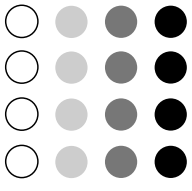


Progress
Review
Groups

Conquering Colorectal Cancer:

A Blueprint for the Future

April 2000

NATIONAL® CANCER INSTITUTE

From the Leadership

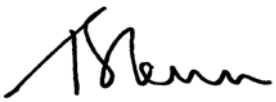
It is with great pleasure that we transmit the Report of the Colorectal Cancer Progress Review Group to the Advisory Committee to the Director of the National Cancer Institute. This assessment of the Institute's progress in colorectal cancer research was undertaken at the request of NCI Director Dr. Richard Klausner.

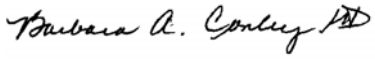
The overall goal of the PRG was to develop a national plan consisting of a description of ongoing scientific activities and investigations relevant to colorectal cancer research and to provide the Institute a list, in priority order, of scientific opportunities that should be pursued.

As leaders of this important effort, we were pleased to serve with a committee of prominent members of the scientific, medical, industrial, and advocacy communities. Our colleagues represented the full spectrum of expertise needed to develop the comprehensive recommendations you will find in this report. We believe that the hard work of this PRG has resulted in recommendations that, if pursued, will do much to eradicate morbidity and mortality due to colorectal cancer.

It is our hope that these recommendations, reflecting the extensive and diligent work of the members, will prove valuable in our shared quest to further reduce the toll of human suffering and death due to colorectal cancer. We look forward to following the progress of the many recommendations made in this report and discussing them with you and the leadership of the National Cancer Institute.

Respectfully,





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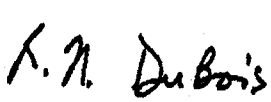
We the undersigned members of the Colorectal Cancer Progress Review Group concur with the enclosed report.



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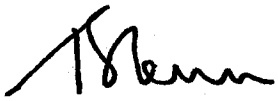

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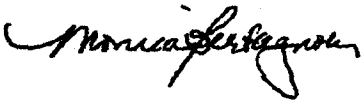

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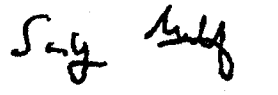

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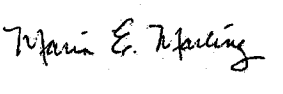

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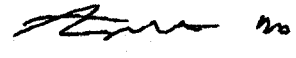

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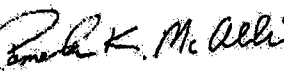

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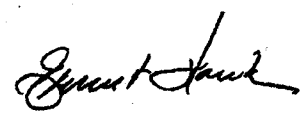

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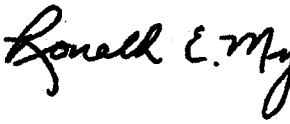

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Acknowledgements

This report is the result of seven months of intense work, drawing upon the combined skills and efforts of many people. Special thanks are extended to the following:

First, we thank the researchers, clinicians, and members of the patient advocacy community who participated in the Colorectal Cancer Roundtable meeting in San Francisco. It was there that the groundwork for this report was laid.

Dr. Barry Kramer, a PRG member, went "above and beyond" the call of duty in providing careful editorial oversight for each chapter of this report, while Dr. Julia Rowland provided extensive and much-appreciated input into the Cancer Control and Survivorship chapter. We also thank Dr. Harold Moses for his inspiring words to the Roundtable participants.

The Progress Review Group benefited from the exceptional staff support and expertise of the Office of Science Planning and Assessment (OSPA), including Dr. Susan Rossi, PRG Team Leader; Program Analysts Kate Nagy and Annabelle Uy; and Program Support Staff Marilyn Duncan and DJ Joya.

In addition, the PRG was fortunate to have the outstanding scientific writing expertise of Lead Writer Deborah Shuman, Co-Lead Eleanor Mayfield, Suzanne Reuben, and San Francisco-based writers Lauren John, Dan Liberthson, Devi Mathieu, and Sheila Stavish. Josette Johnson, Akia Hardnett, and Jessica Harrison provided gracious and helpful logistical support on behalf of Palladian Partners, Inc.

Finally, we offer our heartfelt thanks to the members of the Colorectal Cancer PRG. The success of this document is a testament to their knowledge, insight, and dedication.

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About the National Cancer Institute's Progress Review Groups

The National Cancer Institute (NCI) supports basic, clinical, and population-based research to elucidate the biology, etiology, early detection, prevention, and treatment of cancers of various organ sites. These research efforts have produced a substantial base of knowledge about these cancers that, while providing a wealth of new scientific opportunities that can further advance our knowledge, also requires that limited resources be used to their optimal advantage. To that end, the NCI establishes expert groups to undertake a review of the Institute's cancer research portfolios for the various organ sites and to assist in planning a research agenda to move the field forward toward the next century of progress.

Progress Review Groups (PRGs) have been established to assist the NCI in assessing the state of knowledge and identifying scientific opportunities and needs within its large, site-specific research programs. PRGs fit within the NCI's new overall planning framework, which embraces the use of expert panels and includes the establishment of Working Groups, which are specifically focused on aspects of scientific discovery and technology, as well as more broadly focused Review Groups.

Charge to the PRG

PRGs are charged with assisting the NCI in addressing research specific to various organ sites and comprise prominent members of the scientific, medical, and advocacy communities. These experts outline and prioritize a national research agenda for cancer of a particular organ site, taking a broad view in identifying and prioritizing unmet scientific needs and opportunities that are critical to the advancement of the research field. PRGs are specifically charged with the following:

1. Identify and prioritize scientific research opportunities and needs, and the scientific resources needed to address them, to advance medical progress.
2. Compare and contrast these priorities with an NCI-prepared analysis of its cancer research portfolio.
3. Develop a research plan of action that addresses unmet opportunities and needs.
4. Prepare a written report describing the PRG's findings and recommendations for deliberation by the Advisory Committee to the Director (ACD) of NCI.

To execute these charges, the PRG convenes forums in a given area of cancer research to identify and prioritize the scientific needs and opportunities that must be addressed in order to advance progress against the disease. As part of this effort, input is solicited from the research and advocacy communities through workshops, ad hoc groups, and other means. The PRG may also consider the deliberations of previously convened expert groups that have provided relevant cancer research information.

This report is the final product of the PRG's efforts and deliberations. It describes the group's findings and recommendations for advancing research on cancers of a specific organ site. The following section details the process used in producing this and other PRG reports.

The PRG Process

PRG members are selected from among prominent members of the scientific, medical, and advocacy communities and from industry to represent the full spectrum of scientific expertise required to make comprehensive recommendations for the NCI's cancer research agenda. The membership is also selected for its ability to take a broad view in identifying and prioritizing scientific needs and opportunities that are critical to advancing the field of cancer research.

The PRG Leadership finalizes an agenda and process for a PRG Planning Meeting. At the Planning Meeting, participants are identified to take part in a subsequent Roundtable meeting. Approximately 12 topics are identified for Roundtable breakout sessions to which those participants will ultimately be assigned and for which the PRG members will serve as co-chairs.

A PRG Roundtable Meeting brings together approximately 150–180 leading members of the cancer research and advocacy communities. These experts meet in an open forum in which they formulate key scientific questions and priorities for the next 5–10 years of research on cancer of the organ site(s) under review. Input from the Roundtable is used by the PRG in delineating and prioritizing recommendations for research directions, related scientific questions, and resource and infrastructure needs.

As part of this process, the NCI provides the PRG Roundtable with information about its research program by preparing an analysis of its portfolio of cancer research in the relevant organ site. This analysis does not serve as a critical review of the NCI's research program, but rather is used to compare and contrast the Roundtable's scientific priorities with the research currently being done under the Institute's auspices. On the basis of this review and analysis, the PRG recommends a plan of action to ensure that the recommended priority areas are thoroughly addressed. Recommended actions may be, for example, to shift emphasis; to develop new resources or infrastructure; to issue Requests for Applications, Program Announcements, or Requests for Proposals; or to collaborate with the ongoing efforts of other organizations or agencies.

Development of the PRG Report

After the Roundtable Meeting, an intermediate draft report is prepared, multiple iterations of which are reviewed by the PRG Leadership and PRG Members. Upon completion of the final draft, the report is submitted for deliberation and acceptance by the NCI Advisory Committee to the Director. Finally, the PRG meets with the NCI Director to discuss the Institute's response to the report, which is then widely disseminated and integrated into the Institute's planning activities.

PRG reports on breast cancer and prostate cancer were completed in 1998 and are available on line at http://osp.nci.nih.gov/prg_assess/default.htm. Other PRG reports currently in development or being planned include reports on brain tumor; pancreatic cancer; leukemia, lymphoma, and myeloma; gynecologic cancers; and kidney and bladder cancer.

Executive Summary

Colorectal cancer accounts for a substantial portion of our national cancer burden and constitutes a major health problem: It is projected that more than 130,000 new cases of colorectal cancer will be diagnosed in the United States in 2000, representing approximately 11 percent of all new cancer cases. Although the incidence of colorectal cancer has declined over the past two decades in the overall population, a concomitant decline in rates of death from colorectal cancer has led to a growing number of people who have survived their cancer and/or are now living with the disease.

In the last two decades, the National Cancer Institute (NCI) has sponsored intensive research into all aspects of colorectal cancer. This research has led to many important discoveries: we understand more than ever before how colorectal cancer develops and spreads, which genetic traits predispose to neoplasia, why some tumors are more aggressive than others, and why some patients are more likely to die of their disease. Our discoveries are leading to more refined technologies for detecting and diagnosing colorectal cancer and to better supportive care and improved outcomes for patients during and after treatment. We are also getting closer to identifying effective strategies for preventing the disease, and we are having some success in finding new therapies to extend survival and improve quality of life.

These advances are significant and provide hope for the future, but we still have far to go to remove the threat of colorectal cancer from patients' lives. More work is needed to translate new discoveries about genetics, biology, and etiology into therapies that extend the survival of those who are now free of cancer and improve the quality of life for those who continue to live with the disease. To help chart the next crucial steps toward these goals, the Advisory Committee to the Director of the NCI has requested that a multidisciplinary Progress Review Group (PRG) on Colorectal Cancer analyze the NCI's current research portfolio on colorectal cancer and develop recommendations for achieving the next decade of progress. This report is the product of that effort.

Background

Colorectal cancers are the third most common cancers in men and women[1]. Between 1985 and 1996, the incidence of colorectal cancer steadily declined in the overall population, although no decline was seen in the U.S. black population. Between 1993 and 1997, the incidence of this disease was 52.4 per 100,000 among men and 37.2 per 100,000 among women. Mortality rates have been declining since about 1985, possibly due to increased surveillance of at-risk individuals, wider use of adjuvant therapy, improved diagnostic techniques leading to earlier diagnosis, and possibly, improved therapy for metastatic disease.

The highest age-specific incidence rates per 100,000 persons are observed in men and women ages 70 years and older. Men in this age group have rates of 323.6 (ages 70–74), 413.1

[1]Statistics provided by the NCI's Surveillance, Epidemiology, and End Results Program (SEER).

(ages 75–79), 506.5 (ages 80–84), and 519.0 (ages 85 and over) per 100,000. Among women, these rates are 225.7 (ages 70–74), 290.2 (ages 75–79), 378.8 (ages 80–84), and 423.1 (ages 85 and over) per 100,000. The oldest age groups experience the highest mortality burden: peak rates reach highs of 332.4 and 263.1 per 100,000 among men and women, respectively, ages 85 years and over (SEER, 1993-97).

African Americans are also disproportionately burdened by this disease, in terms of both incidence and mortality. Overall incidence for African American males is 57.8 per 100,000 (as compared to 52.0 per 100,000 in white males), while African American females are diagnosed at a rate of 44.7 per 100,000 (as compared to 36.8 per 100,000 among white females). Overall mortality rates are 27.5 and 19.7 per 100,000 among African American males and females, respectively, as compared to 20.6 and 13.9 per 100,000 for white men and white women.

These numbers show that colorectal cancer exacts a substantial toll on our society, in terms of both health care costs and human suffering. Yet the means to reduce this burden are within our reach today: It is estimated that current screening recommendations, properly employed, could enable us to avoid 50 percent of colorectal cancer deaths per year. Bridging the gap between those who do and do not get screened is an important goal. Development of new screening technologies and raising the awareness of the public and of health care professionals concerning the importance of colorectal cancer prevention, screening, and early detection are of major significance.

The Colorectal Cancer PRG Roundtable was convened in San Francisco on January 5–8, 2000, to consider these and other matters. Over the course of three and a half days, participants discussed our current understanding of the disease and how best to direct research efforts of the next 5–10 years. Having honed their recommendations into a few top priorities within each of 11 content areas, the Roundtable participants have evolved a clear vision of what will be required to achieve breakthroughs in the development of new technologies as well as the application of existing ones. That vision is reflected in the research priorities enumerated in the following section.

Organization of the Report

The full report of the Colorectal Cancer PRG is presented in two major sections. Section I details priority scientific questions and related recommendations in six major areas of colorectal cancer research:

- Biology
- Etiology
- Prevention
- Early Detection and Diagnosis
- Treatment and Prognosis
- Cancer Control and Survivorship

Section II presents recommendations for overarching and resources issues that represent the direction for colorectal cancer research over the next 5–10 years:

- Genetics
- Environment and Lifestyle
- Partnership Platforms
- Imaging
- Behavioral and Health Sciences Research

In addition, the full report includes several appendices. Appendix A is a listing of priorities identified by various breakout groups but not selected for inclusion among the top three or four priorities. Appendix B shows the estimated NCI support for colorectal cancer research in 1999. A roster of the Colorectal Cancer PRG is provided as Appendix C.

Process

Each of the approximately 180 Roundtable participants was assigned to two of the above 12 breakout groups—one assignment in each of the two areas of scientific content and overarching and resources issues. The scientific content groups met in the morning, and the overarching and resources issues groups met in the afternoon. Within each group, participants were charged with brainstorming research areas, opportunities, and new ideas that will move the field forward. Members were urged to take a broad perspective in considering research areas and opportunities, to share their vision of where the field should be in 5 years and beyond, and to focus on broad research goals rather than immediate, incremental steps following current research results.

On the day following the breakout sessions, the various groups reported to the Roundtable as a whole to present and discuss the top research priorities they had identified. Although each breakout group was asked to develop three priorities, in some cases recommendations could more logically be collapsed into two or necessitated expansion into four priorities.

Research Priorities

BIOLOGY

Alterations in key signaling pathways are responsible for the biologic behavior of transformed colonic epithelial cells. The fact that specific sets of genes are activated via alterations in signaling makes it possible to uncover potential biological targets for therapy. With regard to studies on the biology of colorectal cancer, three high-priority areas were identified:

1. Define the biological controls for the development of normal and abnormal colorectal epithelial development.
2. Define the pathways of progression of colorectal neoplasia.
3. Identify the signaling pathways that are activated in vivo during carcinogenesis.

ETIOLOGY

Gene–environment interactions play an important role in the underlying cause of many cancers, including colorectal cancer. The abundance of data now being generated from the Human Genome Project provides significant opportunities to further delineate the genetic alterations modifying the response to environmental factors that could initiate or promote neoplastic transformation. Three major research priorities were recognized as critical to improving our understanding of the underlying causes of colorectal cancer:

1. Support population-based epidemiologic studies, including special populations, that link genetic polymorphisms, diet and lifestyle variables, and endogenous factors with the molecular characteristics of colorectal cancer and its putative precursor lesions.
2. Validate early and intermediate biomarkers of exposure to environmental influences and genetic polymorphisms.
3. Resequence single nucleotide polymorphism–containing genes involved in carcinogen or hormone metabolism, DNA repair, cell growth control, and immune response and assess their functional polymorphisms in molecular epidemiologic studies in diverse ethnic populations using high-throughput genotyping methods.

PREVENTION

The goal of prevention is to decrease morbidity and mortality from colorectal cancer. In order to achieve this goal, it is important to delay the progression of early neoplasia or reverse or inhibit the development of invasive cancer.

Epidemiologic studies have demonstrated that certain nutritional habits and lifestyle choices are associated with an increased risk of colorectal cancer. Identification of risk factors as well as natural and synthetic agents that modulate cancer risk at the molecular and cellular levels in carcinogen-induced, transgenic, and gene-knockout rodent models are crucial. Three priorities for research in these areas are recognized:

1. Define pathways that can be targets for nutritional and chemopreventive agent interventions.
2. Validate the applicability to early clinical trials of surrogate endpoint biomarkers of colorectal carcinogenesis defined in preclinical animal models.
3. Conduct studies of combined lifestyle and chemopreventive interventions.

