C Y

MONOCLONAL ANTIBODY 17-1A

by Mark A. Campbell M.S., R.Ph., Oncology Pharmacist, Kaiser CCOP, San Diego, California

For health care professionals wondering what options are available for patients with Dukes' B₂ colon cancer, CALGB 9581, "Monoclonal Antibody 17-1A versus No Adjuvant Therapy Following Resection for Dukes' B₂ Adenocarcinoma of the Colon," will be open soon.

In 1990, the National Institutes of Health recommended that adjuvant therapy following resection of Dukes' B₂ colon cancer should not be considered the standard of care.¹ This decision was based on studies that failed to show a clear advantage for adjuvant chemotherapy over observation after surgical resection. This perceived lack of efficacy may, however, have been due to the small number of B₂ patients that were enrolled in these research efforts. Also problematic was the inadequacy of available pathologic staging parameters to determine which patients could benefit from adjuvant treatment.

Advances have occurred in this area over the last few years. Recent studies have observed that patients with 17p and 18q deletions are more likely to develop distant metastases.^{2,5} Another series of studies proposed that overexpression of the p53 gene was a prognostic determinant.^{6,8} Also, the presence of DNA aneuploidy had been correlated with prognosis and response to treatment in colon cancer and with 17p deletion, particularly in patients with Dukes' B₂ tumors.⁵ It is uncertain, however, whether these characteristics add any substantive prognostic information compared to pathologic stage, tumor grade, and preoperative carcinoembryonic antigen (CEA) levels.

With the evolution of novel immunocytochemical methods, metastatic epithelial cells can be detected in the bone marrow during early occult stages of tumor dissemination. A study by Lindemann et al.⁹ showed that these disseminated epithelial tumor cells in colorectal cancer can be strong, independent predictors of later clinical relapse. These particular cells can be targets for monoclonal antibodies because of their unshielded location

and low tumor load in the early postoperative period. Additionally, the cytotoxic effect of monoclonal antibodies is independent of the cell cycle, which is ideal since the majority of the micrometastatic cells may be noncycling or dormant and tend to be resistant to antiproliferative cytotoxic agents.^{10,11}

Monoclonal antibody 17-1A (MoAb 17-1A) is a murine monoclonal IgG2a antibody, produced from a murine hybridoma. It recognizes a 37-40 kiloDalton cell surface glycoprotein that is expressed on malignant and normal epithelial cells, including adenocarcinomas such as colorectal, breast, ovarian, and prostate cancers. The function of the 17-1A antigen is unknown. However, data suggest that it may be involved in cellular adhesion to the extracellular matrix in a manner similar to nidogen.¹² The antigen is not shed from the membrane and is not detectable in the serum.¹³ Monoclonal antibody 17-1A appears to work by mediating tumor suppression through antibody-dependent, cell-mediated, and complement-dependent cellular cytotoxicity that allows it to preferentially target and lyse cancer cells.¹⁴

Following a single infusion of monoclonal antibody 17-1A, the plasma half-life is 20-24 hours with a range of 15 to 48 hours.¹⁵ With colorectal carcinoma, there are 1 x 10⁶ CD17-1A antigen binding sites per cell. Only 0.01% to 1% of the infused monoclonal antibody reaches the tumor.¹⁴

Phase II studies of monoclonal antibody 17-1A in metastatic colorectal cancer have reported modest success. Sears et al.¹⁶ from Fox Chase Cancer Center treated 20 patients with single doses of MoAb 17-1A, ranging from 200-850 mg. A partial response was reported in three of the patients. Mellstedt et al.¹⁴ treated a group of 52 patients with metastatic colorectal cancer with either MoAb 17-1A (<2 grams total dose), MoAb 17-1A with cyclophosphamide, MoAb 17-1A with autologous mononuclear cells, or MoAb 17-1A (>2 grams total dose). The best

response was in the group with the MoAb 17-1A plus the mononuclear cells where 5 out of 14 patients responded, including one complete response. The median survival time of all the patients in the study was 11.5 months.

The critical study of monoclonal antibody 17-1A in the adjuvant setting was by Riethmuller et al.¹⁷ They randomized a total of 189 patients following resection for Dukes' C colorectal carcinoma to either monoclonal antibody 17-1A or observation. In the treatment arm, patients received an initial dose of 500 mg. of MoAb 17-1A, followed by four doses of 100 mg. at 4-week intervals. After a follow up of 5 years, they reported a 30% decrease in the death rate in the antibody arm (51%-observation vs. 36%-MoAb 17-1A) and a 27% decrease in the recurrence rate in the antibody arm (66.5%-observation vs. 48.7%-MoAb 17-1A). These results are comparable to those obtained with leucovorin/fluorouracil or levamisole/fluorouracil as the adjuvant therapy. The effect of the monoclonal antibody was most pronounced in the patients who had distant metastasis at the first sign of relapse. The antibody was not as effective in preventing local recurrence, which supports the theory that the antibody is highly effective against minimal residual disease.

Therapy with monoclonal antibody 17-1A is generally well-tolerated. The most common toxicities reported with monoclonal antibody 17-1A are diarrhea (2%), nausea and vomiting (1%), abdominal cramps (1%), cutaneous flushing with rash (2%), and fever and chills (1%). Other effects, which occurred at a lower frequency, included: back pain, chest pain, generalized pain, headache, arthralgia, fatigue, dyspepsia, hypotension, hypertension, and tachycardia. Anaphylactic reactions are rare. An incidence of 2.9% was reported in the German adjuvant trial.¹⁷

The formation of human anti-mouse antibodies (HAMA) occurred in 80% of the patients in the German adjuvant

Pharmacy

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trial after the second or third infusion of monoclonal antibody 17-1A. HAMA was detectable in the serum for two years after treatment. Mellstedt¹⁴ theorizes that this response may be of clinical benefit as HAMA forms complexes with the infused murine monoclonal antibody that might bind to the surface of the tumor cells and might be efficient in activating the complement cascade. It should also be noted that HAMA can interfere with CEA levels, although interference is unlikely to occur with the currently available commercial CEA assays unless the serum is analyzed shortly after an infusion of the monoclonal antibody. An elevated CEA level with elevated HAMA levels may represent a false positive assay rather than recurrent disease.

Monoclonal antibody 17-1A comes from the NCI in 100 mg./10 ml. vials. The solution should be withdrawn into a syringe. The contents of the syringe should be filtered through an 0.2 micron low-protein binding filter into the infusion container. The solution is colorless to light yellow. Since it is a protein solution, it may develop a few fine, translucent protein particles. These particles have not been shown to effect the potency of the antibody. The antibody should be diluted in normal saline 250 ml. in a non-polyvinyl chloride (PVC) container. Since it does not contain any preservatives, the antibody solution should be used within 4-6 hours after dilution.

Prior to administration of the monoclonal antibody, the patient should be

pretreated with diphenhydramine and acetaminophen to avoid fever and flu-like syndrome. Antiemetics for a mild to moderate emetogenic agent should be administered as well. The antibody should be infused over 2 hours through a non-PVC administration set. Following the infusion, the patient should be observed for one hour. Diphenhydramine and corticosteroids may be used to treat urticaria. Epinephrine and corticosteroids should be kept at the bedside in case of an anaphylactic reaction.

CALGB 9581 (Study Chair: Thomas Colacchio, M.D.) is scheduled for activation in Summer 1996. We look forward to the opening of Dr. Colacchio's study and the information that it will provide.