EARLY DETECTION AND DIAGNOSIS

The natural history of colorectal cancer, from dysplastic aberrant crypts to adenocarcinoma, offers multiple opportunities for assessment and intervention. The molecular biology and pathology of colorectal cancer are among the best understood of all human cancers. In the future, early detection of premalignant disease is likely to substantially reduce mortality by decreasing its incidence. To that end, three research priority areas have been identified:

1. Support research into short- to medium-term (5–10-year) strategies for effective implementation of currently recommended methods of early detection at the population level.
2. Conduct rigorous clinical evaluation of promising markers and modalities, especially in adenoma detection, before their implementation at the population level.
3. Support developmental research into new markers and modalities and improvements of current methods.

TREATMENT AND PROGNOSIS

Many new discoveries in the last decade have the potential for improving the management of colorectal cancer. Current adjuvant treatments are effective in reducing mortality for some patients but are associated with toxicities, which would be unnecessary for those who could be cured by surgery alone or who have tumors insensitive to treatment. The ability to identify such groups before treatment is initiated would represent a great advance in therapy. Moreover, a better understanding of the genetic changes that occur in colorectal cancer offers opportunities to better define prognosis, improve detection, and understand the likelihood of treatment benefits. Such improved understanding may also lead to the development of new, rational and/or targeted treatment opportunities.

1. Enhance local and regional therapy for colorectal cancer by fostering uniform delivery of accepted treatments and the development of new treatment regimens.
2. Expedite new drug development by identification of intermediate endpoints and surrogate markers of response that help to define mechanisms of action and predict clinical efficacy.
3. Comprehensively characterize the biological features of both host and cancer in order to discover new indicators of prognosis and of the likelihood of response to chemotherapy and radiation.

CANCER CONTROL AND SURVIVORSHIP

Cancer control is the conduct of basic and applied research in the behavioral, social, and population sciences that, independently or in combination with biomedical approaches, reduces cancer risk, incidence, morbidity, and mortality. Because the use of cancer screening techniques relies heavily on their acceptance and appropriate use by both health care professionals and the general public, the role for cancer control research in reducing the colorectal cancer burden is significant. To further reduce the burden of colorectal cancer, a vigorous and substantial commitment to basic and applied cancer control research, conducted by scientists from diverse disciplines, is needed. To be successful, this must embrace an approach to research that addresses the behavioral, social, and population factors that affect disease across the continuum of health and illness: from monitoring, prevention, and surveillance in healthy and at-risk individuals; to early detection, treatment, symptom management, and follow-up of those diagnosed; to the provision of compassionate palliative care to those with metastatic disease or dying of their illness.

1. Conduct studies to identify the best standards of follow-up care after successful treatment of colorectal cancer, focusing attention on which tests give the most information about important outcomes such as resectability, survival, cost, and psychosocial distress.
2. Develop mechanisms for identifying people at risk for adverse psychological distress and investigate whether psychosocial factors affect compliance with diagnostic and therapeutic regimens and outcomes (e.g., overall survival, cause-specific survival, disease-free survival, and quality of life).
3. Assess the effectiveness of colorectal cancer screening, prevention, and treatment in elderly and special populations.

GENETICS

Key genes responsible for encoding the proteins involved in the pathways that are important for neoplastic initiation and progression of colonic epithelial cells have been identified. This work has led the charge for research on the genetic basis for cancer in general. Three key priorities have been identified to maintain the momentum and continue our progress in understanding the genetic basis for colorectal cancer and to translate this information into clinical trials and clinical practice:

1. Identify the genes that predispose to colorectal cancer (including major and minor alleles of known predisposing genes).
2. Determine how morbidity, quality of life, and mortality are affected by genetic screening and interventions to address human issues (e.g., counseling, disclosure issues).
3. Determine whether there are specific tumor genetic subtypes, how these can be linked to histologic type and other known factors, and how knowledge of such subtypes can be used to improve drug development, intervention selection, and prognosis assessment.
4. Determine how relevant gene targets for new therapeutics can be identified.

ENVIRONMENT AND LIFESTYLE

Better biological markers of exposure variables need to be developed and intermediate biomarkers of risk identified. Integration of screening and epidemiological studies is needed, and collaborations between molecular and population scientists will be essential to achieve the desired level of understanding. Opportunities exist for study of populations at lower risk than that of whites, including Native Americans, Hispanics, and Filipinos, as well as those at higher risk, such as the Japanese in Hawaii. Warranting specific study is the finding that rates of death from colorectal cancer among blacks have not declined. Three specific priority areas warrant further research:

1. Integrate observational screening and interventional approaches in future studies.

2. Improve assessment and characterization of lifestyle and environmental factors.
3. Improve the biological coherence of studies by assessing genetic and environmental factors in studies of the etiology and pathogenesis of colorectal cancer.

PARTNERSHIP PLATFORMS

Greater interaction among the NCI, the Food and Drug Administration, pharmaceutical and biotechnology companies, physicians, and patient advocacy organizations will foster innovative approaches to drug discovery and development. Numerous opportunities exist that can be capitalized on in the near future to enhance such interaction, thus expediting and facilitating the discovery and development of drugs and devices to prevent and treat colorectal cancer.

1. Develop standard agreements for contract or grant award procedures for licensing and intellectual property rights, data collection, and auditing.
2. Develop validated markers of biological activity to facilitate clinical trials, as part of a strategy to link the development of diagnostics and therapeutics.
3. Foster partnerships among oncologists, gastroenterologists, surgeons, and radiologists, as well as pharmaceutical companies, to improve patient access to and facilitate the conduct of clinical trials.

IMAGING

Research support is needed to enhance molecular imaging approaches (radiology and nuclear medicine) to evaluation of disease initiation and progression. Research initiatives include the development of suitable imaging systems, signal amplification strategies, and dedicated imaging systems. Further development of helical computed tomography scanning with two- and three-dimensional reconstruction in screening populations is needed. Although early clinical studies are encouraging, research is needed to perfect the technique in the area of bowel preparation, mucosal contrast agents and computer-assisted diagnosis. Outcomes analysis of the efficiency and cost-effectiveness of new imaging techniques is also critical. Three research priorities have been identified as central to these goals:

1. Apply functional and molecular imaging in the selection of screening, surveillance, and treatment strategies to enhance monitoring of chemopreventive and chemotherapeutic responses.
2. Further refine existing and develop novel imaging technologies for the advancement of colorectal cancer screening, staging, and surveillance strategies.
3. Allow for rapid assessment of the benefits and risks of emerging imaging technologies.

BEHAVIORAL AND HEALTH SERVICES RESEARCH

Despite the availability of effective screening and diagnostic modalities for colorectal cancer, only about 40 percent of the population eligible for screening are actually receiving appropriate screening tests. Four high-priority areas of research will help to understand the problems in this area and lead to improvements:

1. Develop conceptual models and methods that relate to the efficacy, effectiveness, and cost-effectiveness of intervention strategies, including those that increase the use of effective colorectal cancer prevention, screening, diagnostic evaluation, and treatment modalities, as well as those that enhance the quality of care.
2. Characterize variations in patterns of colorectal cancer prevention, screening, diagnostic evaluation, and treatment, including quality of care, for populations, among providers, and in health care systems.
3. Develop and evaluate strategies for (a) improving access to screening, diagnostic evaluation, treatment, and clinical trials and (b) increasing participation in clinical trials of colorectal cancer prevention, screening, diagnostic evaluation, and treatment.
4. Develop and test strategies for increasing the availability of effective colorectal cancer screening, diagnostic evaluation, and treatment methods and opportunities for participation in clinical trials in health care systems.

Common Themes Across the Groups

Several common themes emerged from the various breakout groups. Perhaps the most prominent was the necessity of a multidisciplinary approach to colorectal cancer research to achieve optimal progress. Such an approach will require multidisciplinary training programs in major centers in addition to cross-training of various interested specialties.

Following are the other most prominent themes reiterated among several groups. In general, these themes are related to either challenges confronting the field of colorectal cancer research or opportunities that should be pursued.

- Multidisciplinary collaborative efforts, such as SPORES, should be funded to expand research in colorectal cancer. In addition, the research community in general should be supported with technology development centers (for access to shared technology, development of methodology, and training in new methods) and by informatics centers. The latter would be charged with the development of new mathematical or statistical modeling methods for large data sets and the creation and possibly maintenance of databases to which investigators would have free access.

- Better models and modeling capability are needed, including cell culture and animal models that reflect the full spectrum of human disease. These resources would greatly enhance research in basic science, epidemiology, the development of “markers” of biologic characteristics in preneoplasia and neoplasia, and developmental therapeutics.

Appropriate models for behavioral and outcomes research also need to be developed in order to study and improve the utilization of established screening and treatment guidelines.

- More information is needed about the biology and genetics of normal colorectal epithelia and the genetic and biochemical pathway perturbations that occur with neoplastic transformation.

- Genetic and biologic studies need to be linked to population-based studies. Potential links to the Cancer Genome Anatomy Project and to the Colon Cancer Cooperative Family Registries are to be fostered.

- More information is needed on the role of low-penetrance genetic mutations and the interaction of such mutations with diet and lifestyle risk factors.

- Methods of subtyping tumors on the basis of genetic and biologic alterations need to be developed. Likewise, it is essential to define the biologic characteristics of premalignant and malignant lesions, as well as of the host, that indicate the likelihood of neoplastic transformation, recurrence after initial treatment, and favorable response to a particular treatment.

- Repositories of tumor tissue and blood are needed and should be linked to clinical databases containing information about risk factors, clinical characteristics, and outcome.

- The generalizability of clinical trial results to the general population needs to be assessed. It is estimated that only 2–3 percent of adults enter clinical trials, and these participants are usually younger than the general population with colorectal cancer or precancer. In addition, most are white and have near-normal organ function. Minority populations, elderly populations, and those with comorbidities need to be studied.

- There is a need for increased development of new chemopreventive and therapeutic agents for colorectal cancer. These efforts should include drug design based on targets elucidated by biologic research as well as combinatorial approaches. This effort will also require validation of “markers” of drug target effect. Functional imaging technology needs to be developed to enable the effects of treatment to be ascertained noninvasively and to improve diagnostic ability for premalignant and malignant lesions.

- There is a need to assess the penetrance of recommended screening and treatment procedures into the general population, and to assess the outcomes of these practices in the general population, given the reduction of mortality achievable by screening for colorectal cancer.

- More research is needed on the behavioral determinants of compliance with screening and treatment recommendations in both majority and minority populations. Research is also needed on the effects of screening and treatment on quality of life.

- More information is needed on the epidemiology of colorectal cancer. Innovative methods to obtain such information, such as nesting epidemiology trials into treatment or prevention trials, should be pursued.

- Research is needed across the spectrum of cancer control, including quality of life, stress issues encountered during treatment, the effects of aging, comorbidity, the effectiveness of palliative care and alternative methods of treatment, and the effectiveness and quality of end-of-life care.

- Peer review needs to be enhanced with the addition of the expertise that is required to review multidisciplinary research proposals in prevention, translational research, and behavioral and health sciences research.

- The ethical issues involved in genetic and clinical research are challenging. Efforts should be made to achieve a national consensus on the risks and benefits of such research and the acceptability of such research to the public.

Conclusion

The members of the Colorectal Cancer PRG believe that, by applying and expanding our foundation of knowledge, and by teamwork, new technology, and perseverance, major progress will be made in the coming decade. At this gateway to the next era in colorectal cancer research, the Colorectal Cancer PRG has identified critical areas that span the continuum of colorectal cancer research and care. It is clear that greater emphasis on these critical areas, summarized above and detailed in the following full report of the Colorectal Cancer PRG, is now imperative.

For a hard copy of this report, send an e-mail request to cisocc@nih.gov, or order through the Publications Online Ordering Service database at http://publications.nci.nih.gov.

Biology

Co-Chairs: Sanford Markowitz, Michael Brattain, Joe Gray, Russell Jacoby, Joanna Groden

Research on the biology of colorectal cancer holds the promise of identifying new targets for novel therapeutics and preventive strategies on a scientific basis. The development of a key set of new resources will catalyze research into colorectal cancer through application of the revolutionary technical advances now being developed in the biological sciences. At the same time, many of the barriers that impede the translation of basic research to the clinic will be eliminated.

CURRENT STATUS OF THE FIELD

Normal Epithelial Biology

It is important to define the molecular signatures of individual cell types, both normal and abnormal, in order to further knowledge in the detection, diagnosis, and treatment of colorectal cancer. Characterization of the unique expression pattern of each cell type will enable the recognition of perturbations that signal the presence of cancer or initiation of the transformation process. Specific variations of these signals may also be useful in tailoring treatments or predicting outcomes. New techniques in analyzing gene and protein expression can be applied to the characterization of each histological epithelial subtype in the intestine. Moreover, the development of new model systems (e.g., worm, fly, zebrafish, and mouse) that can be easily genetically manipulated may provide new insights into the in vivo pathways that govern the development of normal and malignant intestinal epithelium.

Pathways of Neoplasia

A key achievement of the past 5 years has been the initial delineation of the pathways that control the growth of colorectal cancer cells. For example, multiple genes have now been clustered into two key pathways, the *APC*/*Wnt* pathway and the *TGF*-beta pathway. The recognition of genes that are turned on by the inactivation of these pathways now makes it possible to develop potential targets for therapy. Drugs that inhibit the activity of the prostaglandin endoperoxide synthase-2 (*COX2*) pathway are exciting new agents for the possible treatment and/or prevention of colon adenomas. Several different pathways of carcinogenesis have been discovered; as an example, one of these is distinguished by a molecular assay for microsatellite instability. These two cancer types differ in their prognosis, aggressiveness, and response to cytotoxic drugs. Lastly, some colorectal cancers employ alternative, potentially reversible, mechanisms for inactivating pathways.

Growth Factors and Signal Transduction

A considerable volume of work supported by the National Institutes of Health (NIH) has focused on determining which growth factor–mediated signal transduction pathways are operable in cultured human colorectal cancer cells. Investigators have documented that the growth of colorectal cancer cells is dependent on various growth factors, including the *EGF* receptor family system, the insulin-like growth factor I receptor system, and gastrin-like peptides. The past 5 years have seen important advances in identifying the signaling

pathways that are associated with several of these systems. Moreover, studies in cultured colorectal cancer cells, as well as in other cancer cells, are helping to elucidate the roles of signal transduction components in controlling cell cycle transit and support of cell survival. Key developments in the advancement of this field have included antibodies that recognize activated forms of receptors and signal transduction components, as well as drugs that selectively block activation of several of these components, such as *ERK* and phosphatidylinositol-3-kinase. The dependency of tumor growth on signal transduction components such as *TGF*-alpha has also been demonstrated in xenografts and genetically manipulated mouse models.

Studies of primary tumor specimens have been limited by the fact that they have been performed with reagents that cannot demonstrate the activation of signaling pathways. Thus, despite a large volume of work, it is not known which signaling pathways are crucial for the growth of normal, premalignant adenomatous tissue, primary tumors, and metastases. This is a timely issue, as a number of new therapies targeted at signal transduction are now being developed. The ability to analyze in vivo specimens for signal transduction activity could have a great impact on how new drugs might be applied to the treatment of colorectal cancer. Such in vivo studies could also lead to the identification of novel subgroupings of colorectal cancer, which would improve our current understanding of disease progression.

Technologies and Instrumentation

The breathtaking pace of technologic change is now making it possible to analyze the molecular alterations that accompany cancer at a level previously beyond hope or reach. New technologies promise to dramatically enhance the power to identify the molecular events involved in neoplastic transformation.

The promise of these new technologies, however, cannot be realized without a mechanism to allow researchers to rapidly access and employ them. A well-developed, interactive network of Centers of Excellence has been highly effective in promoting translational research in cancers such as breast cancer. This approach has been key in creating the critical mass of multidisciplinary and multi-institutional investigators that are crucial to the success of translational research projects. Centers of Excellence have promoted the access of investigators to tissue banks linked to clinical outcomes. Unfortunately, however, such collaborative efforts are seriously lacking in colorectal cancer research.

VISION FOR PROGRESS

Researchers in colorectal cancer must be empowered to rapidly deploy the newest technological tools to address important clinical questions. It is recommended that a community of colorectal cancer researchers be linked together by a network of resource centers. At the center of this network would be Centers of Excellence in Colorectal Cancer Research to facilitate collaboration across disciplines and institutions. These Centers of Excellence would also serve as catalysts for the assembly of repositories of tissues, clinical histories, and genetic descriptors, all of which are requisite for successful translational research.

Resources and Informatics

The proposed Centers of Excellence would be linked to Centers of Technology Expertise and Informatics for Colorectal Cancer Research. The development of these centers will empower individual

investigators to make rapid scientific progress in answering questions about the molecular basis of this disease.

An informatics infrastructure will create for colorectal cancer researchers a "virtual laboratory" where scientific questions about biology can be addressed and translational plans implemented. Such a mechanism will facilitate collaborations across the world. Vital to this effort would be an investment in the infrastructure and training of informatics scientists and technical personnel who will support and develop such electronic networks.

Scientific Understanding

The next 5–10 years are likely to bring success in surmounting the currently formidable obstacles to understanding normal epithelial cell biology in the gut. This understanding has been hampered by the lack of currently available normal cell culture systems for study, as well as by the tissue architecture of the intestine. Understanding the biology and development of normal epithelial cells is likely to facilitate our understanding of the neoplastic growth of colonic epithelial cells, as well as the development of targeted approaches to screening and therapy.

The development of novel targets for the treatment of colorectal cancer will be driven by elucidation of the specific pathways of carcinogenesis and signal transduction. Colorectal cancer researchers should be challenged to achieve a quantum advance in understanding the molecular basis of colorectal cancer by elucidating all of the signal transduction pathways that are critical in the growth and survival of the malignant colorectal cell. Of further importance would be the identification of all the individual components of these pathways and the targets they regulate. Researchers should also strive to identify the mechanisms by which these pathways are inactivated. A particular new opportunity is represented by the identification of genes that are reversibly inactivated by epigenetic mechanisms and the elucidation of the underlying pathophysiologic aberration that leads to such epigenetic gene "silencing."

The development of antibodies to activated signal transduction components would permit recognition of the important changes that take place in signal transduction during the transition from normal to malignant phenotypes. This in turn would lead to new subgroupings of colorectal cancers. Perhaps most important, the ability to analyze activation of signal transduction components in vivo would be invaluable to the development of therapeutic drugs directed at signal transduction targets and could allow for individual optimization of therapy.

CHALLENGES AND OPPORTUNITIES

There is a tremendous need to expand the field's capability to manage and mine the large amount of information being generated in colorectal cancer research. Computer-based technologies allow the integration of large data sets, the analysis of which may generate new insights. Despite the National Cancer Institute's (NCI's) construction of the Cancer Informatics Infrastructure, the required hardware, software, and expertise are seriously lacking in the extramural community.

Barriers and Gaps

Research on colorectal cancer is impeded by the lack of a critical mass of investigators collaborating across disciplines and institutions. Translational studies are also impeded by barriers to the rapid transfer of technology. Another key challenge, therefore, is to broadly enable colorectal

cancer researchers to rapidly access the newest and most powerful technologies for pursuing cancer research. Examples include developing the means for rapidly transferring to the academic community the new technologies developed by industry and by the NCI intramural program. There is a need to maintain and make available large repositories of clones, samples, and databases that are the fruits of new technologies. There is also a need for shared instrumentation centers to provide access to new technologies that otherwise will be beyond the financial reach of many single investigators. Providing the means for pilot projects to rapidly explore the potential of new technologies will contribute to the solution of important questions in colorectal cancer biology. Moreover, establishing a mechanism for rapidly training individual investigators will facilitate the adoption of new technologies.

The challenge in determining the biological controls of normal and adenomatous colorectal epithelial development lies in establishing the ability to support the short-term and long-term culture of epithelial cells, both normal and adenomatous. Although simple in theory, this has proved in practice to be most difficult and constitutes a problem that has impeded the discovery of key growth factors and the contribution of stromal interactions to carcinogenesis.

A further challenge is to develop new model systems that mimic the metastatic behaviors of those colorectal cancers that are lethal. The development of such models would facilitate the elucidation of pathways that are operative in the multistep progression of colorectal cancer and would facilitate the development of new therapies directed at such pathways.

One of the chief limitations in determining signal transduction in vivo is the lack of techniques to detect activated signaling pathways in fixed or frozen tissue. Support for the development of such antibodies should overcome this obstacle.

Resources Needed

It is recommended that a critical mass of enhanced SPORE-like Centers of Excellence for Colorectal Cancer Research be developed. These centers would be charged with the following:

- Fostering interdisciplinary, interactive, translational research initiatives in colorectal cancer
- Fostering multi-institutional cooperation
- Developing resources that are accessible to the colorectal cancer research community, including tissue resources linked to treatment histories and clinical outcomes

The development of colon cancer SPOREs should also be supported by development of colon cancer dedicated centers for Technology and for Informatics. These centers would be charged with the following:

- Centers for Technology:
  - Foster the development of new technologies for colorectal cancer research.
  - Maintain key resources required for the successful use of new technologies by the research community.
  - Act as shared instrumentation resources to enable the research community to access new technologies.

— Facilitate distribution into the research community of new technologies.
— Train members of the research community in the use of new technologies.

! Centers for Informatics:
— Foster the development of user-friendly interfaces for access to databases and informatics resources that are of value to colorectal cancer research.
— Provide for the construction and maintenance of databases, including the compilation of data on tissues, outcomes, and epidemiologic information.
— Provide for the construction and maintenance of databases of molecular fingerprints or signatures of normal cells, tissues, and tumors. These databases would include information on genotype, gene expression, mutations, mutation rates, DNA repair rates, chromosomal aberrations, and epigenetic characteristics such as methylation status.
— Provide for the development of tools for data analysis.
— Provide for support for local informatics work stations.
— Provide broad access to key databases.
— Provide to the broad community of investigators the ability to send their data to the informatics centers for more sophisticated analyses.
— Provide support for maintaining and training a pool of intellectually rigorous informatics personnel.

RESEARCH PRIORITIES

Research should focus on accelerating efforts to answer key scientific questions that hold significant promise for identifying targets for new treatment modalities. Those questions deemed most important are outlined here.

Research Priority 1: Define the biological controls for the development of normal and abnormal colorectal epithecc2(he)6helope.6(n)-1.ft.

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- Identify the major targets regulated by signaling pathways that play a role in carcinogenesis.
- Elucidate the role of epigenetic mechanisms of gene inactivation in colorectal carcinogenesis and their underlying molecular mechanisms.

Research Priority 3: Identify the signaling pathways that are activated in vivo during carcinogenesis.

- Develop methods and reagents to identify the signaling pathways that are activated in vivo during carcinogenesis.

Etiology

Co-Chairs: Fred Kadlubar, Walter Willett

CURRENT STATUS OF THE FIELD

Genetic Determinants of Colorectal Cancer

The Human Genome Project can be expected to have a major impact on the understanding of colorectal cancer. It is expected that a nearly complete sequence of the human genome will soon be available, and the identification of single nucleotide polymorphisms (SNPs), accounting for the genetic diversity of the human population, will follow within a few years.

Nearly 50 years ago, the renowned nutritionist Roger J. Williams reminded us in his book *Biochemical Individuality* (New York, John Wiley & Sons, 1956) that "every individual has his own inborn metabolic characteristics....every application of biochemistry must take these differences into account...and that all diseases, such as cancer...are related to biochemical individuality." Today, we realize that there are an estimated 3.5 billion DNA bases in the human genome. Of these, it appears that humans differ from each other by a frequency of 1/1,000 nucleotides. These differences, or SNPs, thus involve about 3.5 million nucleotides. They can occur in both coding and non-coding regions of genes, and their frequency may vary among genes (from 1/100 to 1/10,000), depending on their function and role in cellular maintenance and survival. Current data indicate that about 10–15 percent, or 350,000–500,000, of these SNPs are likely to be functional in determining the activity or the level of the protein expressed.

Common polymorphisms, often defined as genetic differences occurring in greater than 1 percent of the population, have been associated with susceptibility to cancer. These polymorphisms include the genes involved in carcinogen and hormone metabolism; DNA repair; and control of cell growth, apoptosis, and immune response. Although these polymorphisms usually are not in themselves strong risk factors for a disease (i.e., they are of low penetrance), their high prevalence in the population can result in a high attributable risk, particularly in combination with exposure to dietary and other lifestyle factors. Of these polymorphisms, those involving carcinogen-metabolizing enzymes have received the most attention. It has long been hypothesized that wide variations in metabolic activation and detoxification can be important determinants of an individual's susceptibility to cancer. However, the current development of high-throughput phenotyping and genotyping methods should soon be able to provide the necessary genetic information for population-based risk assessment.

In addition, polymorphisms involving DNA repair or processing have recently received considerable research attention. Rare hereditary disorders in genes coding DNA repair proteins that exhibit high penetrance have long been known (e.g., xeroderma pigmentosum, ataxia telangiectasia, Fanconi's anemia, Bloom's syndrome). Recent studies, however, indicate that low-penetrance, common polymorphisms also exist. At least 70 genes have been identified in the various processes of DNA repair, and lower DNA repair proficiency has been consistently associated with increased

susceptibility to several cancers. Hereditary non-polyposis colorectal cancer (HNPCC), which involves, in large part, base changes in DNA mismatch repair genes, occurs in about one of every 10 cases of colorectal cancer. It therefore seems likely that polymorphisms in other DNA repair genes will play an important role in neoplastic transformation.

Much is known about the mutations in genes controlling cell growth and apoptosis and their role in the molecular pathogenesis of colorectal cancer. More than 100 genes are known to serve as positive (oncogenes) or negative (tumor suppressor genes) regulators of cell growth. Several hereditary disorders associated with increased susceptibility to cancer involve rare polymorphisms in oncogenes or tumor suppressor genes (e.g., multiple endocrine neoplasia [*RET*], retinoblastoma [*Rb*], and breast and ovarian cancer [*BRCA1* and *BRCA2*]). For colorectal cancer, mutations in the familial adenomatous polyposis (*APC*) gene are highly penetrant. A mutation in the *APC* gene also seems likely to serve as an early event in sporadic colorectal cancer. For other genes involved in colorectal cancer, such as beta-catenin, *Ki-ras*, *DCC*, *COX2*, *P53*, and others, it seems likely that common polymorphisms will be functional and will interact with the genetic polymorphisms mentioned above. Polymorphisms in genes involved in immune response are only now being identified and represent another new field of investigation.

Diet, Lifestyle, and Other Determinants

The search for diet, lifestyle, and other factors that can explain risk for colorectal cancer has been driven by two fundamental and powerful observations. First, rates of colorectal cancer differ dramatically among countries, varying by as much as 10-fold, from low-incidence areas in Asia, Africa, and parts of Latin America to much higher rates in northern Europe, New Zealand, Australia, and the United States. Second, migrants from low-risk areas to Western countries experience rapid increases in colorectal cancer risk within the same generation. The incidence of colorectal cancer can also change dramatically over time within countries. For example, colorectal cancer mortality increased 2.5-fold in Japan between 1955 and 1985, a time when diet and lifestyle changed dramatically. These findings clearly indicate that non-hereditary factors have a major etiologic role in colorectal cancer. In principle, these factors could be identified and preventive actions taken to reduce the level of risk to that of low-incidence populations.

Until recently, the factors thought to be largely responsible for these major international differences were dietary fat and fiber. These beliefs were primarily based on ecological correlations among countries in combination with data from case–control studies of colorectal cancer. Recent data, however, do not support an association between dietary fiber and risk of adenomas and colorectal cancer in adults. Moreover, intake of total fat, and animal fat in particular, does not appear to be associated with risk of colorectal cancer in either case–control or cohort studies when total energy is accounted for in the analysis. In addition to fat and fiber, consumption of red meat was suspect because the correlation with national colorectal cancer mortality was among the strongest of all diet–cancer associations. Much evidence still exists that high consumption of red meat may increase the risk of colorectal cancer. Considerable evidence has accumulated that this increased risk may be due to the presence of carcinogenic heterocyclic amines that are formed during the high-temperature cooking of foods and burning of meat juices.

In contrast to the diminished support for hypotheses relating dietary fiber and fat intake to colorectal cancer risk, substantial evidence suggests that low levels of physical activity and greater adiposity increase risks. These associations have been seen in both case–control and cohort studies and, because high levels of physical activity and low rates of adiposity characterize low-risk countries in general, could account for much of the international differences in colorectal cancer rates. Although many case–control studies have suggested the beneficial effects of high intake of fruits and vegetables—findings that have stimulated a large research effort to identify the responsible constituents—recent evidence from prospective studies indicates a weaker overall association with high consumption of fruits and vegetables.

Additional nutritional factors appear promising as potential means to prevent colorectal cancer. Folic acid supplements have been associated with a preventive role and reduced risks of colorectal cancer and adenomas in both case–control and cohort studies. A particularly striking finding came from the Nurses' Health Study, which showed that consumption of multiple vitamins containing folic acid for more than 15 years was associated with a risk of colorectal cancer that was 75 percent lower than that in non-users. A preventive role of folic acid intake is further supported by studies in animals, as well as by mechanistic investigations. Findings from the latter demonstrate that low folic acid concentrations greatly increase the substitution and incorporation of uracil for thymine into DNA due to the depletion of essential methyl donors in the cell.

Additional support for a preventive role of calcium is provided by the results of animal studies and an adenoma prevention trial in which a calcium supplement modestly reduced the recurrence of adenomas. Epidemiologic support for a beneficial effect of calcium supplementation has been mixed, but data are compatible with a modest benefit. Although less extensively investigated, other epidemiologic and mechanistic evidence suggests a possible benefit of adequate vitamin D.

In addition to nutritionally related factors, cigarette smoking has been associated with increased risks of colorectal cancer in many, although not all, studies. In particular, smoking for 35–40 years has been most strongly associated with risk, suggesting an impact of smoking in the initiation of this cancer. High alcohol consumption has also been associated with increased risks of colorectal cancer in many studies, but the data have not been entirely consistent. In several studies, high consumption of folic acid appeared to mitigate the excess risk associated with alcohol, which could account for some of the inconsistencies.

A collective impact of diet and lifestyle factors has been identified in the last decade, suggesting that a large proportion of colorectal cancer is preventable on the basis of currently identified risk factors. For example, in a recent analysis among women, a low-risk group was identified on the basis of lower-than-average body mass index, moderate physical activity, low alcohol consumption, use of folic acid supplements, little or no history of smoking, and low consumption of red meat. Although only a small fraction of the total population fell into this low-risk group, it could be hypothesized that a substantial proportion of the incidence of colorectal cancer in westernized countries could be avoided were everyone to adopt this low-risk lifestyle.

In another line of investigation, endogenous hormones and other physiologic intermediaries are currently being evaluated

in relation to colorectal cancer risk. In particular, high levels of insulin-like growth factor 1 (IGF-1) and low levels of IGF-binding proteins 1 and 3, have been associated with higher risks of colorectal cancer. Other findings suggest that high levels of C peptide, reflecting hyperinsulinemia, may increase the risk of colorectal cancer. These physiologic intermediaries may mediate the relationships between obesity and physical activity that have been observed in many studies and could also be related to diets with a high glycemic load.

Several important risk factors for colorectal cancer identified during the last decade could collectively account for a large proportion of cases. Causal relationships with colorectal cancer incidence, however, have not been definitively proven. For most of these risk factors, it will be difficult or impossible to establish causality in large randomized trials because, as in the case of obesity, physical activity, and smoking, long-term primary prevention studies are logistically difficult to carry out. In the case of folic acid, vitamin D, and calcium, it may be difficult to maintain compliance in a large population for a sufficient time if prolonged intervention is needed. Similar difficulties may be involved in studying consumption of red meat with colorectal cancer as the endpoint. Proof of causality would give greater force to preventive efforts and could possibly result in more focused interventions. For example, it would be important to know whether the incidence of colorectal cancer could be substantially reduced by folic acid supplements, because the intervention is inexpensive and safe and has other potential benefits.

Technologies and Instrumentation

Two areas of advancement involve exposure measurements and high-throughput genotyping. Exposure measurements include new techniques in mass spectrometry (MS) (micro- and nanospray liquid chromatography [LC]–MS), array-based capillary electrophoresis with laser fluorescence, gas chromatography– and LC–accelerator MS, and immunoslot blots with improved monoclonal antibodies. These techniques will soon make possible the sensitive and specific detection of carcinogen exposure by detection of metabolites in biological fluids and as carcinogen–DNA adducts in the colon obtained during routine colonoscopic biopsy procedures.

Also under development is high-throughput genotyping with DNA microarray technology, which has the potential to allow facile genetic screening of human samples (“pharmacogenomics”) for studies of colorectal cancer susceptibility. This would allow characterization of human tissue samples (>1,000 samples per day) for 10–100 genes or alleles concurrently with small sample volumes at relatively low cost. Potentially, one can design oligonucleotide probes, fixed on glass surfaces or “chips,” to conduct allele-specific hybridization of polymerase chain reaction (PCR)–amplified DNA samples. After washing and activation of a fluorescent or other suitable signal, the information can be captured by image analysis and sorted by bioinformatics systems. These and other methods should soon be able to provide the necessary genetic information for population-based risk assessment.

VISION FOR PROGRESS

Recent advances in a number of fields now make possible enormous progress in the elucidation of colorectal cancer etiology over the next decade. Knowledge of the molecular changes involved in colorectal carcinogenesis, along with technological

advances in the ability to characterize both germ line and tumor DNA, offer great potential for etiologic studies. For the first time, it will be possible in epidemiologic studies to link nutritional and lifestyle factors and endogenous hormone levels with genetic variations (e.g., SNPs) and to follow the other molecular changes that occur in the DNA of premalignant lesions and of colorectal cancer itself. Newly available knowledge and techniques will also allow intervention studies to identify high-risk individuals by high-throughput genetic screening, to examine the effects of changes in diet and lifestyle on hormonal intermediates that affect colorectal cancer risk, and to closely monitor relevant genetic changes in precursor lesions.