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THE PATIENTS' PERSPECTIVE

Putting People Into Human Subjects Regulation

by Deborah Collyar, President of Patient Advocates In Research (PAIR)

I recently spoke at a conference sponsored by the Office of Protection from Research Risks (OPRR) and the Department of Energy (DOE) for all federal agencies dealing with human subject regulations. Attendees included individuals from the Department of Health and Human Services and the National Institutes of Health (NIH) agencies, the National Cancer Institute (NCI), the Department of Education, the Food and Drug Administration, bioethicists, and many Institutional Review Board (IRB) chairpersons. I was also the first patient invited to speak to them. This lack of patient input during trial development may explain why regulations can sometimes impede, rather than help facilitate, better treatment for people.

Informing people about research and protecting them from unscrupulous practices is critical. The OPRR administers the regulations that govern IRBs. These regulations are highly relevant and quite reasonable, but also as ambiguous as the U.S. Constitution. The problem is one of interpretation. Another problem is that zealotry exists at all levels—OPRR, NCI, cooperative groups, IRBs, and individual investigators. Some researchers have pushed to stop IRB “meddling.” That approach, however, overlooks the fundamental reasons we need protections. While most scientists don’t intentionally hurt people, they can become so focused on the science that they overlook the participants’ needs.

The conference proved to be an eye-opener for all involved. Part of the problem is the messages these agencies are getting from attorneys and bioethicists. Researchers and participants need to infuse reality into the process. I was shocked and appalled when some bioethicists classified “terminally ill” cancer patients as “incompetent.” Our discussions caused lively debate and raised many issues when we applied their theories to real life. For example:

- How do we conduct research in humans if we can’t involve Stage IV cancer patients?

- The feasibility of getting another physician (not nurse or research coordinator), who is not involved in the research, to sit down and explain everything about the clinical trial to the patient in today’s healthcare system.
- Learning from the advances that AIDS activists have made in dealing with human issues, which prove that terminally ill patients *are* competent and that patients can impact the system.

There are a growing number of patients who educate themselves, understand the risks involved, and are willing to take them. However, many times, they are prevented by regulations and the assumption that others know what is best for their personal situation. While protection against excess risk is important, we must stop protecting people against themselves and let them decide what risks they are willing to take.

My presentation focused on issues related to tissue banking that will have the most impact on patients’ lives. As you read through the following points, please think about how you as clinical researchers might incorporate these thoughts into your protocols and procedures as well.

Research Guidelines

Since the public wants to see progress, I warned against impeding research through overprotection. An “us against them” mentality hurts everyone involved, and interaction must occur. I also explained the differences between diagnostic and research materials, and between somatic and germline research. Limiting repositories of tumor tissue to anonymous material won’t solve the problem because of limits on research, and many participants will want to know the results of the study.

Informed Consent

While the intent of informed consent is sound, in the real world, patients view

it more as CYA (cover your aspirations) for institutions rather than as quality information for themselves. People are required to sign a generic hospital consent and are probably unaware of its research clause that allows the institution to perform research on tissue. The current approach to informed consent also scares away many viable candidates, and yet, if they take the drugs outside a clinical trial, they are unprotected and unaware of potential dangers. Here is an interesting analogy: Parts removed from your car are required to be turned over to you by law, but tissue removed from your body must be signed away before the repair can even take place. It is time to match the needs of medicine and people through informed consent.

Protection and Confidentiality

The key to protecting people while allowing them to make appropriate choices for themselves is very simple. **Research information cannot be used against people.** This requires a coordinated effort for legislation that prohibits the collection and use of an individual’s DNA research results by any third party (including insurance companies, employers, government agencies, and social and business entities). If people are worried about losing insurance for their families, they won’t enter clinical trials, and we won’t find the new solutions. I also offered a few suggestions to help limit the amount of accessible information in today’s computerized world:

- Research information must be kept separately from a patient’s regular medical records because medical records are as confidential as your local library book.
- Nucleated cells need protection at EACH location through which they pass—the source, intermediaries, and the final lab.
- If there is any chance that

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Patients Perspective

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somatic tissue will be used for heritable research, a re-consent process must be done.

Participants' Issues

The most fundamental criteria to any policy is the individual's right to choose. They must have good information, but only they can evaluate what will work best for their particular lifestyle. This issue becomes critical when we start discussing whether they want to know test results (like BRCA1). If they choose not to know, no one else should either, including family members. Test results that are validated and under protocols are crucial as commercial tests become available.

Most people want to be educated, but don't know what questions to ask. Informed consent should give them the whole picture in context with the daily risks in a manner that they will understand, not with a lengthy document that explains every horrible thing that might happen.

People also want to know how their tissue will be used and how to restrict that use to specific kinds of research. They should not have to allow insurance companies to review research records in order to get insurance, or reveal what medical tests they've received.

Finally, genetic counseling is crucial to the ramifications of testing. The psychological impact in high-risk families affects everything from treatment decisions to relationships, fears about puberty, attitudes about life, and raising a family. Counseling for BRCA1, for example, should blend the strengths of traditional genetic counseling and HIV counseling. Training is critical for everyone involved; physicians, counselors, participants, and the public. After all, once we decipher the entire DNA map, everyone may be predisposed to some kind of illness. Training like CALGB's genetic counseling program will help us deal with the social issues our scientific discoveries uncover.

PROTOCOL UPDATES

⌘ Protocol Activations

◆ 4/15/96

CALGB 9531: High-Dose Carboplatin and Paclitaxel with G-CSF and Peripheral Blood Stem Cell Support Followed by Surgery and/or Radiotherapy for Stage III Non-Small Cell Lung Cancer: A Phase II Study. Study Chair: Thomas Shea, M.D.

CALGB 9534: Phase II Study of Paclitaxel, Carboplatin, and Radiation Therapy for Inoperable Stage IIIa/IIIb Non-Small Cell Lung Cancer. Study Chair: Wallace Akerley, M.D.

CALGB 9551: Phase II Study of 9-Aminocamptothecin (9-AC/DMA, NSC#603071) in Previously Treated Hodgkin's Disease and Non-Hodgkin's Lymphoma: IWF Grades A-H. Study Chair: Nancy Bartlett, M.D.

CALGB 9565: Phase I Study of Gemcitabine in Patients with Organ Dysfunction. Study Chair: Alan P. Venook, M.D.

◆ 5/15/96

CALGB 9411: Economic Analysis of CALGB 9111: Filgrastim vs. Placebo During Acute Lymphoblastic Leukemia Induction and Consolidation Therapy: A Limited Access Study. Study Chair: Thomas J. Smith, M.D.

CALGB 9665: The CALGB Leukemia Tissue Bank. Study Chair: Michael A. Caligiuri, M.D.