The benefits of such research are multiple. First, susceptible individuals can be identified and provided with increased opportunities for early detection and preventive interventions, possibly tailored to their particular mechanistic susceptibility. For example, individuals with a genetic variant in carcinogen metabolism might specifically be instructed to avoid meat cooked at high temperatures. The ability to study genetic predisposition and DNA markers in tumors also offers opportunities for strengthening the evidence for causality of diet and lifestyle variables. For example, a documented association between colorectal cancer risk and a polymorphism in a gene coding for an enzyme that metabolizes a specific dietary factor (e.g., folic acid) would greatly strengthen the evidence for an etiologic relationship between the substrate for that enzyme and colorectal cancer risk. Further evidence for causality would be provided by documentation of an association between a specific dietary factor and a specific DNA abnormality linked to colorectal cancer, for example, between a dietary factor and microsatellite instability or a *Ki-ras* mutation.

On the basis of current evidence, it is clear that a large proportion of colorectal cancer cases are potentially preventable, and in the next decade the preventable factors can be known with a high degree of confidence. Further, susceptible individuals can be identified and a combination of broad public health preventive strategies or individually tailored interventions can be implemented. Because the risk of colorectal cancer appears to be modifiable during adulthood, a further reduction in the incidence of this disease during the coming several decades is a realistic possibility.

CHALLENGES AND OPPORTUNITIES

Resource Issues

To address the research priorities listed below, knowledge is needed of the important allelic variants of the genes involved in the development of colorectal cancer (metabolism, DNA repair, cell growth, apoptosis, immune response). Obtaining this knowledge will require new efforts in gene discovery, including genes that modify the function of the proteins involved. The frequency of new alleles and their penetrance will require resequencing and testing in appropriately designed transitional epidemiologic studies. In other words, as new SNPs are identified by the Human Genome Project, their enzymatic or structural function will need to be determined and a number of relevant molecular epidemiological studies will be needed to assess their role in cancer etiology and attributable risk.

The availability of high-throughput methodologies in molecular epidemiology studies, especially for rapid genotyping in population-based studies, is clearly needed.

Although this technology is currently under rapid development, much work is needed to validate this approach by comparing its results with those of conventional techniques in smaller, carefully designed, case–control studies or intervention trials.

The development of bioinformatics will be needed to study multiple gene–environment interactions, possibly in a spreadsheet-like format that allows the investigator to probe selected, biologically plausible interactions. Algorithms that are capable of "data mining" to detect unforeseen relationships will also become necessary. Such information should reside in the public domain, allowing web site databases for query by laboratory scientists, epidemiologists, clinicians, and others in the health care and research fields.

Barriers and Gaps

The legal and ethical implications of genetic screening and biomonitoring have led to variability in the interpretation of guidelines for project approvals by Institutional Review Boards and informed consent forms. Concerns are often based on 1) legal issues related to discrimination by employers, insurance companies, or licensing agencies and the rights of individuals to litigate such discrimination; 2) ethical issues related to the rights of individuals to choose whether to accept administration of a test for susceptibility, to know the results, to decide to accept a hazardous situation, to avoid particular drugs or exposures, or to take preventive measures; and 3) psychosocial issues related to knowledge of personal health risks that provokes anxiety and confusion, damages family relationships, and compromises the quality of life or lifestyle for an individual. Potential approaches to this problem involve legislation to prevent discrimination based on genetic screening and a universally accepted set of rules that ensure, when desired, the anonymity of participants in population-based or biomarker studies.

Another major barrier to the implementation of studies on the etiology of colorectal cancer arises as a consequence of the multidisciplinary nature of such efforts. Current peer review processes often are deficient in the multidisciplinary expertise (e.g., in the area of molecular epidemiology) that is necessary to provide adequate review of such project proposals.

RESEARCH PRIORITIES

Research Priority 1: Support population-based epidemiologic studies.

- Link genetic polymorphisms, diet and lifestyle variables, and endogenous (hormonal) factors, with the molecular (e.g., *APC* and *Ki-ras* mutations) characteristics of colorectal cancer and its putative precursor lesions (e.g., aberrant crypt foci, small versus large adenomas).
- Encourage studies on special populations (e.g., specific ethnic groups and those with hereditary predisposition) and early-life exposures.

Research Priority 2: Validate early and intermediate biomarkers of exposure and genetic polymorphisms.

- Support studies on specific dose–response relationships.

Research Priority 3: Resequence SNP-containing genes involved in carcinogen or hormone metabolism, DNA repair, cell growth control, and immune response, and assess their functional polymorphisms in molecular epidemiologic studies in diverse ethnic populations using high-throughput genotyping methods.

Prevention

Co-Chairs: Bandaru S. Reddy, David Alberts

CURRENT STATUS OF THE FIELD

Despite the identification of some of the risk factors for colorectal cancer, there is a dearth of funded research on the prevention of this disease in the general population. The goal of prevention is to decrease morbidity and mortality from colorectal cancer or to delay the progression of, reverse, or inhibit invasive disease. Recent prevention studies have emphasized the pinpointing of risk factors associated with the development of colorectal cancer; the identification of natural and synthetic agents that modulate cancer risk at the molecular, cellular, and tissue levels, or that inhibit colorectal carcinogenesis in carcinogen-induced, transgenic, and gene knockout rodent model systems; and the use in high-risk groups of chemopreventive agents that have been found to be effective as preventive agents in rodent models. The mechanisms of action of these agents are defined by activities at the molecular and cellular levels, whereas chemopreventive efficacy is evaluated by clinical outcomes. Potential chemopreventive agents and nutrients that have been systematically identified in rodent models include the following:

- Anti-inflammatory agents, including several classes of compounds that interfere with arachidonic acid metabolism (e.g., the nonsteroidal antiinflammatory drugs), with cyclooxygenase-2 (e.g., celecoxib), and with lipoxygenase (e.g., curcumin)
- Inducible nitric oxide synthase inhibitors
- Antimutagens (e.g., phase II enzyme inducers)
- Antioxidants (e.g., selenium and curcumin)
- Ornithine decarboxylase inhibitors (e.g., difluoromethylornithine)
- Terpenoids (e.g., perillyl alcohol)
- Apoptosis inducers (e.g., sulindac, sulindac sulfone, curcumin)
- Vitamin D analogs
- Dietary nutrients (e.g., calcium, vitamin D, folic acid, selenium)

Both animal models and epidemiological studies have shown that several nutrients, provided in adequate dietary amounts, have inhibitory activity against colorectal cancer. In a controlled human intervention trial, calcium was associated with a modest but significant reduction in the sporadic recurrence of colon adenomas. Further clinical trials are needed with other dietary nutrients that have been demonstrated as inhibitors in model systems. Supplying specific nutrients in adequate dietary amounts—for example, by food fortification—represents a low-cost, low-risk approach that could be readily implemented on a large scale for the prevention of colorectal cancer.

The movement of many of these chemopreventive and nutritional agents into the clinical setting has been slow because measurement of their effects has been limited to small Phase I and Phase II clinical trials, where cancer cannot be the endpoint. Lacking are highly predictive short-term indicators—termed surrogate endpoint biomarkers (SEBs)—that are directly involved in the carcinogenesis pathway and could thus accurately predict the impact of the drug or nutritional agent on the development of clinically invasive cancer. If

these SEBs could be modulated by prevention strategies and validated, they could be used as endpoints in clinical trials. The development of effective chemoprotective strategies will require collaboration among nutritionists, biochemists, behaviorists, molecular biologists, pharmacologists, and clinical investigators.

Basic and applied research on colorectal cancer prevention is needed to identify the molecular changes that occur during the progression of normal tissue to precancerous tissue and to cancer. Research is also needed on the level of risk associated with these changes and the effect of modulating them in preclinical trials and in humans through intervention with micronutrients, diet, and chemopreventive agents. Finally, research is also needed to evaluate combinations of nutrients and chemopreventive agents both in vitro and in vivo.

VISION FOR PROGRESS

A major goal of research on colorectal cancer prevention should be to develop minimally toxic and affordable intervention strategies that are based on scientifically sound data. Recent advances in the understanding of carcinogenesis can and should influence strategies aimed at blocking the initiation, promotion, and progression of carcinogenesis.

Most treatment strategies focus on the elimination of invasive cancer and the prevention of its recurrence. In contrast, preventive strategies focus on precancerous lesions to avoid the development of invasive cancer. The nature of colorectal carcinogenesis, and therefore the potential for its inhibition, should be explored by experimental and clinical scientists from various disciplines, focusing on the molecular, cellular, tissue, and clinical aspects of this process. Specific research goals include the following:

- Validate, singly and in combination, promising chemopreventive agents and nutrients in preclinical models, and prioritize them for clinical efficacy studies.
- Develop relevant transgenic, gene knockout, and xenograft animal models to test nutritional and chemopreventive agents. These models are useful tools for elucidating mechanisms of carcinogenesis and for identifying new targets and SEBs.
- Provide targeted funding to cancer centers or institutions that are specifically involved in studies on colorectal cancer prevention in order to accelerate nutrition and chemoprevention research.
- Develop and validate SEBs for the testing of nutritional and chemopreventive agents in animal models and humans.
- Use recently developed laser-assisted microdissection and gene array technologies to fingerprint precancerous lesions and evaluate the potential efficacy of chemopreventive agents.
- Define molecular and phenotypic changes in the progression of normal tissue to precancer and cancer in experimental animal models and in humans.
- Conduct definitive Phase III prevention trials of promising agents.

A very limited proportion of the NCI budget is currently allocated to colorectal cancer prevention. An analysis of the current NCI portfolio revealed four program projects and 22 R01s and N01s related to colorectal cancer prevention. Insufficient support is

provided for the evaluation of nutritional and chemopreventive agents, both natural and synthetic, against colorectal cancer in preclinical models and in human Phase II and Phase III clinical trials.

CHALLENGES AND OPPORTUNITIES

Studies of combined nutritional and chemopreventive agents in preclinical models—There is a need to evaluate combinations of low doses of nutritional and chemopreventive agents that differ in mode of action as a means of obtaining increased efficacy and minimized toxicity. This approach is extremely important when promising chemopreventive agents demonstrate significant efficacy but may produce toxic effects at higher doses.

Validation of surrogate endpoints and prospective biomarkers—Validated biomarkers are needed for human clinical trials as well as for mechanistic studies in in vitro models and in vivo animal models, including transgenic, gene knockout, and chemically induced rodent models. These endpoints could supplement currently used morphologic endpoints, such as aberrant crypt foci, which are difficult to quantitate and thus subject to marked variation.

Integration between basic and clinical scientists—A Prevention Research Working Group would be an effective mechanism for quickening the pace of progress and fostering interdisciplinary collaborative research on colorectal cancer prevention. This entity would advise the NCI of new opportunities for multidisciplinary research and would provide a scientific forum to facilitate the collaborative research efforts of basic and clinical scientists.

Barriers and Gaps

- Inadequately defined molecular, genetic, and epigenetic targets and pathways of colorectal carcinogenesis
- Inadequate preclinical models for colorectal cancer
- Limited number of medicinal and organic chemists involved in the development of nutritional and chemopreventive agents
- Inadequate resources for the discovery and development of chemopreventive agents
- Limited involvement of the pharmaceutical industry in the development of nutritional and chemopreventive agents
- A shortage of basic, behavioral, and clinical scientists in the area of colorectal cancer prevention

Resources Needed

- Increased support for prevention research, particularly biomarker research and animal models
- Increased training and career development grants for nutritional science aspects of cancer prevention research
- High-throughput molecular technologies for SEBs—development, validation, and application in preclinical and clinical trials of colorectal cancer prevention
- Increased funding for and availability of the existing NCI Rapid Access to Prevention Intervention Development mechanism

RESEARCH PRIORITIES

Research Priority 1: Define pathways that can be targets for nutritional and chemopreventive agent interventions.

Research Priority 2: Validate the applicability to early clinical trials of SEBs of colorectal carcinogenesis defined in preclinical animal models.

Research Priority 3: Conduct studies of combined lifestyle and chemopreventive interventions.

Early Detection and Diagnosis

Co-Chairs: Stanley Hamilton, Bob Smith, Graeme Young

CURRENT STATUS OF THE FIELD

The natural history of colorectal neoplasia—from intraepithelial neoplasia (dysplasia or adenoma) to adenocarcinoma—offers multiple opportunities for assessment and intervention. The detection of premalignant disease and the early diagnosis of malignant disease depend on the development and application of methodologies that quantify an individual's risk for neoplasia; indicate the likely presence of neoplasia; and aid in its detection, diagnosis, and removal. Such methodologies may be either "biomarkers" of a molecular or biological nature or clinical characteristics such as age, lifestyle, familial occurrence, or personal incidence of relevant colorectal disease. Methodologies for detection include invasive or noninvasive imaging techniques, such as endoscopy and radiology, with goals that include the following:

- Assessment of the risk of developing disease, whether inherited or acquired
- Population screening for colorectal cancer
- Screening of asymptomatic individuals who are at average or increased risk for colorectal cancer
- Screening and surveillance of asymptomatic individuals who are at above-average risk for colorectal cancer and who have no known premalignant states, such as IBD or history of adenoma, and no history of colorectal carcinoma
- Surveillance of asymptomatic individuals who are at above-average risk, identified by a personal history of adenoma or cancer or chronic inflammatory bowel disease
- Diagnosis of symptomatic patients
- Prognosis of the course of disease in patients with colorectal neoplasia, represented by development of metachronous benign precursors or carcinomas as well as outcome after treatment of malignancy (see the section "Treatment and Prognosis")
- Prediction of therapeutic response or resistance (see the section "Treatment and Prognosis")
- Prediction of therapeutic toxicity

The substantial investments made by the NCI and other institutions in the early detection, diagnosis, and prognosis of colorectal neoplasia have resulted in significant progress in these areas. The molecular biology and pathology of colorectal cancer are among the best understood in human cancers. Clinical tools, such as fecal occult blood testing, endoscopy, and radiologic imaging, are widely and routinely available to diagnose and assess the disease. As such, detection of early curable malignancy should no longer be considered the only goal of colorectal cancer screening and surveillance. Rather, detection of the disease in the premalignant phase is likely to be a significant additional target of prevention strategies and is most likely to substantially reduce mortality rates of colorectal cancer by reducing its incidence. In this section, detection of early disease is addressed; prognosis of the disease is discussed in the Treatment section.

Although the NCI has made a substantial investment in research on colorectal cancer

(as evidenced by a review of the grant funding portfolio and intramural efforts), it is clear that most funded research activity is directed at the elucidation of basic biological mechanisms. Insufficient funding is available to translate markers and modalities such as those mentioned above into clinical testing in order to evaluate effectiveness on patient outcomes (i.e., reduced incidence and mortality). Consortia between NIH and industry for early detection appear to be primarily focused on discovering technology. In contrast, there is little funding for research into the clinical application of technological and methodological discoveries.

VISION FOR PROGRESS

The nation's burden of colorectal cancer can be lightened by reducing morbidity and mortality from the disease. The process should involve not just detection of curable cancers but should also expand to involve adenoma detection and effective means of achieving this.

CHALLENGES AND OPPORTUNITIES

Barriers and Gaps

Gaps and limitations in the early detection of colorectal cancer, and in the detection and eradication of adenomas, exist in the following areas:

- Outcomes research directed at the effectiveness, potential harms, and cost-effectiveness of current screening guidelines
- Research into risk assessment to categorize individuals and evaluate screening strategies and their outcomes, including cost-effectiveness
- Translational research to move technological biomarkers and innovative methodologies into population studies
- Clinical trials methodology for evaluation and validation of surrogate biomarkers
- Basic research to better understand mechanisms and control of biomarker release (e.g., exfoliation into stool or blood) and post-release distribution, metabolism, and excretion of markers
- Accessible repositories of well-characterized specimens, informatics support, and biostatistical methodologies to address the multiple endpoints inherent to panels of biomarkers
- Missed opportunities to gather additional data by "piggybacking" evaluation of useful methodologies onto funded prospective clinical trials
- Research into educational methods for the public and for health care providers
- Research into the role of primary care providers in reducing the incidence and mortality of colorectal cancer

Resources Needed

The following resources are required to facilitate research on early detection, diagnosis, and prognosis of colorectal neoplasia:

- Comprehensive banks of matching tissue, blood, and feces linked to demographic and clinical data
- Advertisement of existing tissue banks and resources
- Image data banks (radiographic, pathologic, and section array, etc.)
- Definition of the clinical methodology required to justify evaluation of a marker or modality at

the clinical and population levels (analogous to Phase I, II, and III trials for new drugs or other interventions), including possible harms. Similarly, agreement is needed as to when a modality should move into routine practice.

- Clarification of processes for comparing new and existing markers and modalities, short of needing to proceed to randomized clinical trials with mortality as the endpoint
- Processes for sharing of expertise in the areas of behavior, public health, health economy, outcome, and education
- Databases for matching clinical practice to outcome, tracking outcomes, and monitoring quality assurance of early detection tests
- Public, patient, and health professional education material
- Database development for tracking outcomes of screening

RESEARCH PRIORITIES

Research Priority 1: Support research into short- to medium-term (5–10-year) strategies for effective implementation of currently recommended methods of early detection at the population level.