⌘ Protocol Closures

CALGB 9332: A Phase II Trial of Intravenous Navelbine or Intravenous Navelbine Plus Doxorubicin in Previously Treated Patients with Small Cell Lung Cancer. Study Chairs: Diana Lake, M.D. and Elizabeth Johnson, M.D. (2/15/96)

CALGB 9221: A Randomized Phase III Controlled Trial of Subcutaneous 5-Azacytidine (NSC# 102816) vs. Observation in Myelodysplastic Syndromes. Study Chair: Lewis R. Silverman, M.D. (4/9/96)

CALGB 9267: Analysis of Neuroendocrine Markers in Patients with Locally Advanced Unresectable Non-Small Cell Lung Cancer. Study Chair: Stephen L. Graziano, M.D. (4/15/96)

CALGB 9336: Comparison of the Abilities of Videothoracoscopy and Open Thoracotomy to Detect and Remove All Metastatic Tumors in the Lungs of Patients Thought to Have Only One or Two Tumors Based on CT Scan Imaging. Study Chair: Patricia M. McCormack, M.D. (4/17/96)

⌘ Protocol Suspensions

CALGB 9511: A Pilot Trial with Limited Pharmacokinetic Monitoring of Peg-Asparaginase During Remission Induction and Consolidation Chemotherapy for Adult Acute Lymphoblastic Leukemia. Study Chair: Stanley R. Frankel, M.D. (2/16/96)

CALGB 9430: Novel Doublets in Extensive Small Cell Lung Cancer: A Randomized Phase II Study of Topotecan (NSC#609699)/Cisplatin, Paclitaxel (NSC#125973)/Cisplatin, and Paclitaxel (NSC#125973)/Topotecan (NSC#609699). Study Chair: Thomas J. Lynch, Jr., M.D. (3/1/96)

PROTOCOL UPDATES

⌘ Patient Registration Requirements for CALGB 9495/SWOG 9416/INT-0160 and CALGB 9592/RTOG 9309

A reminder for those institutions who would like to register patients to the following studies:

CALGB 9495/SWOG-9416/INT-0160 INDUCTION CHEMORADIO THERAPY FOLLOWED BY SURGICAL RESECTION FOR NON-SMALL CELL LUNG CANCER INVOLVING THE SUPERIOR SULCUS (PANCOAST TUMORS): A PHASE II TRIAL

CALGB 9592/RTOG 93-09 A PHASE III COMPARISON BETWEEN CONCURRENT CHEMOTHERAPY PLUS RADIO THERAPY, AND CONCURRENT CHEMOTHERAPY PLUS RADIO THERAPY FOLLOWED BY SURGICAL RESECTION FOR STAGE IIIA (N2) NON-SMALL CELL LUNG CANCER

◆ **CALGB 9495.** Before an institution can register a patient to this study, the CALGB participating investigators must be approved by the SWOG Study Coordinators. To obtain approval, a thoracic surgeon, medical oncologist, and radiation therapist from your institution must fill out their respective questionnaire found in Appendices 19.4-A, 19.4-B, 19.4-C of the study. All three questionnaires must be faxed to Laurie Druse, CALGB Regulatory Affairs Coordinator, at 312-345-0117. The CALGB Central Office will then fax the questionnaires to the SWOG Study Coordinators for their approval. Once the Central Office has received approval from the Study Coordinators, Ms. Druse will notify the Registrar at the CALGB Data Management Center and your institution. Patient registration can then begin. This process needs to be completed only once for each institution. Once approved, the institution will be able to register patients for the duration of the study. Please note that all three investigators (thoracic surgeon, medical oncologist, and radiation therapist) must be approved before an institution can register patients.

◆ **CALGB 9592.** Before an institution can register a patient to this study, the CALGB participating investigators must be approved by the RTOG Study Coordinators. To obtain approval, a thoracic surgeon, medical oncologist, and radiation therapist from your institution must fill out their respective questionnaire, which is found in Appendix VI:A-C of the study. The same procedure should be followed as in CALGB 9495 described above and, as in CALGB 9495, Ms. Druse will notify the Registrar at the CALGB Data Management Center and your institution when approval has been received.

Please be aware that without the approved questionnaire documentation for your institution, patients cannot be registered to this study. We suggest that institutions submit the three completed questionnaires to Ms. Druse when submitting their IRB approval of CALGB 9592 and 9495 in order to avoid delays in patient registration.

⌘ CALGB 9592

Chemo-Radiotherapy vs. Chemo-Radiotherapy Plus Surgery in Stage IIIA (N2) Non-Small Cell Lung Cancer. Revisions to Eligibility Section. (Issued February 1996.)

This protocol is difficult to accrue patients to because it compares surgery with a nonsurgical arm, and most patients have pre-existing ideas about whether or not they want surgery. Nonetheless, it is now much easier to enter patients on this extremely important, high-priority study. Highlights of the revisions are:

- In the case of a pleural effusion that can be tapped, ONLY ONE (1) thoracentesis is required rather than two.
- Scans may be done up to 42 days (rather than 28) prior to registration.
- Proof of N2 positivity may be obtained by cytology (needle aspiration) or histology (mediastinal node sampling). Biopsy of contralateral nodes is NOT required if the CT scan shows no nodes > or = 1 cm. The documentation of N2 disease may be done up to 56 days prior to registration.
- It is no longer necessary to determine the presence of extranodal extension of N2 disease or of single vs. multilevel nodal involvement.

⌘ Study Funding

Support is available to qualifying institutions for participation in these studies. Payments are made through the main member institution.

- 9170 Febrile Episodes in Neutropenia
- 9254 NHL: Anti-B4-bR Post-ABMT
- 9270 Asprn: Early Stage Colorect. in Hi Risk Pats
- 9293 13-cRetin: 2° Prim. Tmrs (NSCLC) (MDAnderson)
- 9334 Sclerosis: Pleural Effusns- Talc Thoracos. vs Slurry
- 9335 NSC: Video Asstd Wedge Resctn + RT in High risk T1
- 9371 Weight Loss Prgrm of Women w. BR Cancer
- 9399 Prostate Cancer Prevention Trial (SWOG 9217)
- 9473 Trial of Omega 3 Fatty Acids for Cancer Cachexia
- 9484 Linkage Mol & Epidem Br Ca Invest Spec Registry Comp
- 9490 Oral Analgesic Protocol Improve Pain Control?
- 9499 13-cRetin:2nd Prim Tmrs H&N (RTOG 9115/MDACC)
- 9511 PEG-Asparaginase During Chemo for Acute ALL

For more information, contact:

Mary Sherrell

CALGB Financial Officer

(312)702-9856

e-mail: msherrel@midway.uchicago.edu

1996 SPRING GROUP MEETING

Plenary Session Opening Remarks

Group Chairman's Remarks

Dr. Richard Schilsky noted a number of changes are taking place within the Group. At the CALGB Statistical Center, Faculty Statisticians Gina Petroni, Ph.D. and Mark Conaway, Ph.D. have accepted faculty positions at The University of Virginia and will be leaving the CALGB. Gina worked with the Lymphoma and GI committees and Mark with the Prostate and Cancer Control committees.

The Correlative Sciences for Solid Tumor Committee is being reorganized. Since Dr. Ed Liu assumed the Chairmanship of this Committee, its research agenda has blossomed. Dr. Schilsky noted that this Committee has done an excellent job in developing the scientific agenda for the Group in many of the solid tumor areas. To handle the work of the Committee, three Vice Chairs have been appointed: Fummi Olopade, M.D., from the University of Chicago, will be Vice-Chair for Genetics; Debasish Tripathy, M.D., from the University of California, San Francisco, will be Vice-Chair for Biomarkers; and Lynn Dressler from the University of North Carolina at Chapel Hill, will be the Vice-Chair for Pathology Coordination and Administration.

Last Fall, a group of external advisors was convened to evaluate Cancer Control research activities. Among the recommendations they made were to build on the Group's existing strengths and to focus in the broad area of health outcomes research. Because this type of research is approached by different groups in different ways, and because there is a desire for good communications among the groups within the CALGB that are working in this area, a Health Outcomes Research Council has been formed. It will consist of the Chairs of the Psycho-Oncology, Cancer Control, and Clinical Economics committees and the Epidemiology Working Group (Jimmie C. Holland, M.D., Electra Paskett, Ph.D., Jane C. Weeks, M.D., and Dale P. Sandler, Ph.D.). The goal is to create a great deal of cross fertilization across these disciplines, all of which relate to various aspects of outcomes research. Concept

sheets that are developed in one Committee will be shared with others in order to bring all the expertise that can be brought to bear on a particular problem. Dr. Schilsky stated that he is optimistic that with the interaction of these four individuals in a productive fashion that health outcomes research will continue to be a major strength of the CALGB. It is very clear that the CALGB leads the other cooperative groups in a number of areas, particularly Psycho-Oncology and Clinical Economics. This will be an increasingly visible and important activity for the Group in coming years.

Finally, Dr. Schilsky reminded the Group that competing renewal time is upon us. The CALGB is funded primarily by the NCI, and our competing renewal application is due at the NCI on June 1, 1997. This is a very lengthy process, and all components of CALGB will be competing at the same time—the Central Office, Statistical Center, any Committee that has its own grant, and all institutions. In the Fall, first drafts from Disease, Modality, and Administrative Committee Chairs are due, and by December 1996, drafts of institutional grants are due. In January, the Executive Committee will review drafts of grants and provide feedback to PIs. The final versions of all grants are due April 15, 1997, to give the Central Office time to assemble the entire application and submit it by the June 1 deadline.

Appointments

Ted Sztatrowski, M.D., replaces Richard Silver, M.D., as PI at New York Hospital.

Michael Grossbard, M.D., replaces Philip Amrein, M.D., as PI at Massachusetts General Hospital.

Robert Diasio, M.D., replaces Francisco Robert, M.D., as PI at the University of Alabama.

Electra Paskett, Ph.D., Chair of Cancer Control Committee.

Deborah Berg, R.N., Chair of the Oncology Nursing Committee; Shelly Slabe, R.N., Vice-Chair of the Oncology Nursing Committee.

Julie Vose, M.D. Vice-Chair of the Lymphoma Committee.

New Main Members

University of Illinois at Chicago
Chicago, Illinois
PI—Jeffrey Sosman, M.D.

New Affiliate Members

Veterans Administration West Side
Medical Center
Chicago, Illinois
RI—Thomas Ladd, M.D.
MM—University of Illinois at Chicago

Lutheran General Hospital
Park Ridge, Illinois
RI—Brian Samuels, M.D.
MM—University of Illinois at Chicago

Southern Ocean County Medical Center
Manahawkin, New Jersey
RI—Victor Ruiz, M.D.
MM—University of Maryland Cancer Center

Iredell Memorial Hospital
Statesville, North Carolina
RI—Ruby Ann Grimm, M.D.
MM—Bowman Gray School of Medicine

Gaston Memorial Hospital
Gastonia, North Carolina
RI—Steven W. Yates, M.D.
MM—Bowman Gray School of Medicine

Kirkville Osteopathic Medical Center
Kirkville, Missouri
RI—Ralph D. Reynolds, M.D.
MM—University of Missouri Medical Center

Lakes Region General Hospital
Laconia, New Hampshire
RI—Robert J. Friedlander, M.D.
MM—Dartmouth Medical School

✓ MARK YOUR CALENDAR ✓

CALGB 1996 Fall Group Meeting



November 1–4, 1996

Pittsburgh Hilton, Pittsburgh, PA

The Pittsburgh Hilton is located one block from downtown Pittsburgh, and a unique dining and shopping arcade is just minutes from the Hilton. Pittsburgh's new airport is among the world's most efficient, rated one of the nation's top five for service and convenience.

PLENARY SESSION HIGHLIGHTS

AIDS-Related Malignancies

Substituting for Dr. Marie Swanson, who was unable to attend the Spring 1996 Group Meeting, Dr. Lawrence Kaplan, of San Francisco General Hospital, addressed the Plenary Session on AIDS-related malignancies. A subcommittee was established within the CALGB Lymphoma Committee dealing with AIDS-related lymphomas, and recently, the NCI funded a new cooperative group called the AIDS Malignancies Consortium (AMC). About half of the 14 institutions that participate within the AMC are also CALGB members. The Co-Chairs of the AMC are from CALGB institutions—Susan Krown, M.D., of Memorial Sloan Kettering Cancer Center, and Lawrence Kaplan, M.D.

Dr. Lawrence Kaplan stated that his aim in addressing the Spring Plenary Session was to raise the level of interest in AIDS-associated oncology within the CALGB by providing a broad overview of HIV-associated malignancies. He focused on Kaposi's Sarcoma (KS) and non-Hodgkin's lymphomas (NHL) and provided both a clinical- and pathogenesis-based perspective.

Cancers are referred to as being AIDS defining if their incidences increase in the HIV-infected population as compared with the general population. Epidemiologic data indicate an increase in incidence in KS and NHL in the HIV-infected patient population. A broad range of neoplastic diseases are reported in patients who are infected with HIV disease. Many represent the chance occurrence of a malignancy in an individual who also happens to be HIV infected, but for several of these neoplasms, investigators suspect a relationship between the underlying immunodeficiency disease and the subsequent occurrence of a malignancy.

It has often been stated that any neoplasm that occurs in the setting of HIV infection is associated with a poor prognosis. This may not necessarily be the case. For example, HIV-infected patients with testicular germ cell tumors, which is one of the more highly treatable group of neoplasms, have a very high response rate, and the 65% three-year survival is comparable to that of the non-HIV-infected general population. On the other hand, with a neoplasm that is less easy to treat in the general population—e.g., lung cancer—the opposite is true. Here the median survival in HIV-infected patients is only four months despite a median CD4 count of

close to 300. This suggests that prognosis may not be exclusively related to the underlying HIV disease as was previously believed, but that prognosis is dependent upon the type of neoplastic disease.

Kaposi's Sarcoma

The fact that KS is almost exclusively confined to the gay male population has long suggested a sexually transmissible etiology. The recent identification of Human Herpes Virus-8 (HHV8) sequences in a large proportion of KS lesions supports this concept.

In addition, in vitro data indicate that at some level Kaposi's Sarcoma is a cytokine-driven process. A number of cytokines have been implicated, including IL-1 β , TNF α , Oncostatin M, IL-6, bFGF, VEGF, and the HIV TAT gene product. Recent therapeutic efforts have focused on means of inhibiting these cytokine pathways. The suggestion has also been made, based on in vitro and preclinical data, that there may also be some hormonal influence on the pathogenesis of this disease.

Clinically, KS in the setting of HIV infection is an aggressive mucocutaneous disorder that tends to be widespread at the time of diagnosis and to involve visceral sites; visceral disease is often asymptomatic, but when KS involves the lungs, it may cause severe respiratory symptoms, even respiratory failure. The disease tends to have an unpredictable natural history, which makes assessment of response to therapeutic agents difficult. As the disease tends to worsen in the setting of opportunistic infection, some have suggested that this may be due to increases in production of cytokines associated with infection.

Local therapeutic modalities for treatment of KS include: intralesional vinblastine, cryotherapy for the treatment of small, cosmetically unsightly lesions, or the use of local radiotherapy for management of more bulky, locally symptomatic disease.