- How can public participation in screening tests of proven value be enhanced?
- What are the barriers to participation in screening? What is the relative importance of consumer and provider barriers and their interaction?
- How is screening made more accessible to all groups? Does access and participation relate to characteristics such as age, sex, ethnicity, and socioeconomic status?
- What are the outcomes and cost-effectiveness when current screening recommendations are followed by the general public?
- What are the performance characteristics and cost-effectiveness of current screening tests, especially fecal occult blood testing and sigmoidoscopy, in the general population?
- What is the appropriate target population for screening, including age range?
- What are valid and feasible follow-up processes for individuals with positive or negative results? Can those with negative colonoscopy be removed from screening?
- What roles (endorsement, involvement, etc.) can and should be played by the primary care physician?
- What are the harms of screening? How do they relate to expectations of the population?
- Does a comprehensive analysis of outcomes of existing population programs (e.g., HMO, NCI-supported PLCO) answer some of the above questions?
- How should effective reminder systems be designed?
- What constitutes an effective routine risk identification strategy (e.g., identification of individuals with symptoms, family or personal history risk factors that warrant an alternative and perhaps more intensive surveillance or diagnostic process)?
- Is detection of curable cancer adequate? What is the added or alternative value of adenoma detection?

Research Priority 2: Conduct rigorous clinical evaluation of promising markers and modalities, especially in adenoma detection, before their implementation at the population level.

- What are the feasibility and effectiveness of screening colonoscopy?
- What are the feasibility and effectiveness of screening radiological methods?
- How does immunochemical methodology compare with chemical (guaiac) fecal occult blood testing for adenoma and early cancer detection?
- What are the feasibility and effectiveness of other fecal markers, including molecular and gene-based markers?
- What are the adverse outcomes of the above detection tests in average risk groups?

Research Priority 3: Support developmental research on new markers and modalities and improvement of current methods.

- Are there new molecular, biological, and imaging technologies for improved identification and characterization of preneoplasia?
- What is the biology of these biomarkers, and how does it relate to their detection in feces and/or blood?
- Are there targets that could refine risk assessment?
- What are the criteria for moving putative biomarkers into clinical evaluation?

Treatment and Prognosis

Co-Chairs: Michael O'Connell, Margaret Tempero[2]

CURRENT STATUS OF THE FIELD

SEER statistics show that, in addition to a declining incidence of colorectal cancer, substantial improvements in age-adjusted mortality are being observed. These findings suggest that important advances have occurred in the prevention, early detection, and treatment of this disease. Numerous studies have documented an important role for adjuvant therapy for colorectal cancer. Regimens based on 5-fluorouracil (5-FU), given after potentially curative surgery, can increase the absolute 5-year survival rate by 10–15 percent. Similar improvements are observed with the application of 5-FU–based chemoradiation in patients with rectal cancer that has extended through the bowel wall or has spread to regional lymph nodes. Colorectal cancer can lead to blood-borne metastases in vital organs such as liver and lung. Even in this setting, available therapies such as surgical resection, with or without regional cytotoxic therapy, can be curative in highly selected cases.

For patients whose disease cannot be cured, standard treatment options focus on the use of a relatively small repertoire of chemotherapeutic drugs. Historically, 5-FU has been the mainstay of initial treatment, and recent developments have shown that biochemical modulation (e.g., with leucovorin) can lead to improved response rates. A relatively new agent, irinotecan, has been shown to produce modest prolongation of survival after therapy with 5-FU. In addition, the combination of irinotecan and 5-FU has shown improved partial response (tumor shrinkage) over 5-FU alone. Other new agents for colorectal cancer are analogs or prodrugs in the same class as 5-FU and have the advantage of oral administration. An investigational agent, oxaliplatin, has been widely tested in both Europe and the United States and should soon be included in the list of available agents.

Many new discoveries in the last decade have the potential for improving the management of colorectal cancer. Current adjuvant treatments are effective in reducing mortality for some patients but are associated with toxicities. Such toxicities are unnecessary for those who would be cured by surgery alone, as well as for those with tumors insensitive to the treatment, if such groups could be identified before treatment were initiated. Likewise, 20–40 percent of patients respond to systemic chemotherapy for metastatic disease. As more therapeutic agents become available, a method to discern whether an individual is likely to respond to a given treatment would represent a great advance in therapy. A better understanding of the genetic changes that occur in colorectal cancer offers opportunities to better define prognosis, improve detection, and understand the likelihood of treatment benefits. Such improved understanding may also lead to the development of new, rational and/or targeted treatment opportunities, as illustrated by the following examples:

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[2] Dr. Joel Tepper played a key role in writing this report; Pamela McAllister, Ph.D. (patient advocate) also contributed significantly.

- The discovery of molecular genetic abnormalities, such as allelic loss of 18q or microsatellite instability, has highlighted potentially important new predictors of prognosis. Further study is needed to determine whether these molecular defects may provide prognostic information that is independent of routine staging classifications and that could assist oncologists in determining the need for adjuvant treatment after surgery. It is possible that tumors without allelic loss of 18q or other, as yet undefined, molecular profiles may not require adjuvant treatment, which would otherwise be recommended on the basis of routine staging classifications.

- The identification of tumor-associated factors, such as CEA or cytokeratin, in negative lymph nodes (that is, nodes without evidence of cancer cells on microscopic examination) may indicate a higher risk for recurrence and could expand the indications for adjuvant therapy.

- Tumors with abnormal enzyme activity, such as high thymidylate synthase levels, may be less likely to respond to 5-FU treatment. This finding could help to direct or individualize therapy.

- Abnormal genes, such as mutated *P53*, a tumor suppressor gene, are often found in colorectal cancer. Understanding the function of this gene in colorectal cancer could provide clues about possible gene-based treatment or could enable the identification of new targets for therapy with agents that interfere with critical biochemical pathways.

Despite these advances, much remains to be learned and put into practice. To improve outcomes, variability in conventional practice approaches needs to be minimized. In addition, it is not yet known how best to apply new radiation treatment and planning methods, imaging techniques in clinical staging, and new molecular testing in pathologic staging. New putative prognostic and predictive markers await validation. Tissue data banks with good clinical correlation are being developed to help accomplish this goal. Finally, the expanding array of new therapeutic agents begs for an expedited approach to testing these agents in patients with colorectal cancer.

An analysis of the NCI's colorectal cancer research portfolio reveals that most current funding supports investigation of biochemical pathways that may lead to the identification of new therapeutic targets. In contrast, clinical genetics and immunotherapy research receive less support. There is limited support for studies of predictive markers for currently available therapies and virtually no support for research specific to colorectal cancer in the areas of quality assurance, the accrual and maintenance of a comprehensive tissue data bank, intermediate markers for therapy, and innovative clinical endpoints. Also limited is support for the development of informatics systems and mathematical models and preclinical models for colorectal cancer.

VISION FOR PROGRESS

Molecular targets for novel therapeutics—Advances in scientific understanding of the molecular makeup of colorectal cancers should make it possible to identify specific pathways that can be modified by new therapeutic agents. These agents, used either alone or in combination with standard therapy to enhance established treatment modalities, have the potential to

be more selective for colorectal cancer and less toxic to the patient.

Immunotherapy—A better understanding of the human immune system and tumor immunology affords the possibility of modulating host immunologic status with agents that can stimulate cytotoxic immune cells. Immunotherapy may offer the greatest potential after surgical resection in the adjuvant setting.

Anti-angiogenesis therapy—Preclinical research indicates the importance of angiogenesis in facilitating tumor metastasis and growth in host tissues. Development of agents that interfere with tumor angiogenesis may hold promise in the future treatment of patients with colorectal cancer.

Prognostic markers—At present, adjuvant therapies are delivered to large numbers of patients on the basis of relatively crude information, suggesting that these patients are at high risk for treatment failure. Newer prognostic markers, better collection of conventional surgical and pathologic data, and improved use of these data offer the potential to determine which patients are most appropriate candidates for studies of adjuvant therapy.

Predictive markers—As the molecular characterization of colorectal cancers is better understood, and as therapies directed at specific molecular targets are developed, it should be possible to predict which therapeutic interventions will have a high likelihood of success for an individual patient.

Intermediate markers—Newer therapeutic modalities directed at specific molecular or biochemical targets will need to be evaluated through the use of intermediate markers to determine whether they achieve their intended effects on the target. In addition, the development of treatment combinations—of drugs or of drugs with radiation therapy—will be aided by the ability to discern additive or synergistic molecular effects of such combinations. Multiple tissue biopsies or noninvasive functional imaging techniques may be used to examine these intermediate markers. Use of these markers will be an important consideration in deciding to commit major resources to evaluate novel therapies in large comparative clinical trials.

Surrogate indicators of response—Many therapeutic interventions produce physiologic, molecular, immunologic, or biochemical effects that could potentially be measured noninvasively to help predict clinical benefit early in the course of treatment.

Wider application of optimal practices—Many studies have indicated that major clinical benefits can result from the use of high-quality surgical care and pathologic evaluation. These benefits cannot be realized unless optimal patient care practices are comprehensively applied in the general population.

CHALLENGES AND OPPORTUNITIES

Barriers and Gaps

- Many patients are initially treated in the community, where there is wide variability in the number and complexity of cancer cases. Evidence suggests that surgical outcomes are associated with the volume of cases handled and the experience of the surgeon. In addition, specialized pathological techniques can facilitate

colorectal cancer staging, but these techniques are not widely utilized.

- For rectal cancer in particular, the benefit of pre- versus postoperative chemoradiation therapy is unknown. In addition, newer schedules for radiation delivery, such as large doses over a short time or hyperfractionated or accelerated fractionation schedules, have not been rigorously evaluated. Conformal radiation therapy, as well as intensity modulated radiation therapy, have likewise not been adequately explored in this setting.

- Inadequate participation in clinical trials (estimated to be 2–3 percent of colorectal cancer patients) makes it difficult to quickly complete clinical studies of promising therapeutic approaches. Some of the reasons for inadequate participation include the unwillingness of many physicians to refer patients to clinical trials; many patients' lack of knowledge and inaccurate understanding of clinical trials; lack of resources to pay the patient costs associated with participation in trials apart from the medical costs; lack of awareness and understanding of the potential benefits of participation in a clinical trial; and lack of reimbursement of patient care costs by third-party payers.

- Although clinical trials in colorectal cancer have defined treatments associated with improved survival, the population enrolled in these trials may not be reflective of the population at large. The median age of patients in clinical trials, for example, tends to be somewhat younger than that of the overall population with colorectal cancer, and patients in clinical trials are usually required to have reasonably normal organ function and good performance status. The applicability of trial results, such as recommended treatments, to patients with different characteristics, such as advanced age, comorbidities, or belonging to minority ethnic groups, is not well studied. The effect of genetic heterogeneity affecting drug metabolism or immune response of patients with colorectal cancer is also not well defined. Better definition and careful assessment of the effect of such characteristics on outcome may lead to rational and effective treatment modifications to individualize therapy.

- Inadequate support is provided for tissue banking efforts, including accrual, clinical follow-up, and maintenance of the bank.

- Informatics systems and mathematical models are insufficient to adequately analyze the very large databases generated by new technology such as microchip arrays.

- Existing preclinical models are limited in their ability to identify the therapeutic potential of new agents in patients with colorectal cancer.

- Funding of clinical and laboratory investigators fails to cover the full costs of clinical and translational research, impeding progress in colorectal cancer research.

Resources Needed

- Development of infrastructure for quality assurance of staging, surgery, histopathology, imaging, tissue procurement, and testing for molecular markers
- Programs to educate the public and physicians about the value of clinical trials
- Negotiation with third-party payers, including private insurers and Medicare, to obtain reimbursement of patient care costs (apart from medical costs) associated with participation in clinical trials
- Increased funding for informatics systems and mathematical modeling to adequately analyze and interpret the huge research databases currently in development
- Development of appropriate preclinical models to screen new therapeutic agents and identify intermediate markers
- Increased funding for clinical and translational investigators involved in clinical research

RESEARCH PRIORITIES

Research Priority 1: Enhance local and regional therapy for colorectal cancer by fostering uniform delivery of accepted treatments and the development of new treatment regimens.

- Support health services research and the development and implementation of quality control techniques to minimize variability in the application of current standards of care (primarily surgery and pathology, in addition to diagnostic imaging, medical oncology, radiation therapy, and tissue handling).
- Support research to optimize regional therapy for metastatic disease by identifying the most effective applications of available and novel treatment approaches.
- Support research on radiation biology in order to optimize radiation treatment schedules and chemoradiation regimens.

Research Priority 2: Expedite new drug development by identifying innovative clinical trial endpoints.

- Expedite new drug development by identifying intermediate endpoints and surrogate markers of response that help to define mechanisms of action and predict clinical efficacy in order to guide choices of the best agents for randomized comparative trials. This is particularly relevant for agents that are not expected to be cytotoxic.
- Develop noninvasive tumor imaging techniques, both for diagnosis and for selection and evaluation of specific therapeutic agents.

Research Priority 3: Comprehensively characterize the biological features of both host and cancer in order to discover new indicators of prognosis and the likelihood of response to chemotherapy and radiation.

- Define prognostic and predictive molecular and biologic markers through biological, immunological, and biochemical studies of the tumor.

- Thoroughly elucidate host factors, such as advanced age, comorbid illnesses, immunological competence, and genetic predispositions) that may affect treatment outcome.
- Develop statistical and mathematical models to assess panels of multiple biomarkers and their effects.

Cancer Control and Survivorship

Co-Chairs: Edith Mitchell, Paul Engstrom

CURRENT STATUS OF THE FIELD

Cancer control is the conduct of basic and applied research in the behavioral, social, and population sciences that, independently or in combination with biomedical approaches, reduces cancer risk, incidence, morbidity, and mortality. The NCI has supported and promoted significant gains in research on colorectal cancer control by advancing understanding of colorectal cancer epidemiology, particularly in the areas of environmental, individual, and genetic risks. Still unknown, however, is whether and how specific interactions occur between specific risk factors (e.g., dietary, nutritional, genetic, behavioral) and outcomes.

Advances in screening technology and efficacy have provided a broader appreciation of the relationship and input of behavior in the screening process, in particular the impact of behavior (e.g., risk perception, health beliefs and practices, physician–patient communication) on participation in screening programs and adherence to surveillance and follow-up recommendations. Similar to the Pap smear for cervical cancer, colorectal cancer screening tools hold the promise of preventing or reducing the risk of invasive disease. However, because the use of these techniques relies heavily on their acceptance and appropriate use by both health care professionals and the general public, the role of research on cancer control in reducing the colorectal cancer burden is significant.

In addition, there has been a growing focus on cancer control relative to survivorship. Research is expanding on the management of colorectal cancer in the young and the elderly, as well as on the rehabilitation, psychosocial, and quality-of-life issues of survivors and their families. The establishment in July 1996 of the Office of Cancer Survivorship and, more recently, the Outcomes Research Branch within the Division of Cancer Control and Population Sciences (DCCPS) has provided an important opportunity to expand research initiatives in tracking health outcomes for patients and to promote rehabilitation and survivorship studies.

VISION FOR PROGRESS

To further reduce the burden of colorectal cancer, a vigorous and substantial commitment to basic and applied cancer control research, conducted by scientists from diverse disciplines, is needed. To be successful, this commitment must embrace an approach to research that addresses the behavioral, social, and population factors that affect disease across the continuum of health and illness: from monitoring, prevention, and surveillance in healthy and at-risk individuals; to early detection, treatment, symptom management, and follow-up of those diagnosed; to the provision of compassionate palliative care to those who have metastatic disease or are dying of their illness. As part of this effort, attention must be given to the impact on the patient's family of colorectal cancer risk and illness, ethical concerns, and the use and role of complementary approaches to care. In particular, given the growing use of complementary and alternative medicine in the population at large, a greater understanding of the psychosocial aspects that influence use of alternative therapies

and their impact on outcomes is much needed. Progress in cancer control research will depend to a great degree on the existence of a critical mass of dedicated experts, as well as on expanding training opportunities for those already involved in or wishing to develop expertise to conduct cancer control research.

The increasing number of survivors of colorectal cancer and those living with the disease, currently estimated as more than 866,000 individuals in the United States alone, has created a new challenge to the health care system to track and measure morbidity outcomes. The majority of individuals diagnosed with colorectal cancer today can expect to be cured of their disease or to live with it for long periods. Yet survivors face a spectrum of physical and psychosocial sequelae, among which are second cancers; adverse effects on major organ, cognitive, and sexual function; problems in the performance of work and social roles; and diminished quality of life. The incidence of long-term and late effects of treatment is likely to increase as access to treatment increases and the therapies themselves become more intense and hence potentially toxic.

Many early studies on the well-being of colorectal cancer survivors focused on their adaptation to colostomy. This research found high levels of psychosocial distress and dysfunction in treated patients and their partners. Much of this distress was associated with the physical demands and the sense of stigma associated with living with a stoma. Relatively less is known about patients' quality of life in the more modern era of reversible stoma procedures. Growing awareness of the multiple quality-of-life issues faced by cancer survivors has brought attention to the urgent need for more research on interventions that will reduce or, when possible, prevent adverse disease- and treatment-related outcomes.