Effective systemic therapies include alpha interferon or a variety of cytotoxic agents. Although interferon when used as a single agent for the treatment of KS requires high doses (>20 million units/m²) and efficacy is directly related to the level of immune function, combination of lower doses of alpha interferon (1-18 million units) with nucleoside analogs (AZT, ddI, ddC, d4T) has been associated with significantly less toxicity and better response rates at a given level of immune function when compared with high-dose, single agent alpha interferon. Response to interferon tends to be slow, however, making it an inappropriate choice of therapy for individuals with severely symptomatic disease.

Standard cytotoxic regimens include bleomycin/vincristine (BV) and Adriamycin/bleomycin/vincristine (ABV). These regimens can provide effective palliation in patients with extensive symptomatic disease, including individuals with pulmonary involvement.

Novel cytotoxic agents studied in the last few years include the liposomal anthracyclines and Taxol. Liposomal doxorubicin—20 mg/m² every 2 weeks—was compared to the standard ABV regimen in patients with advanced KS. The overall response rate was significantly higher with the liposomal product as compared with the ABV regimen. Taxol has been associated with significant response rates in patients with both untreated and previously treated refractory disease, and toxicities have been low.

More novel approaches to therapy, such as a more pathogenesis-based approach to treatment, are also being explored. Several angiogenesis inhibitors have been evaluated, but so far, none have been effective. A variety of cytokine inhibitors are being examined, and there is interest in antiviral agents,

1996 SPRING GROUP MEETING

AIDS-Related Malignancies

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particularly in view of the potential viral etiology that has been identified for this disease. There is still interest in use of retinoids. A trial of topical *cis* retinoic acid demonstrated a significant response rate in KS patients. An oral form of this drug will soon be studied in a clinical trial.

Non-Hodgkin's Lymphomas

Non-Hodgkin's lymphoma (NHL) is a molecularly heterogeneous group of neoplasms of uncertain etiology. Most have been categorized as either intermediate- or high-grade B-cell neoplasms, and patients present with advanced extranodal disease. Non-Hodgkin's lymphoma generally occurs in 5-10% of the HIV-infected population. The etiology of lymphoma within the setting of HIV is unclear. It appears to arise out of a background of polyclonal B-cell lymphoproliferation. Some tumors appear to be polyclonal and, as in KS, there is a significant body of data suggesting that these disorders may be cytokine driven at some level and overexpression of IL6 and IL10 have been demonstrated in some of these tumors. Overall there's a great deal of molecular heterogeneity in this group of tumors, suggesting that there may be multiple pathways by which lymphoma may arise in this patient population.

Systemic Lymphomas

Problems in the management of patients with systemic lymphomas include opportunistic infections and poor hematologic reserve, which is directly related to the level of immune function. The overall outcome of therapy in this population is disappointing, with complete response rates roughly in the 50% range and median survival falling in the five-to-six month range. Features associated with improved outcome include CD4 counts of over 100, absence of a previous AIDS diagnosis, absence of extranodal disease, and a good performance score. Data from the largest prospective clinical trial conducted in this disease, the ACTG 142 study in which close to 200 patients were enrolled, indicated that patients with

CD4 counts under 100 had a significantly worse prognosis as did those with stage III or IV disease, age over 35, or those with a history of I.V. drug use.

Approaches utilized to get around the problem of poor hematologic reserve in these patients include low-dose chemotherapy, or standard dose chemotherapy with a colony stimulating factor. Both approaches have been associated with less hematologic toxicity in clinical trials.

The ACTG 142 study was a direct prospective randomized comparison of standard-dose mBACOD with GM-CSF support versus low-dose mBACOD with GM-CSF administered only as required for neutropenia. Among the 196 randomized patients, no differences could be demonstrated between treatment arms with respect to response rate, time to progression, or median survival. However, severe toxicities were significantly less frequent in patients randomized to low-dose mBACOD. These toxicity differences were almost all accounted for by hematologic toxicity. Although patients with CD4 counts < 100/mm³ survived longer than did those with fewer CD4 cells, no differences in clinical outcome were observed with respect to treatment assignment within each of these two CD4 cohorts. As a result, our current recommendation is that most patients with HIV-associated lymphoma be treated with some form of dose-modified regimen, e.g., mBACOD or a reduced-dosage version of CHOP.

But how important is it to maintain dose intensity for overall clinical

outcome in this patient population? Although dose-intensive chemotherapy has been studied in phase II clinical trials and has been associated with improved clinical outcomes in patients with better levels of immune function, no randomized comparisons between regimens of varying dose intensity have been performed until recently.

In terms of the new approaches to treatment of this patient population, there are a few novel cytotoxics being studied. MGBG, a non-myelosuppressive agent has been studied over the last two years in patients with refractory disease. A response rate of about 25% has been demonstrated with this agent. Studies of the camptothecins are just beginning. There is also interest in the use of cytokines and cytokine inhibitors, antibodies, and immunotoxins.

There is clearly a long way to go in the management of HIV-associated malignancies. The current focus is on developing more novel, pathogenesis-based approaches to therapy and to learn how to combine those therapies with some of the more standard cytotoxic regimens. It is important to realize that as the potential for improved survival grows in patients with HIV disease as a result of improvements in anti-retroviral therapies and antibiotic prophylaxis, prognosis in patients with HIV-associated neoplasms is going to become more dependent upon the underlying malignancy rather than the underlying immunodeficiency disease. It will be up to us to try to develop more effective approaches to the management of these diseases.

To mark the 40th anniversary of the CALGB, all of the Group Chairs, past and present, were in attendance at the Plenary Session. From right to left: Drs. O. Ross McIntyre, Richard L. Schilsky, Emil Frei, III, and James F. Holland.

PLENARY SESSION HIGHLIGHTS

Reflections on 40 Years of the CALGB

To celebrate the 40th anniversary of the founding of the CALGB, three of the Plenary Session's speakers were the former CALGB Group Chairs—Drs. Emil Frei, III, James F. Holland, and O. Ross McIntyre. They reflected upon their tenures with the CALGB and commented upon strides that the Group has made in cancer research and factors affecting clinical cancer investigators today. Following are excerpts of their addresses.

Emil Frei, III, M.D.

Dr. Emil Frei's plenary session address focused on the past achievements of the CALGB and offered insight on what course the Group should chart for the future. Dr. Frei began by sharing with the Group a term coined by Dr. James Holland: "Rainbow Vision." By this he meant the ability to perceive the outlines of the distant shores by a vision, like a rainbow that arches over the obstacles to the goal. The Group's first vision was that one would be able to apply scientific methodology to clinical trials. The goal was to cure cancer. The greater the vision, the greater the obstacles; and there was no shortage of obstacles in the late 1950s. The main obstacle was the disease itself. It has been the Group's fundamental challenge and obstacle for 40 years.

Within the United States at the time, there was a bias against research protocols. It was deemed unethical to subject patients to a scientific method that prescribed treatment in advance. It was more desirable to treat each patient individually, without the prejudice or constraints of a prospective protocol. Also, protocols often required more in the way of procedures, such as bone marrows and lumbar punctures.

There was an anti-science bias. In those days, those who shared the vision were advised that the biologic and pharmacologic sciences had not developed enough to warrant a major investment in clinical therapeutic research. And finally, there was an anti-cure bias. No cancer had ever been cured by chemotherapy; the magnitude of the pessimism was sounded by a famous pathologist who concluded a 3-day meeting on cancer therapy with the following: "finding a drug that can cure cancer is like finding a drug that can dissolve off the left ear and leave the right intact."

It remained for Dr. Gordon Zubrod, Clinical Director at the NCI, to express the incremental approach, which encompassed such factors as control of bleeding with platelet transfusions and increased complete response rates with combination chemotherapy. He postulated that a certain number of increments would be required to pass the cure barrier. Beyond and through the obstacles was the pot of gold at the end of the rainbow—the cure for acute lymphocytic leukemia and the establishment of many of the principles of cancer therapy that remain fundamental today for the treatment of all cancer.

There were many firsts that were achieved. They included: the science of the clinical trial; the definition of complete response, and that complete response correlated with survival and was therefore a surrogate endpoint; the increase of complete response with combination chemotherapy; the remission model, i.e., the use of addressing micrometastatic disease—the first really adjuvant study—by treating patients in complete remission; and the use of that model to evaluate new agents and dose combinations. Among the major contributors to this progress, who are no longer members of the CALGB, include Drs. Jay Freireich, Ed Gehan, and Don Pinkel.

After serving as Chairman of the ALGB from 1956–1964, Dr. Frei returned as Chairman in 1981, and James Anderson, Ph.D., became the Group Biostatistician. The Executive Committee developed a more focused vision, which included quantitative studies of the impact of dose and neoadjuvant chemotherapy and, most particularly, the development of a basic science program within the Group. These were controversial issues of the 1980s and

required a vision that would rainbow over some of the immediate obstacles and pessimism. The results of these studies were 1) the demonstration that high-dose Ara-C substantially increases the cure rate in patients with AML under the age of 60; 2) that a twofold difference in dose of CAF makes a highly significant difference in relapse-free survival of patients with node positive primary breast cancer; 3) that neoadjuvant chemotherapy applied prior to local therapy in patients with stage III non-small cell lung cancer increases the cure rate; and 4) the transfer of numerous seminal contributions in the molecular, immunologic, and cytogenetic pathobiology of the leukemias from the laboratory to the clinic. Dr. Clara Bloomfield pioneered and continues to lead this important scientific effort.

Dr. Frei then posed the question: What should be the CALGB's vision as we approach the millennium? He stated that clinical and scientific prospects have never been brighter. The revolution by molecular medicine is proceeding with extraordinary rapidity, and novel therapeutic targets that are being discovered make it a certainty that treatment will be increasingly specific for the tumor and less toxic for the host. With increasing knowledge and understanding of the mechanisms of sensitivity and resistance, it should be possible to perform a profile of molecular tests on the tumor biopsies and to select treatment on that basis.

A major impediment to clinical cancer research that influences the directions of the CALGB's research—and the resources to do that research—is managed care. Investigators have been extensively educated and trained to implement studies aimed at curing cancer. Yet today, the agenda for the future of medicine and for clinical cancer research is increasingly con-

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trolled by the directorship of HMOs. Dr. Frei urged that Group members should be concerned about cost effectiveness. The perturbations of health care delivery at the patient level that have resulted from the HMOs have been enormous and time consuming. We need to regain the freedom to focus back on the real enemy: cancer.

How do we get over the rainbow? One possible way is that the leadership of the CALGB should meet with the leadership of other cooperative groups to develop a common agenda. Together these groups represent the majority of cancer care givers. The other generalists, specialties, and subspecialties should be encouraged to do the same. Training is also important. Clinical oncology trainees enter practice and research in complex medical and scientific areas, but few are trained to deal with managed care and the many ramifications of public health. Role models, training tracks, and resources for such training for selected young M.D.s are vitally important.

As a Group, the CALGB ultimately has power if it seizes that power and organizes behind a common vision. Dr. Frei concluded by saying: "We were told it couldn't be done in 1956 when we cured leukemia, and yet again in 1985 when we set out to integrate science directly into our clinical trials. Given the vision, we can do it."

James F. Holland, M.D.

For his Plenary Session address in recognition of the CALGB's 40th anniversary, Dr. James Holland recalled the events that led to the formation of the CALGB and highlighted some of the notable achievements in the field of clinical oncology that the Group has been instrumental in bringing to the scientific community. In 1953, with the intellectual input of Dr. Lloyd Law, Dr. Holland began to study combination treatments in acute leukemia in children

in clinical trials at the NCI, which were the beginnings of the cooperative group structure. The late Mary Lasker successfully lobbied for the creation of the Cancer Chemotherapy National Service Center (CCNSC) to fund cooperative research endeavors. In 1956, a Clinical Studies Panel was established at the CCNSC to organize the cooperative group efforts, from which evolved several groups, including the Acute Leukemia Group A and the Acute Leukemia Group B (ALGB), the precursor of the CALGB. The Acute Group A is now the Children's Cancer Group.

After Dr. Holland's departure from the NCI to go to Roswell Park, Dr. Gordon Zubrod recruited Dr. Emil Frei, III, to continue the work at the NCI in acute leukemia. It was through Dr. Zubrod that Drs. Frei and Holland were introduced and Dr. Holland commented: "Gordon was the grease that put Tom and me together."

The ALGB's first study was published in 1958, the first cooperative clinical trial in cancer to be published in the U.S. The study compared two regimens of combined chemotherapy for children with acute leukemia. Of great importance was the finding that the small number who achieved complete remission benefited from the therapy. These patients lived for as long as a year and a half, which was unprecedented at that time.

Next, the ALGB undertook a study in dose scheduling, after vincristine + prednisone induction therapy, the first use of this regimen in a multi-institutional program. The remission induction frequency was 80%. Those in complete remission were randomized to methotrexate, 30 mg/m² IM twice weekly versus the standard 3 mg/m² PO daily. A fourfold longer remission was achieved in the intermittent high-dose arm, with some children living more than five years. The high-intensity dosing that was first explored within the ALGB is still a part of protocol design today.

Study 6601 was designed by the ALGB, a factorial design with eight arms in which patients received, after induction, methotrexate with vincris-

tine and prednisone reinforcement. While some arms were closed because there weren't enough patients, the intensive methotrexate arm with vincristine and prednisone reinforcement showed much better results than any previous results.

In a 1972 article published in the *New England Journal of Medicine*, Dr. Holland and Oliver Glidewell, Ph.D., the ALGB Biostatistician, published the results of protocol 6801, which tested vincristine and prednisone induction and consolidation with combination methotrexate and 6-mercaptopurine, with intrathecal methotrexate. This treatment is still the basis of many of today's treatment protocols.

Other important events were occurring during the 1970s that had an impact on clinical cancer research. Many of the ALGB's studies were realized because of federal support. During this period, President Nixon was planning to decrease the NCI budget. Mrs. Lasker again leaped into the fray and mobilized her political resources and galvanized support in both houses of Congress for a war against cancer. When enacted, the bill became the National Cancer Act of 1971 and a major increase in funds became available for cancer research. Dr. Holland pointed out that Senator Ted Kennedy, who proposed the bill, does not get enough credit for the National Cancer Program.

In the 1980s, Dr. Holland came to the conclusion that a chemotherapist should think of tumors in three categories: curable; subcurable, those that require another discipline; and precurable. He stated that there are no incurable cancers; only oncologists who have not yet learned how to cure them. Curable cancers, as of 1980, included: choriocarcinoma; Burkitt's tumor, Hodgkin's disease; acute promyelocytic leukemia; large follicular center cell lymphoma; diffuse histiocytic lymphoma; and embryonal carcinoma of the testes. Subcurable tumors without regional therapy comprised: acute lymphocytic leukemia of adulthood; acute

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myeloid leukemia; and hairy cell leukemia, which today appears to be curable in about 50% of the cases. Subcurable cancers with regional therapy include: Wilms' tumor; osteosarcoma; squamous cell carcinoma of the upper digestive tract; adenocarcinoma of the ovary; and adenocarcinoma of the breast.