Health communications research, in particular research on screening and surveillance behaviors, has significant potential for the control of colorectal cancer. New communication tools, such as interactive CD-ROM programs, on-line health resources, informational videotape and media projects, and tailored messages delivered to targeted communities, can potentially enhance information exchange among patients, families, friends, caregivers, and health care providers. More research is needed, however, to assess the effectiveness of these new communication modalities and their impact on information acquisition, behavior change, and overall health care decision-making. Importantly, this research must examine the impact of such communications with respect to diverse populations, taking into account the role or effect of gender, ethnicity, educational level, socioeconomic status, health experiences, age, cultural and religious beliefs, and language and reading ability. More knowledge about which communication strategies and formats are most effective in specific situations is needed so that interventions can be appropriately tailored and targeted.

Collaborations between the NCI and other public and private agencies and patient advocacy organizations have the potential to provide excellent opportunities for the development of research strategies in colorectal cancer control. Needed are research initiatives that explore how various research centers and health delivery organizations can successfully create partnerships to improve outcomes.

CHALLENGES AND OPPORTUNITIES

Monitoring and follow-up guidelines for patients successfully treated for colorectal cancer vary tremendously with respect to who follows these patients, the selection of diagnostic procedures, and the recommended frequency of testing. Decisions about follow-up are often made arbitrarily. Good clinical trials are needed to determine the best tests for the detection of recurrent or metastatic disease; the ideal monitoring interval; and the impact of testing on patient outcomes, including the assessment of psychosocial distress engendered by positive or false-positive results. Monitoring must also focus on the occurrence of second primary tumors, late effects of treatment and adverse organ function, tumor recurrence, mortality, and behavioral adjustments to the surveillance process.

The costs of follow-up testing should also be analyzed. Clinicians need to consider issues such as how patients respond physically to invasive procedures and how they manage the costs of additional testing, as well as the burden and costs of testing for patients, their families, and society. In this same vein, it is also recognized that, when the disease progresses, little consensus exists on the optimal management of patients at the end of life. Nor is information available on the cost of such care to society or on the physical and psychosocial impact of metastatic illness on patients and their families. Colorectal cancer care calls for the establishment and evaluation of the benefits of treatment guidelines that span the continuum of survivorship.

The impact of colorectal cancer on the physical, psychological, social, and economic well-being of patients and their families and caretakers is not well understood. Access to this information becomes increasingly important if physicians are to assess the effectiveness of different treatments and to facilitate informed patient decision-making regarding therapeutic options. Research is needed to identify the psychological and behavioral factors that put individuals at risk for poor adherence to colorectal cancer prevention and screening recommendations, or for poor outcomes (higher morbidity and mortality) once diagnosed.

Given that the majority of individuals at risk for and diagnosed with colorectal cancer are over age 65, it is important to examine the role of not only comorbid illness, but also concurrent life stressors (e.g., illness or loss of a spouse, social isolation, restricted mobility and income), on risk, behavior, and outcomes. On the basis of this information, psychological and behavioral interventions need to be developed that will reduce cancer-related anxiety and enhance screening and prevention behaviors among the "worried well," as well as improve physical and psychosocial functioning for those treated for or living with the disease. Interventions are also needed to promote healthy lifestyles for survivors and their families. Because of the potentially high health-related concerns among the affected population, providing interventions that encourage optimal fitness, both emotional and physical, may have benefits beyond improved colorectal cancer survival.

Results from clinical trials may not reflect the overall population in terms of ethnicity, income, gender, heterogeneity of age distribution, and other issues defining special populations, thus limiting the generalizability of data. The evaluation of therapeutic options in clinical trials, cancer control research, and epidemiologic studies should be made more pertinent to the

majority of patients experiencing colorectal cancer.

In particular, 72 percent of incident colorectal tumors affect persons ages 65 and older who may have concomitant major illnesses. Researchers need to evaluate the effects of comorbidity on colorectal cancer treatment. Although disease stage at the time of colorectal cancer diagnosis is a crucial determinant of outcome, comorbidity increases the complexity of cancer management and may affect the duration of survival. Moreover, older patients and their doctors often may delay diagnosis, considering changes in bowel function and other symptoms as generalized or indicative of benign conditions. Research on colorectal cancer in the 65-and-over age group needs to address a broad array of concerns, from surveillance of individuals at high risk (those with previous colorectal cancer, a family history of the disease, or specific genetic syndromes) and average risk (those with no predisposing factors) to the influence of concomitant age-related problems on clinical decisions, surgical management, and adjuvant treatment and survivorship.

Barriers and Gaps

- Clinicians and patients may have different expectations of follow-up testing. For example, results of tests such as the CEA change may generate panic or a false sense of security. Some clinicians order frequent tests, whereas others minimize testing. Few prospective, randomized clinical trials have been conducted to compare follow-up techniques, and retrospective studies are subject to numerous design biases.

- Information is scanty on behavior as it relates to screening, early detection, treatment, and follow-up surveillance. Little data exists on possible variations among individuals or populations in response to the signs and symptoms of colorectal cancer. In addition, assessment of the effectiveness of different treatments relative to characteristics of age (e.g., poor repair mechanisms, functional loss, increased susceptibility to treatment toxicity) is lacking. The multiple clinical problems of the aged necessitate examination of older persons for subtle or masked features of comorbid conditions in addition to the presenting cancer symptoms.

- Existing mechanisms fail to adequately define special populations or to identify methods to enhance their participation in clinical trials. Awareness of community-based oncology resources is low. Communication between cancer centers and community-based care providers is poor. Participation in clinical trials is affected by language variations, Institutional Review Board and informed-consent requirements, access to state-of-the-art care, cultural considerations, treatment preferences (of both patients and physicians), and socioeconomic status.

- Studies of colorectal cancer have to date paid too little attention to older patients (those aged 65 years or older). Many trials and cancer centers limit enrollment in clinical trials on the basis of age, and concurrent medical conditions may also exclude individuals from participation. Older patients'

knowledge base regarding colorectal cancer and their physical, social, and economic ability to participate in screening programs all may contribute to a more advanced stage of disease at diagnosis. Preoperative assessment of comorbid health problems, a major issue for older patients, is not standardized and may result in increased risk for adverse outcomes in the elderly.

- Although complementary and alternative therapies are widely used by patients with colorectal cancer, evaluation of the efficacy of these therapies is inadequate. Nonconventional treatments are not defined in a standardized manner and often lack measurable outcomes. They are not government regulated and usually are not covered by insurance. Members of peer review panels lack expertise in complementary and alternative medicine. Patients are reluctant to discuss their use of complementary and alternative care with their physicians.

- Patients may often resist screening for colorectal cancer because they perceive it as onerous. Older patients may not know they are especially vulnerable to this malignancy because they have not been targeted as a high-risk group for colorectal cancer screening. Health insurance may not cover the costs of screening. Adherence to prevention and surveillance regimens is often poor. Participation in screening may cause psychological distress or social consequences that are not well understood.

- Survivors of colorectal cancer may be reluctant to identify themselves as such, making it difficult to track or examine quality-of-life outcomes for those who have been successfully treated.

- Information about the quality of medical care for terminally ill patients is lacking. Access to patients to obtain such information is limited, because most of these individuals are confined at home or are cared for by multiple provider agencies. Pain assessment and management is inadequate among the elderly, disproportionately affecting those with colorectal cancer. Insufficient information exists about early referral and use of hospice services for colorectal cancer patients. This is particularly true for older patients, whose pain experience is often neglected, whose social support diminishes with advancing age because of loss of friends and family, and whose primary caregiver may be a spouse who is also in poor health. Some of the unique issues of those with advanced colorectal cancer (i.e., hepatic failure, bowel obstruction, and privacy issues) are poorly understood by both patients and those providing end-of-life care. Moreover, there is regional and national variability in the availability and standardization of medical care provided by hospice and long-term care organizations.

- Methodologies are lacking to evaluate the effectiveness of informed-consent procedures, particularly in older adults.

- Participation of consumers, including healthy and at-risk individuals and

colorectal cancer survivors and their family members, has often been lacking in the development of screening, treatment, and follow-up programs.

Resources Needed

Research resources—The NCI should support a network or consortium of hospitals, physicians, and cancer control researchers to systematically address the cancer control issues that attend colorectal cancer, including end-of-life issues. This network should include consumers, whose voices often are not considered in the decision-making process concerning the development and application of programs of care. Allocation of resources should accommodate patients' experiences, late effects of treatment, ethnicity, gender, socioeconomic status, age, and life experiences, as well as their physical, occupational, and emotional states. Consideration should be given to providing financial and infrastructure support for psychosocial and behavioral committees in clinical trials groups or establishing a psychosocial network of researchers in this area.

Strengthening of clinical trials—Resources are needed to train new clinical investigators. Educational and other programs are needed to enhance awareness of clinical trials and to foster more positive attitudes toward participation in clinical trials among special populations. Insurance issues that inhibit participation in clinical trials also need to be addressed.

Resources for complementary and alternative medicine—In addition to collaborating actively with the NIH Center for Complementary and Alternative Medicine, NCI should continue to have an Office of Alternative Care to collect and review information about complementary and alternative treatments used by cancer patients. Cancer centers' expertise in complementary and alternative treatment approaches should be enhanced.

Promotion of screening programs—Educational and other programs are needed to enhance the awareness of both the public and health care providers concerning the value of colorectal cancer screening. This effort should include exploration of the application of different screening strategies and possibly messages for different individuals or populations on the basis of their cancer risk status and the acceptability of, access to, and cost of testing. Models for prompting patient and/or physician use of screening should also be explored. Third-party payers should be involved in the process to improve insurance coverage of screening tests.

Expansion of population-based data sets—There is a need to expand the SEER database, health maintenance organization client databases, cooperative group treatment trials data, and comprehensive cancer center databases to study cancer control treatment outcomes. There is also a need to expand long-term surveillance and effectiveness of outreach to people at risk for colorectal cancer. Large, population-based data sets on effectiveness in outcomes are needed to enhance our understanding of treatment outcomes, pathways, and interactions among host, disease, and treatment. Expansion and use of the SEER database for special studies that can address many of these issues could expedite this process. In addition, expansion and support of the cooperative group clinical trials databases to gather outcomes information (in particular, tracking patients over time)

would also broaden our understanding of treatment outcomes.

Training of researchers and clinicians in cancer control—Additional efforts are needed to ensure that we will have a future generation of high-quality researchers and practitioners who are trained and invested in furthering understanding of, as well as disseminating findings related to, colorectal cancer control. Training programs are needed to increase the number of providers of appropriate end-of-life care.

RESEARCH PRIORITIES

Research Priority 1: Conduct studies to identify the best standards of follow-up care after successful treatment of colorectal cancer, focusing attention on which tests have the most impact on important outcomes such as resectability, survival, cost, and psychosocial distress.

- Develop a survey of patterns of care that are population based and connected to outcomes.
- Develop research designs such as randomized clinical trials to evaluate follow-up methods in various populations in order to develop evidence-based practice.

Research Priority 2: Develop mechanisms for identifying people at risk for adverse psychological distress and investigate whether psychosocial factors affect compliance with diagnostic and therapeutic regimens and outcomes (e.g., overall survival, cause-specific survival, disease-free survival, and quality of life).

- Develop and standardize survey instruments to assess psychosocial and functional quality of life, rehabilitation, and employment-related issues.
- Design and conduct studies of long-term psychosocial impact on patients currently in colorectal cancer trials.
- Develop and evaluate interventions in populations at increased risk for adverse psychosocial outcomes.

Research Priority 3: Assess the effectiveness of colorectal cancer treatments in elderly and special populations.

- Increase awareness of and focus on

- Evaluate age variation in cancer pathogenesis and progression and assess the effectiveness of different treatments relative to disease stage and age-related characteristics.
- Conduct research to determine the best clinical trial recruitment and retention programs.
- Study the influence of coexisting diseases and limited physical function on the surgical management and subsequent medical treatment of older patients with colorectal cancer.
- Develop and standardize interventions for alterations to or modifications of colorectal cancer treatment modalities in older patients due to noncancer pathology.
- Develop preoperative evaluation standards and evaluation tools (e.g., comorbidity status) to assist in the assessment of prognosis and treatment in older patients with colorectal cancer.

Genetics

Co-Chairs: Richard Kolodner, Raymond White

VISION FOR PROGRESS

The mutant alleles of specific cell regulatory and metabolic genes present in tumors are a major driving force in carcinogenesis, representing the most proximal causes of cancer. Just as the identification and characterization of the microbial agents that cause human infectious disease have led to interventions (e.g., public health measures, vaccination, antibiotics) that have greatly reduced the human burden of infectious disease, so do we expect characterization of the genes that drive the development of cancer to lead to new interventions that will prevent or effectively treat many cancers, including colorectal cancer. It is not feasible to specify at this point exactly what form the new interventions based on our genetic understanding will take; new chemotherapeutics and chemopreventive agents, nutritional additives, vaccines, and lifestyle changes are all possibilities, as are others not yet conceived.

The next 5–10 years will usher in an era of new gene-based diagnostics, some perhaps as components of new imaging systems, that will allow earlier diagnosis and intervention before metastasis, or even before the development of tissue invasion. There is evidence from observational studies, for example, that surveillance and removal of adenomas can have a great impact on colorectal cancer incidence and mortality. New diagnostic techniques may be based on the detection of adenomas through analysis of stool or blood samples for the presence of genetic changes or their metabolic consequences. This could enable much more widespread targeting of colorectal adenomas as a preventive measure or the very early detection of carcinoma as a basis for very early therapeutic intervention.

The next 5–10 years are also likely to see the development of new genetic diagnostic methods that will help individuals with specific, genetically based risks to determine their vulnerabilities and take appropriate action in terms of surveillance or prevention. Similarly, genetic analysis of individual tumors could provide guidance as to the most appropriate therapeutic approach.

In sum, the next decade could see accelerated reductions in colorectal cancer morbidity and mortality. As with infectious diseases, progress will be stepwise and may come from surprising directions. Increased knowledge of the primary causes of colorectal cancer, however, will in turn increase our ability to prevent or intervene in the progress of this disease.

CHALLENGES AND OPPORTUNITIES

Barriers and Gaps

The major challenge in colorectal cancer genetics is to complete the genetic characterization of tumor initiation and progression. This task can be accomplished through the creation of a library or "catalogue of parts" describing the genes and their protein products that play a role in the etiology of colorectal cancer. Such an undertaking will enable the identification of new targets for drug and diagnostic development and improve our ability to identify individuals at higher risk who may benefit from enhanced surveillance or preventive measures.

A second major challenge, as understanding of the catalogue of parts is expanded, is to understand how those parts work together normally in preventing the uncontrolled growth of cancer cells, or how they work pathologically in enabling the uncontrolled growth of cancer cells. Because the signal processing systems of the cell make up a network with built-in redundancies rather than separate pathways, the analytical complexity of the problem is greatly increased. This very complexity may also, however, ultimately result in the development of combinatorial approaches that offer much greater antitumor specificity.

Opportunities to discover and characterize the genetic basis of cancer are enabled by the generation of new research tools. Multiple new technologies in cellular and molecular biology, combined with the powerful analytical tools created through genome projects, could have the potential to yield an understanding of the genetic basis for cancer and create a new level of description and analysis.

BALANCING CONFIDENTIALITY AND IRB ISSUES

An important challenge in cancer research is the need to accommodate patients' rights to privacy and confidentiality while allowing investigators to address opportunities to gain fundamental insights into disease processes. This is a serious challenge both to the research community and to patients who want to contribute to an increased understanding of their disease.

TUMOR ACQUISITION SYSTEMS

Many of the costs associated with tumor acquisition, preservation, labeling, storage, and distribution and related paperwork are not covered under patient care costs, and other funding mechanisms are important. Moreover, pathologists cannot devote the time necessary to participate in tumor tissue acquisition without cost reimbursement.

Technologies for genotyping from paraffin blocks are inadequate. Support for the cost of providing human tissue samples is another component of this barrier. Whereas in the past the pathologist had supported time available to provide pro bono services, the much more stringent economic requirements of the environment of managed health care have made this extremely difficult. Without subsidy for the patient costs associated with tissue procurement under research protocols, access to patient samples is dwindling. Without human tissue samples, exploration of the genetic basis for human cancer could slow dramatically. A secondary, but related, barrier is in the difficulty of taking advantage of samples that are already archived in tissue blocks. The presently available technologies for obtaining access to the DNA of such samples are only barely effective. Improved technologies would free up an abundance of research opportunities through analysis of archived samples.

INFORMATICS DEVELOPMENT AND INFRASTRUCTURE

Information systems to archive and permit access to the abundance of data generated by increasingly powerful research tools have not been traditionally supported as part of NCI research funding. The computer and informatics capabilities of the colorectal cancer research community and laboratories are, therefore, well below what will be required for the genetic analysis of human cancer. The costs are not only time wasted applying primitive and cumbersome methodologies to data and information analysis, but are also very likely to be the inability to detect important connections among heterogeneous data sets.