Dr. Holland stated that the Group has spent a great deal of time over the past 40 years looking at dose. He thinks that we have to look to the future for new factors that could lead to major advances in cancer therapy. We now are fully aware of oncogene activities, and what is needed are gene repressors and drugs that elicit tumor suppressor gene activities.

The CALGB's work is of world-wide importance—what we do in cancer research influences the entire world. To conclude his remarks, Dr. Holland shared his version of the 10 commandments for the Group.

1. Honor the Group.
2. Honor your comrades who also battle cancer, whatever their weapon, for one day they might deliver the essential stroke.
3. Thou shalt not lie down with pot boilers; wrestle with the big problems.
4. Thou shalt not be content with the old ways. Create new leads and bring them to the Group.
5. Thou shalt randomize only when in doubt; some truths are self evident.
6. Thou shalt gird thy loins for the sacred quest: Cure cancer.
7. Thou shalt unsheathe the terrible swift sword of the Group to prevent cancer.
8. Thou shalt leave a trail of thy labors; finish studies and publish.
9. Thou shalt remember that the mind is the only organ function affected in every patient with cancer; embrace it.
10. Honor thyself, for thou art involved in noble strife; the taste of victory is sweet.

O. Ross McIntyre, M.D.

Dr. O. Ross McIntyre's remarks for the CALGB's 40th Anniversary celebration focused on the challenges facing clinical investigators today. He highlighted these challenges by placing them within a framework of a historical perspective on the ethics and regulations of clinical research and how these challenges impact investigators today.

Dr. McIntyre pointed out an article published in 1966, ten years after the CALGB began, in the *New England Journal of Medicine* by Dr. Henry K. Beecher, the Chief of Anesthesiology at Massachusetts General Hospital. This article first raised concern in the U.S. about ethics in clinical research. At that time, there were no IRBs, no written consents, no audits, and no costs related to these activities. As a result of Dr. Beecher's article and the activities it galvanized in like-minded individuals, we have the system we live with today.

The article described the "increasing number and variety of ethical errors" in medical research and enumerated 22 examples taken from the medical literature. With a sense of urgency, Beecher called attention to the increase in funding for all medical research, including that performed on humans, as well as the likelihood that new resources and research techniques would increase the risk of harm to research subjects. Beecher manifested an absolute view of what is and is not ethical. He quoted Pope Pius XII in the introduction to his paper, "...science is not the highest value to which all other orders of values...should be subordinated." Clearly, to this Pope science was not a philosophy for exploring and understanding nature but, rather, a value.

Beecher's article concluded with two major recommendations:

- "...the first being informed consent....it is absolutely essential to strive for it for

moral, sociologic and legal reasons."

- "Secondly, there is the more reliable safeguard provided by the presence of an intelligent, informed, conscientious, compassionate responsible investigator."

Dr. Beecher felt that obtaining truly informed consent in many situations was difficult or impossible. That is, many patients cannot understand, remember, or integrate what they are told or what they read concerning the experiment. Dr. McIntyre stated that unless the research community truly strives to reach the goals set in Beecher's second recommendation, patients will not be protected by whatever bureaucracy is established to achieve the first objective.

Dr. McIntyre then provided an example of how "ethical absolutes" change over time. During the late 1930s, his father, a Professor of Pharmacology at the University of Nebraska, worked with investigators at Squibb to develop Intocostin, the first standardized curare preparation for muscle relaxant anesthesia. In the laboratory, mice were lined up with their tails overhanging the edge of the bench top. Progressively stronger dilutions of the raw material were given until a dose was reached that caused the tail to sag, the so called "tail drop dose." Subsequently, the chemists prepared various fractions of the crude material and returned them for further mouse testing. By this approach, it was eventually possible to isolate the active component in pure form.

At that time, as is the case now, the therapy of last resort for severe depression was to apply strong electroshocks to the brain. This was not undertaken lightly, as the tremendous muscle spasms produced by the

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shock caused muscle and bone injury at times, particularly vertebral body collapse. Within days of completion of animal testing of the standardized curare preparation, Dr. McIntyre's father gave it to a psychiatrist who, in turn, used it as an adjunct to anesthesia for electroconvulsive therapy. No written consent was obtained. The report of this experience in 1940 was the first of many on this topic that revolutionized the field of anesthesia.

Shortly after the introduction of muscle relaxants into anesthesia, it was recognized that rare patients metabolized these drugs more slowly than others, and some deaths occurred. These tragedies would not have been prevented by years of additional animal-based research or additional meetings of learned committees. Those developing the field recognized the dangers of this technique in the hands of the inexperienced or careless. The advantage of light anesthesia with muscle relaxants in the hands of the expert was unequivocal, at least so they thought.

In 1954, Dr. Beecher presented a paper, published in the *Annals of Surgery*, that called attention to shifting trends in anesthesia and presented an amalgamation of current anesthesia practice at major teaching centers. However, what the press focused on was Beecher's conclusion that muscle relaxant anesthesia appeared to greatly increase the likelihood of death due to anesthesia.

On the basis of this study, some would have been happy to bar further use of the technique. However, because this paper did not give rise to regulatory dogma, and because some felt it ethical to continue to use an anesthesia that on paper had a sixfold increase in apparent risk of death, the truth eventually came out, and this type of anesthesia is standard today.

Update on Slowly Accruing Studies:

CALGB 9484, which attempts to link biological characteristics of patients with breast cancer with various epidemiological and familial aspects, is an active protocol that has been slow in accruing patients. The study is funded by the U.S. Army and the Department of Defense (DoD). At the Plenary Session, O. Ross McIntyre, M.D., Study Chair for CALGB 9484, discussed some of the difficulties this study has been experiencing and posed some ways to boost accrual and move the study forward.

Dr. McIntyre began by suggesting an analogy between ancient soothsayers, who were consulted on what the future held in store, and the scientific community's version of the soothsayer who, in today's society, is the individual who can look at a patient's genomic DNA and predict whether that individual is predisposed to certain diseases. Breast cancer is a disease in which the scientific soothsayers are becoming active. With the BRCA1 gene, the present-day soothsayer can correctly predict 85% of the time that a carrier of this gene will get breast cancer. What is also of importance is that 15% of the patients with this gene do not develop breast cancer. Additionally, some who carry the gene may develop breast cancer at age 25 while others may develop the disease at age 65. There are still many things the soothsayers cannot explain about the BRCA1 gene. Clearly this is a very complex issue that may be entirely dependent upon the presence or absence of other genes or may hinge upon such factors as environmental exposure and reproductive and dietary histories.

The goal of CALGB 9484 is to allow the Group to define, in a large number of patients already diagnosed with breast cancer, what that person's genomic makeup is, to what environmental factors she was exposed, and to examine her diet and reproductive history. This information is gathered in the context of patients' response to treatment they received on CALGB breast cancer treatment protocols and how long they were in response. In addition to supporting the collection of genomic DNA, tissue blocks, plasma, and urine samples, the project—with funding from the Army—supports a detailed phone interview. Patients who are going on

other CALGB treatment studies are interviewed in order to obtain a careful family history, which is often lacking in hospital charts, and to detail each woman's dietary and reproductive history.