Resources Needed

LARGE POPULATION-BASED SAMPLE SETS

Large (i.e., tens of thousands) population-based sample sets are ideally suited to the discovery and characterization of new predisposing genes and to the support of genetic studies of allele frequency and penetrance (sampling and genetic characterization of populations). The research community also needs access to new technologies that will permit the genotyping of these large numbers of samples; this cannot be accomplished at reasonable cost with existing technologies.

Large population-based sample sets are needed to determine the population frequency and relative risk associated with alleles that predispose to colorectal cancer. Initial studies are almost always based on sample sets that have been selected for a high density of affected individuals. This gives an artifactually inflated estimate of both the frequency and the penetrance of the allele in the nonselected population. These are important numbers, both in counseling to appropriately communicate risk and in determining the need and appropriateness of, for example, community-based screening programs. Many studies would benefit from access to such a large sample set. Establishing the sample set as a central resource would be much less expensive than independently funding individual groups to establish multiple large sample sets.

Large sample sets are also required for the discovery of new predisposing gene/allele systems. These sample sets are most efficient to the extent that they take advantage of the constraints of Mendelian inheritance to establish the association between a gene/allele system and predisposition to colorectal cancer. Thus, traditional case–control sample sets are the least efficient, sib–pair sample sets are more efficient, and large pedigrees would be the most efficient, if they were available. The PRG urges the creation of such resources that are available to the community at large. A useful example might be the consortium originally established in Paris for the mapping of human genetic markers as an international, collaborative effort. Lymphoblasts and DNA samples from 50 large families were obtained and archived for distribution to many research groups, who in turn contributed their primary data back to the consortium after publication.

For the resource proposed here, the sample sizes would be larger and population based, numbering even tens of thousands of samples. Furthermore, clinical characterization of the subjects with respect to colorectal cancer parameters would be necessary. Nevertheless, the principles could be similar; clinically characterized but anonymous DNA samples could be centrally archived and distributed to groups for testing of genetic hypotheses. The individual groups would publish their findings but be under constraint to report back their primary data in detail. Thus the combinatorial genetic profiles of the members of the sample sets would accumulate, offering new opportunities for analysis, including analysis of gene interactions.

MORE ACCURATE ANIMAL MODELS

Animal models that more accurately reflect human colorectal disease and response to therapeutics and preventive agents are needed for gene modifier discovery, hypothesis testing, and other types of studies. Animal models can also be used to generate hypotheses about biomarkers as surrogate endpoints.

A large number of genes seemingly relevant to human cancer have now been identified,

and many more are certain to be identified in the immediate future. In most cases, however, it is challenging to determine their specific role in tumorigenesis and to experimentally verify genetic hypotheses based on observations in the human system. Animal models are thus needed, for example, to test hypotheses of inherited predisposition. Genetically manipulated mice can be used to experimentally prove the hypotheses based on circumstantial evidence from the human system.

Furthermore, current animal models are only approximate reflections of human disease. More predictive models are needed and would be a worthwhile investment to help understand tumorigenesis, evaluate drug candidates, and explore biomarkers as potential surrogate endpoints of disease outcomes. Many groups are already profiling mouse strains to look for genes that modify the number and size of tumors. We do not have, however, a good model of distant metastasis (the *SMAD-3* knockout is best so far). Currently, mouse models are not held in high esteem by pharmaceutical companies because of their low predictive value for drug development. The NCI Mouse Models for Human Cancer Consortium is working on this; a problem, however, is that there is no drug for which a mouse model reliably predicts human response. The goal is to develop different predictive models and identify drugs that are most effective for different types and stages of disease genesis and progression. Models are also needed with which to look at the effects of smoking, diet, exercise, and other environmental influences. The new models should be in immune competent, fully mouse models (not transplanted human tumors) and should reflect human disease sites (i.e., tumor induction in cecum, not subcutaneous). Such models are likely to be highly useful, even given the limitations in studying different species.

Increasing knowledge of the genetic basis of human tumors now offers important opportunities to create more accurate and effective mouse models. Furthermore, increasing knowledge of dietary components that give more accurate reflections of human tumorigenesis also provide a new basis for optimism that better models can be developed. If models that could predict the response of human tumors to new drugs could be developed, it would save a great deal of cost in human clinical testing as well as reducing the burden of patients who may participate in trials of drugs that ultimately prove to be ineffective. Invertebrate animal models are useful for studies of some pathways and perhaps normal intestinal development, but it is unclear how useful they are in drug development. The zebrafish system should be more carefully considered, however, as it shares much of the flexibility of invertebrate genetic systems but in fact is a vertebrate and thus is much closer biologically to the human system.

ETHICS CLEARINGHOUSE

A clearinghouse should be established to help Institutional Review Boards (IRBs) and investigators more consistently address confidentiality, consent, and other ethical issues. A center or clearinghouse is needed to advise subjects/patients, investigators, and IRBs on ethical issues. The Department of Health and Human Services is proposing to establish Information Protection offices; rather than creating another bureaucracy, the recommendations of the National Bioethics Advisory Board should be adopted at the national level and distributed as guidelines to the local IRBs.

RESEARCH PRIORITIES

Research Priority 1: Identify the genes that predispose to colorectal cancer (including major and minor

alleles of known predisposing genes).

The following need to be identified:

- New genes with predisposing alleles
- Less penetrant alleles of known predisposing genes
- Allele frequencies and penetrances of known gene/allele systems
- Modifiers of penetrance or expressivity of predisposing genes

A major goal in the study of the genetics of colorectal cancer is not only to understand the genetics of inherited predisposition, but also to understand the critical pathways in the more common sporadic cancers. A small proportion (2–5 percent) of colorectal cancer cases can be attributed to the inheritance of strongly predisposing alleles at the known loci (*APC*, *MSH2*, *MLH1*). However, it is likely that a much higher percentage of cases may result from inherited susceptibility due to medium- or low-penetrance alleles, which may also require an interaction between environmental and inherited factors. A more detailed understanding of the underlying genetic susceptibility to colorectal cancer offers an important opportunity to improve the prevention, early diagnosis, and treatment of colorectal cancer. A natural outcome of these studies will be the development of improved molecular diagnostic methods for use in applying genetics to the management and treatment of colorectal cancer.

Knowledge of the population frequency and penetrance of predisposing mutations that cause these syndromes is imperfect. Large-scale, population-based studies are needed to determine the prevalence and penetrance of predisposing mutations in the population and identify the interactions between these alleles and environmental factors and other genes. It will be preferable to link such genetics studies to functional studies in order to understand the basis of mutations that show reduced penetrance. It will also be preferable to develop patient populations that facilitate studies of association of genetic traits with Mendelian inheritance, clinical outcomes, prognostic factors, and interaction with diet and other environmental factors and that ultimately allow the use of genetically defined populations in clinical studies.

Studies of familial risk suggest that there may be inherited risk, albeit with reduced penetrance, involved in many cases of colorectal cancer, thus providing a rationale for searching for medium- and low-penetrance predisposing genes and alleles. Indeed, recent studies have suggested that such moderately penetrant alleles of the *MSH6* and *TGFBR1* genes may be present in the human population at a moderate frequency. It is important to continue the search for additional medium- and low-penetrance genes that predispose to colorectal cancer and to study both their penetrance and their population frequency, as is proposed for the high-penetrance genes. Included in these genes would be those that are important in combination with environmental factors, such as modifier genes and genes that may play a role in response to environmental and lifestyle components.

Research Priority 2: Determine how morbidity, quality of life, and mortality are affected by genetic screening and interventions to address human issues (e.g., counseling, disclosure issues).

Theoretically, individuals identified by genetic screening as carrying specific genetic risk factors could benefit from enhanced screening programs and genetic counseling. Substantial efforts now go into

these programs, based on the assumption that there are features associated with genetic risk that distinguish it from other forms of risk more familiar to the medical profession, such as high cholesterol or hypertension. Proof is needed of an association between decreased morbidity and mortality or enhanced quality of life and the identification of individuals carrying specific, genetically determined risk factors and support of these individuals with testing and intensive counseling efforts. Research efforts aimed at measuring these potential benefits or risks would be extremely useful in refining our approaches to these challenging new areas.

It has been shown, for example, that screening compliance increases with better delineation of risk. FAP and HNPCC families often have good screening compliance, but they may also have fatalistic attitudes that cause them to avoid screening. There are very few funded studies that specifically address the effect of genetic information on screening behavior for colorectal cancer. More work, however, is needed in this area (e.g., how information about genetic risk is communicated to the individual). These and other psychosocial issues might also have an impact on how recruitment for chemoprevention studies should be structured. Follow-up in these studies would be essential.

Research Priority 3: Determine whether there are specific tumor genetic subtypes, how these can be linked to histologic type and other known factors, and how knowledge of such subtypes can be used to improve drug development, intervention selection, and prognosis assessment.

Genetic and other analyses indicate substantial heterogeneity among tumor samples with respect to the presence or absence of mutations in specific genes. Sometimes, specific complementarity of mutations can be seen, as in, for example, the appearance of beta-catenin mutations in tumors not mutant for the *APC* protein. Because both mutations affect the same signaling (*Wnt*) pathway, this example would suggest that the activation of the *Wnt* pathway may be essential to colorectal carcinogenesis. However, analysis of other colorectal carcinomas fails to reveal mutations in either gene. It will be important to determine whether there is an alternate signaling pathway that can be activated or inactivated, leading to colorectal cancer. Furthermore, substantial variation is also seen in other components: sometimes *P53* is found to be mutant, whereas at other times it is not. Sometimes the *TGF*-beta pathway (*TGF*-beta receptors or an *SMAD* allele) is found to be inactivated, whereas at other times it is not. Substantial variation among tumors is also seen in the pattern of expressed transcripts; although the patterns overlap, there are also differences. Finally, the histology or morphology (an endpoint of changes in gene/protein activities) of colorectal tumors also varies. In sum, this variability strongly suggests that there may be considerable heterogeneity among those tumors classified as colorectal: although they appear grossly similar, at a more basic level they may be quite different.

In addition to the need to determine and define subtypes of colorectal tumors, there is an opportunity provided by the increased power of genomic technologies. Methods for efficient, high-throughput sequencing and mutation detection, as well as technologies to scan entire genomes for small rearrangements, amplifications, and deletions through microarrays, are maturing rapidly. These approaches now need to be applied to large sets of clinically characterized tumors and the data linked to

therapeutic response and outcomes. More specifically, an extension of the current CGAP program, where transcription profiling is already underway, might be expanded into a colorectal cancer tumor heterogeneity program to identify the broad spectrum (type, number, patterns) of mutations, as well as the extent and character of genomic instability, that occur in colorectal cancer tumors. Such a project could also involve full sequencing of a relatively small chromosomal region across a small number of tumors to assess the background frequency of mutation in tumors. Other correlates (e.g., environmental factors, response to specific therapies) could be studied once tumor subtypes have been identified.

Key issues would also include determination of mutations that occur early in tumor pathogenesis, as seen in precancerous lesions, and the identification of tumor suppressors and dominant alleles that occur later. Specifically in the area of tumor progression, research is needed to identify the later mutations in the tumor pathway that drive invasion and metastasis. Research questions would thus include how many distinct pathways lead to colorectal cancer, whether there are clinical differences in prognosis and therapeutic recommendations associated with tumor subtypes, and whether there are essential genes induced in tumors whose proteins are candidates to become chemotherapeutic drug targets or diagnostic markers. Research approaches for the future thus include gene expression profiling, identifying fingerprints of genetic change, mutational and expression definitions for tumor subtypes, clinical studies of the natural history of tumor subtypes, and development of new therapeutics or diagnostics based on genetically defined targets.

Research Priority 4: Determine how relevant gene targets for new therapeutics can be identified.

One of the major long-term challenges of research on the genetics of cancer is to facilitate the development of better drugs for the treatment of colorectal cancer, particularly metastatic disease. What is ultimately needed in this endeavor is the identification of targets that can be applied to the treatment of colorectal cancer. Predisposing genes identify pathways that can initiate tumorigenesis. The analysis of the genetic, epigenetic, and expression pattern changes that occur during colorectal tumor progression and metastasis could lead to the identification of crucial proteins and pathways that are inactivated, have altered activity, or are misregulated in cancers. These latter studies could also help determine the number of colorectal cancer types and facilitate their identification. It is crucial to understand how to exploit these changes for the development of therapeutics.

An innovative research program stressing novel approaches will be required to fully exploit the discoveries of cancer genetics in the development of improved therapeutics. Once the genetic and epigenetic changes that underlie cancer predisposition, progression, and metastasis have been identified, sophisticated model systems ranging from yeast to mice and human cell systems will be required in order to fully understand the cellular consequences of these defects. Once such studies have led to potential candidate targets, appropriate cell-based and animal model systems will be required for proof of principal experiments and, ultimately, for evaluating therapeutics. All of this will have to be linked to appropriate translational research efforts to demonstrate applicability to the clinical situation.

Environment and Lifestyle

Co-Chairs: María Elena Martínez, Tim Byers

VISION FOR PROGRESS

Over the past decade, a great deal has been learned about the etiology of colorectal cancer as it relates to lifestyle and environmental factors. The next decade offers many unique opportunities to refine current knowledge, study mechanisms, and merge the perspectives of various disciplines.

CHALLENGES AND OPPORTUNITIES

Barriers and Gaps

Among the most significant gaps in colorectal cancer research is the scant interdisciplinary training of investigators. Few scientists are cross-trained to conduct and interpret complex investigations of biologic mechanisms and assessment of behavioral risk factors. There is a need to attract and train such investigators, preferably through the career development award mechanism. Peer review of interdisciplinary projects is similarly inadequate. Attracting and training young investigators will increase the number of qualified peer reviewers to judge interdisciplinary studies.

A second barrier relates to the scarcity of culturally and ethnically diverse populations under study. Minority populations are not enrolled in sufficient numbers in observational studies and prevention trials. Much of the accumulated knowledge of environmental and lifestyle etiologic risk factors can be applied with confidence only to whites (and sometimes, only to select subpopulations of whites), who have made up the great majority of study populations. The reasons for this disproportionate representation are complex, and recruiting more minority volunteers will not be easy. However, broadening current understanding of risk factors for colorectal cancer will require conducting additional studies across diverse populations.

Resources Needed

Interdisciplinary and interinstitutional research consortiums need to be established to advance the study of molecular nutrition in human populations. Such collaborative resources could link investigators with molecular nutrition expertise with those at institutions with a clinical and epidemiologic focus. This could facilitate joint projects, enabling pooled analyses with adequate statistical power for valid subgroup analyses. Such an infrastructure would support collaborative research on molecular nutrition and genetics linked to observational and clinical studies of nutritional factors for colorectal cancer prevention. If this capability were established, critical research questions could be investigated more quickly and efficiently.

It is difficult to justify new, large-scale, randomized controlled trials for the prevention of advanced adenomas or cancer if these trials are aimed at testing the effects of primary prevention (i.e., diet, tobacco, physical activity) for either adenomas or cancer, given the latency of the effects and the lack of cost-effectiveness compared with possible alternatives. An alternative for current ongoing trials would be to consider studies to perform endoscopic examinations (i.e., screening for adenomas) piggybacked onto other studies. These might include

studies such as the Diabetes Prevention Program, the Women's Health Initiative, the SHOW trial, the SELECT trial, and the STAR trial.

RESEARCH PRIORITIES

Research Priority 1: Integrate observational screening and interventional approaches in future studies.

- Identify lifestyle and environmental factors that could decrease the risk of cancer in order to help to identify individuals who may need less frequent screening.
- Identify risk factors that increase an individual's risk of adenoma recurrence in order to help in the development of specific recommendations for surveillance.
- Determine how prevention interventions might be used to complement surveillance protocols.
- Encourage epidemiologic studies nested within cancer treatment studies.
- Collect risk factor data from participants enrolled in randomized controlled treatment trials in order to identify environmental and lifestyle factors related to treatment outcome.

Research Priority 2: Improve assessment and characterization of lifestyle and environmental factors.

- Characterize dose-response relationships with known environmental risk factors (e.g., physical activity, diet, and obesity).
- Study the potential additive effects of combined risk factors. Whereas a single beneficial factor might have only a small impact, a combination of two or more factors may greatly alter the risk of developing colorectal cancer. Likewise, combinations of two or more adverse risk factors, or combinations of both beneficial and adverse risk factors, may have definable and predictable impacts on the development of cancer.
- Study nutrient combinations that might be delivered through food fortification.
- Develop better biological markers of exposure variables and identify intermediate biomarkers of risk in order to improve assessment of lifestyle and environmental factors. For example, in dietary assessment, data generated from questionnaires can be greatly enhanced by the use of biochemical markers in blood, urine, or other tissues. The availability of accurate and complete nutrient databases is also important.
- Improve appraisal of potential bias in exposure measurements in order to draw sound conclusions about the relationship of various lifestyle and environmental factors to cancer etiology. Study bias and contradictory findings with respect to nutrition and lifestyle factors have decreased confidence in study results. This problem must be addressed if further progress is to be made in the evaluation of nutrition and lifestyle interventions.