Protocol 9484 was opened in June 1995, and as of the Spring Group Meeting in May 1996, 20 patients were entered, and 31 institutions had approved it. During this same time, hundreds of patients were entered onto the CALGB's primary breast cancer treatment protocols. It is important to obtain genomic DNA information, exposure history, etc., on as many patients in CALGB breast cancer treatment trials as possible to allow later analysis of these factors. They may prove important in the outcome of treatment and, ultimately, they may allow investigators to become better soothsayers with respect to what will happen to a person based upon her genetic makeup.

One of the problems that has been encountered in getting this protocol activated is that, as written, it allows for results concerning genomic DNA to be conveyed back to the patient, should she wish to know the results. Institutions also receive the test results, and another problem that has arisen is how institutions will handle the results once they receive them. There are numerous other issues. At the February 1996 Core Meetings, it was pointed out that a person wishing to know if she has a familial breast cancer gene can find this out since there are now commercially available tests that will provide that information. However, because the CALGB will be performing tests on familial cancer genes that are not necessarily identified by the commercially marketed tests, and because the CALGB results will flow from a research laboratory rather than a service laboratory, it was suggested that we change the protocol and not provide information back to the institution or the patient. The protocol is in the process of being amended so that we will not have this hurdle to overcome with IRBs. It is hoped that this change will boost the accrual to a level that is commensurate with the number of patients who go on

SPRING GROUP MEETING - RECEPTION

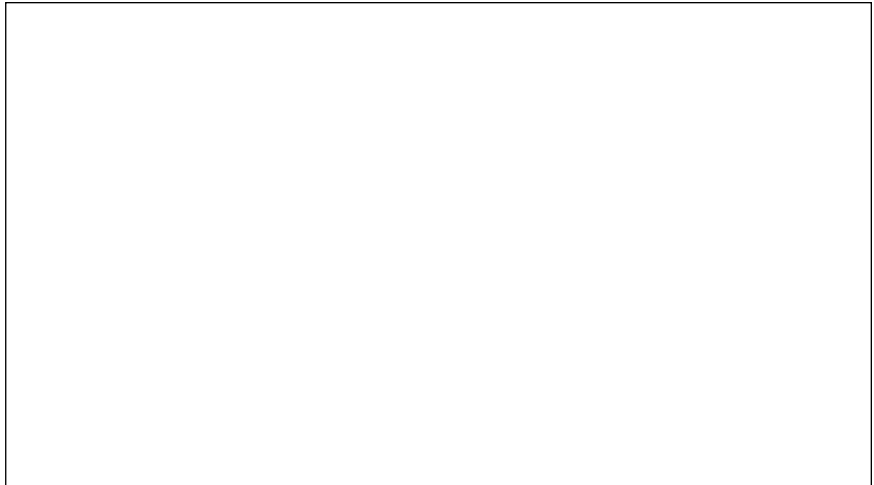
CALGB 9484

other CALGB breast cancer protocols.

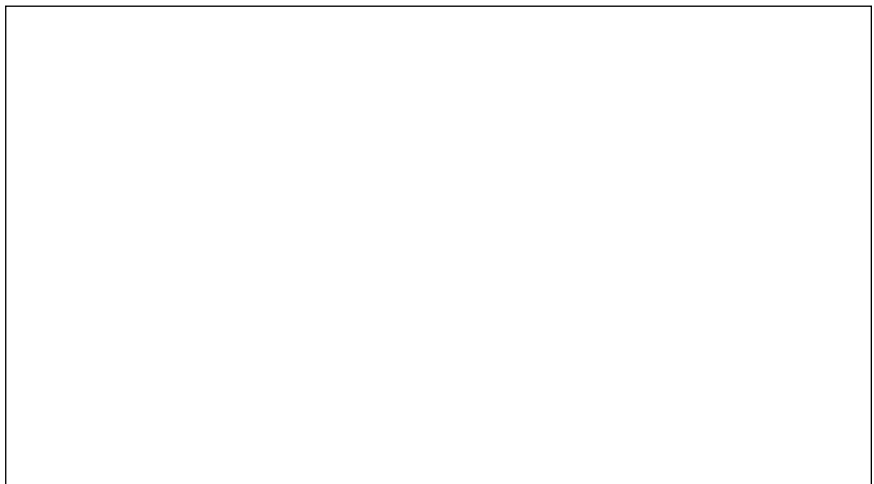
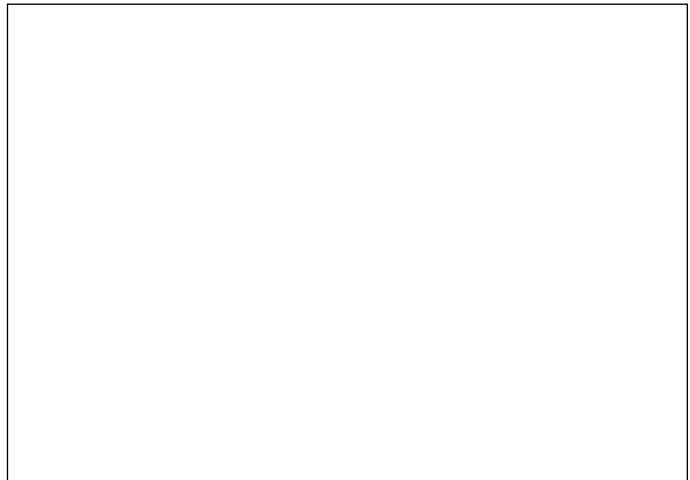
One question that was raised at the Group Meeting concerned the availability of legal counsel in the event that individuals might sue to obtain their test results under the Freedom of Information Act. Dr. McIntyre stated that one option is to get a certificate of confidentiality, which would protect that information. However, as originally written, the protocol offers to furnish information to almost 200 institutions. The agency that grants certificates of confidentiality is overwhelmed by the idea that there is such a large amount of information that would need to be retained as confidential. If we can amend the protocol so that information resides only in the CALGB database, it would be relatively easy to get a certificate of confidentiality protecting the database from discovery.

Another question that was raised was why so many IRBs do not want to approve this protocol. The DoD requires a statement in the protocol consent form that differs from the consent statement in a typical NIH-supported research study. The NIH allows an institution to state that if an individual is injured or made ill by participating in a research study, the institution will offer medical assistance to correct the medical problem. However, the standard language in a DoD consent form says that if a patient is injured as a result of participating in a research study, the Army or its contractor will correct the problem; in this case, the contractor is Dartmouth College. Dartmouth has had a major problem with this, but since the research involves administering a telephone questionnaire and drawing some blood, the likelihood of a suit is small. Dr. McIntyre said that he is attempting to have the DoD remove this clause, but that in any event, the risk to any institution is so small and the types of injuries so remote that we shouldn't let this stall the study.

Dr. McIntyre warned that the CALGB's funding will be in jeopardy if this study does not get under way. It is a tremendous opportunity for the Group to learn about the nature vs. nurture issues that exist for all of us.



At the Spring Group Meeting reception, Drs. Arthur Sawitsky, Mark Green, and Emil Frei, III (l to r. above) enjoy the ambiance of the historic Biltmore Hotel. CALGB Group Chair Richard L. Schilsky, M.D., (center, left) discusses the days' events with CRA Anita Johnson and Group Statistician Stephen George. Meanwhile, Drs. O. Ross McIntyre, L. Herbert Maurer, and Wallace Akerley (l to r. below) reminisce and catch up on events since the last Group Meeting.



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