Research Priority 3: Improve the biological coherence of studies.

- Assess gene-environment interactions within the framework of specific biological hypotheses.
- Examine both genetic and environmental risk factors in a unified approach to study the etiology of colorectal cancer.

- Specify and study specific biologic mechanisms through which multiple etiologic factors operate. For example, it has been proposed that the modifying effect of factors such as physical inactivity and obesity on colon cancer might be acting through their effects on growth factors such as IGF-1.
- Foster collaboration between molecular and population scientists.

Partnership Platforms

Co-Chairs: David Parkinson, Philip Frost, Ernest Hawk

There is general agreement on the need for interactions among organizations involved in the discovery and development of new technologies and therapeutics. Currently, however, little such interaction occurs. Cooperative relationships between the NCI and pharmaceutical companies are almost exclusively based on the NCI's interest in a particular product. Interaction between the NCI and the Food and Drug Administration (FDA) to define criteria for undertaking clinical development has been limited, as has use of patient advocacy groups to assist in protocol development and clinical recruitment. Finally, interactions between medical oncologists and other specialties, including gastroenterologists, surgeons, and radiologists, have not been extensively fostered. Thus, important opportunities to improve the validity, reliability, and efficiency of clinical trials have been missed.

VISION FOR PROGRESS

Greater interaction among the NCI, the FDA, pharmaceutical and biotechnology companies, physicians, and patient advocacy organizations will foster innovative approaches to drug discovery and development. Numerous opportunities exist that can be capitalized on in the near future to enhance such interaction, thus expediting and facilitating the discovery and development of drugs and devices to prevent and treat colorectal cancer.

CHALLENGES AND OPPORTUNITIES

The development of standardized agreements for NCI contracting and grant award procedures relating to licensing and intellectual property rights would relieve some of the legal barriers to collaboration. Such standardization could facilitate legal and contractual agreements between academic institutions and pharmaceutical companies by establishing basic criteria for these relationships. In short, if NCI clearly defines intellectual property ownership, a similar pattern could be used for interactions between academia and industry.

The establishment of minimum criteria for clinical data collection, monitoring, and auditing would considerably facilitate drug development and dramatically reduce resource expenditures. Currently, investigators accumulate excessive amounts of information for fear of not meeting FDA guidelines. Although every clinical trial has unique characteristics, it should be possible, for example, to define the assessment of toxicity parameters in a standardized manner. The perception of the NCI as a neutral evaluator would facilitate acceptance and trust of these criteria by all involved parties. This approach does not rule out the need to collect, for specific purposes, data in addition to the core data set.

Investigators working on selective targets should be encouraged to consider the early development of diagnostics that could ultimately be used in clinical assessment. For example, the development of a kinase inhibitor requires the use of assays for the enzyme in preclinical studies. However, many of these assays cannot be adapted to human tissue and so cannot be used in clinical trials. Addressing this issue early by testing assays in available human tissues would facilitate their ultimate use as markers of biologic activity. Clearly, one cannot

biopsy all patients to measure drug effect for a particular target, but the availability of tissue from a small number of patients would be sufficient to demonstrate proof of concept.

Refinement of FDA review procedures would allow for co-development of a diagnostic device and therapeutic agent within the same protocol and review setting. This approach would permit the diagnostic and therapeutic components of a product to be reviewed in parallel rather than independently.

Fostering of relationships between the NCI and patient advocacy groups could facilitate the development of clinical protocols and the recruitment of subjects for trials. Drug development time might be reduced through the use of advocacy groups to direct patients to appropriate clinical trials, including those conducted by pharmaceutical companies.

Clinical trial endpoints can be more clearly defined. This need is particularly acute for newer "cytostatic" agents that may not fulfill the standard criteria for response used in the past for cytotoxic agents—namely, tumor shrinkage. Although prolongation of survival is widely accepted as a valid endpoint, other endpoints—such as time to progression, time to recurrence of symptoms, and endoscopic- or tissue-based markers—have not been validated. An example is adenoma recurrence in high-risk patients. The planned American Association for Cancer Research (AACR)/FDA meeting on intraepithelial neoplasia is an example of how such interactions could be fostered. This approach could shorten development time for preventive agents and increase the willingness of both investigators and patients to participate in trials.

Interdisciplinary interactions among clinical oncologists, gastroenterologists, surgeons, and radiologists would facilitate the conduct of clinical trials. Gastroenterologists have technical expertise in evaluating premalignant and malignant lesions, whereas oncologists contribute extensive experience in the design and conduct of clinical protocols. Surgeons and radiologists will participate more enthusiastically in trials in which they have had some design input. Members of all of these disciplines should be accepted as part of the development team and given the resources and ability to participate fully in the design and conduct of trials.

Pharmaceutical companies need economic incentives to perform prevention studies. Without such incentives, most companies are unwilling to undertake the costs and liabilities of large, long-term prevention trials. Examples of such incentives include extending the patent life of a compound that enters prevention trials and providing specific tax incentives for conducting prevention trials.

Protocol design consistent with international regulatory standards would foster the pharmaceutical industry's ongoing global development efforts.

Factors limiting interactions among organizations involved in drug discovery and development include the following:

- Financial issues related to patient rights, intellectual property, and study costs
- Differing institutional priorities
- Compartmentalization of thinking
- Institutional reticence to interact because of fear of losing control
- Poor communication
- Misperceptions of regulatory agencies' requirements
- Lack of standardization of rules and regulations across agencies

RESEARCH PRIORITIES

Research Priority 1: Develop standard agreements for contract or grant award procedures for licensing and intellectual property rights, data collection, and auditing.

Research Priority 2: Develop validated markers of biological activity to facilitate clinical trials, as part of a strategy to link the development of diagnostics and therapeutics.

Research Priority 3: Foster partnerships among oncologists, gastroenterologists, surgeons, and radiologists to improve patient access to and facilitate the conduct of clinical trials.

Imaging

Co-Chairs: David Vining, Gerald Dodd

VISION FOR PROGRESS

Imaging plays a central role in every aspect of colorectal cancer management, including population screening, surveillance, staging of disease, and assessment of patients undergoing treatment. Potential roles yet to be explored include functional/molecular imaging to enable more refined and effective therapies and basic research to shed light on the genetics and biochemistry of colorectal cancer. Although most imaging advances have occurred over the past 30 years, more recent developments in molecular biology and genetics suggest that functional imaging techniques on the horizon will lead to a better understanding of colorectal cancer.

Future imaging modalities may eventually be able to identify tissue characteristics down to the cellular and even molecular level, a giant leap beyond the whole-organ view of current clinical imaging. Tissue characterization presents the most difficult challenge and yet holds the greatest promise for the detection of microscopic disease. Basic sciences have generated important information about tissue processes (e.g., angiogenesis, growth kinetics, drug delivery), cellular dynamics (e.g., tumor markers, drug targeting), and genetics (e.g., gene mutations, gene therapy). However, a major gap in communication between the fields of basic science and imaging inhibits the development of functional/molecular imaging techniques. Imaging scientists in radiology and nuclear medicine need to interact more closely with basic and translational researchers who have developed animal models of colorectal cancer. Together these groups need to develop optimal imaging technologies dedicated to evaluating disease initiation, progression, and response to alternative therapies in both patient and animal model studies. Research initiatives are needed to develop suitable imaging markers, targeting/delivery systems, signal amplification strategies, and dedicated imaging systems.

CHALLENGES AND OPPORTUNITIES

Imaging Modalities

Barium enema—Despite its poor public perception and competition from endoscopy, the barium enema remains a useful procedure for visualization of the colon in cases of failed or incomplete endoscopy and where populations lack endoscopic services. However, the true efficacy of the barium enema as a screening test has not been determined.

Endoscopy—Numerous ancillary technologies have allowed endoscopy to extend beyond the macroscopic, normal-spectrum visualization of mucosal surfaces to include fluorescent imaging, high-magnification endoscopy, and endoscopic ultrasound.

Computed tomography—Computed tomography (CT) is used frequently for the primary workup and staging of colorectal cancer as well as assessment of treatment response and surveillance after initial curative therapy. Recent advances in CT technology, such as multi-detector helical CT scanners, have significantly improved image resolution, shortened examination times and radiation exposures, and fostered new procedures such as CT

colonography/virtual colonoscopy. Exploration of these new modalities is fertile ground for continuing research.

Ultrasound—The use of ultrasound in colorectal cancer imaging is focused on specific needs, such as local tumor staging with endoscopic ultrasound or biopsy guidance for suspected liver metastases. It remains to be seen whether the development of sonographic contrast agents for liver imaging may establish new opportunities for this modality.

Magnetic resonance imaging—The tissue contrast resolution achieved with magnetic resonance imaging (MRI) is superior to those of other imaging modalities. MRI thus has proven beneficial for the evaluation and characterization of suspected liver metastases from colorectal cancer. Unfortunately, costs and limited availability of state-of-the-art MRI scanners have limited its widespread use. Specialized techniques, such as endorectal MRI for staging rectal tumors and MRI colonography/virtual colonoscopy, may prove beneficial. The development of novel MRI contrast agents and MRI spectroscopy for colorectal cancer imaging is a goal for future exploration.

Nuclear medicine—Nuclear medicine resolution has improved dramatically with the use of single-photon emission computed tomography (SPECT). The design of monoclonal antibody tagging agents and molecular imaging techniques have restored interest in this modality. Future progress of molecular imaging research will depend on the development of specific targeting reagents.

Positron emission tomography—Positron emission tomography (PET) was slow to emerge in the clinical arena, but the recent development of more affordable PET scanners and reimbursement by insurers has stimulated its use in colorectal cancer imaging. Recent reports of PET's ability to detect earlier metastases and to monitor tumor response to chemotherapeutic agents has made this one of the most exciting technologies in the radiologic armamentarium. Further investigation is required into PET's ability to characterize the biology of an individual patient's tumor in order to select the best treatment regimen.

Barriers and Gaps

- Costs of equipment and development of techniques are high.
- The risks of imaging procedures are often misunderstood, leading to poor acceptance by patients.
- Inadequate understanding of the benefits and limitations of imaging techniques often leads to poor utilization of imaging by clinicians.
- Issues regarding data ownership and confidentiality impede the establishment of image databases and the sharing of research information.
- Intellectual property issues frequently inhibit the imaging industry's support of research activities.
- Lack of standardized image reporting techniques (e.g., how a radiologist describes a tumor on a CT image) could affect treatment decisions.
- Lack of standardized imaging protocols can lead to variations in a lesions's appearance on an imaging examination. Uniform scanning protocols need to be designed to ensure reliable study results.

Resources Needed

- As imaging scientists and radiologists enter the arena of colorectal cancer research (many for the first time), the availability of databases listing image-based projects and colorectal cancer researchers would greatly benefit collaborative efforts.

- The establishment of digital image databases linked to proven clinical outcomes and electronic medical records would enable the development and testing of image processing and analysis algorithms. Such databases should be made accessible via the Internet while patient confidentiality is maintained.

- Standardized lexicons and structured reporting methods (as opposed to conventional narrative descriptive reports) are needed to facilitate clinical trials and patient care by improving communication between radiologists and clinicians.

- The establishment and support of consortia to assist in shared instrumentation (e.g., cyclotrons), software, and multidisciplinary approaches (e.g., ACRIN) are needed to foster colorectal cancer research. More direct involvement of radiologists in clinical trials and cooperative groups could prove to be advantageous.

- Development of dedicated small-animal MRI, CT, SPECT, and PET imaging systems need to be designed to take advantage of the exploding knowledge of genetics and biochemistry of colorectal cancer and emerging animal models of this disease.

- Education of patients and primary care physicians regarding existing imaging technologies is needed to overcome widespread ignorance and fear of screening and diagnostic procedures. Primary care physicians generally do not follow established guidelines for colorectal cancer. Education and prompting of both primary care physicians and their patients is needed to increase compliance with guidelines.

RESEARCH PRIORITIES

Several initiatives involving imaging technologies are already described in the National Cancer Institute's (NCI's) 2001 budget proposal. However, the Progress Review Group (PRG) participants determined that the initiatives pertaining to 1) functional/molecular imaging, 2) advancement of existing and novel technologies, and 3) outcomes analysis could greatly benefit colorectal cancer research and yield significant public health benefits within the next decade.

Research Priority 1: Apply functional and molecular imaging in the selection of screening, surveillance, and treatment strategies to enhance monitoring of chemopreventive and chemotherapeutic responses.

- Accelerate research in this area by developing animal models to test functional imaging.

Research Priority 2: Further refine existing and develop novel imaging technologies for the advancement of colorectal cancer screening, staging, and surveillance strategies.

- Endoscopic techniques, including photodynamic and fluorescent imaging, may prove valuable for identifying patients with premalignant dysplasia in the colorectum as well as in other areas of cancer research, such as cancers of the oral cavity, tracheobronchial tree, esophagus, stomach, bladder, and uterine cervix.
- High-magnification endoscopy may enable identification of the earliest neoplastic lesions in the colorectum, called aberrant crypt foci, that may allow for risk stratification or may be useful in monitoring chemopreventive efficacy.
- Endoscopic ultrasound and other imaging modalities, with or without guided biopsy, may allow for more accurate staging, which would direct the selection of preoperative radiation or other management decisions.

Research Priority 3: Allow for rapid assessment of emerging imaging technologies.

- Continue to support the goals of the NCI-sponsored American College of Radiology Imaging Network (ACRIN) to implement standardized and streamlined methods to guide cost modeling, assess cost-effectiveness, and develop practice guidelines for patient management.
- Support outcomes research to assess the efficacy of imaging modalities, specifically as they relate to patient management, are desperately needed.
- Determine the frequency with which patients should be imaged postoperatively to detect treatable colorectal cancer metastases or recurrence.
- Determine the outcomes and cost-effectiveness of current screening recommendations, stratified to adenoma size and patient cohort.

Behavioral and Health Services Research

Co-Chairs: Ronald E. Myers, Monica Bertagnolli, Sally W. Vernon, Linda Rabeneck

VISION FOR PROGRESS

Effective prevention, screening, diagnostic evaluation, and treatment modalities are currently available for the management of colorectal cancer. There is an unprecedented opportunity to substantially reduce colorectal cancer morbidity and mortality in the near future through the optimal application of current and emerging modalities that are on the horizon. Developing effective approaches for bringing scientific discoveries to populations at risk will hasten the day when prevention and cure of colorectal cancer are the rule rather than the exception.

CHALLENGES AND OPPORTUNITIES

Development of effective strategies to reduce colorectal cancer morbidity and mortality requires investment in an integrated approach that engages researchers, diverse populations , providers, policy makers, and health care systems. Behavioral and health services research is needed to accomplish the following:

- Identify variations in the availability of, access to, and utilization of effective cancer prevention, screening, diagnostic evaluation, and treatment modalities in diverse populations and settings
- Develop effective methods for increasing the availability of, access to, and utilization of effective cancer prevention, screening, diagnostic evaluation, and treatment modalities in diverse populations and settings
- Link variations in utilization and related changes to practice and outcomes

Barriers and Gaps

Translational research is commonly understood as research that moves new scientific discoveries from the bench to the patient bedside. Although this process generates technologies to combat colorectal cancer, research that translates effective technologies from the bedside in the clinical setting to standard medical practice for populations is necessary to realize significant public health gains. Several factors currently restrict society's capacity to achieve that goal:

- Prevailing patterns of colorectal cancer prevention, screening, diagnostic evaluation, and treatment are not well characterized.
- Determinants of colorectal cancer prevention, screening, diagnostic evaluation, and treatment utilization are not well understood.
- Optimal methods for achieving widespread utilization of effective colorectal cancer screening, diagnostic evaluation, and treatment modalities are not well developed.
- Definitive behavioral models that can guide research on the utilization of current and future colorectal cancer prevention, screening, diagnostic evaluation, and treatment modalities are needed.
- Precise measures of colorectal cancer risk and quality of care are not available.

- Special and underserved populations have limited access to effective methods of colorectal cancer prevention, screening, diagnostic evaluation, and treatment.
- Limited participation in clinical trials delays the identification and validation of prevention, screening, diagnostic evaluation, and treatment modalities.
- The availability and/or utilization of colorectal cancer screening is limited in health care systems.

Resources Needed

- Support for the development and maintenance of prevention, screening, diagnostic evaluation, and treatment databases that are linked to outcomes.
- Support for theoretical model and intervention development, measurement instrument design, and the synthesis of related research information (e.g., systematic literature reviews and meta-analyses).
- Support for interdisciplinary colorectal cancer research that involves health services researchers and behavioral, clinical, and basic scientists.
- Support for training programs in colorectal cancer research that serve to facilitate interdisciplinary collaborations.
- Support for the development of systems for archiving and disseminating information about methods for facilitating the use of effective modalities of colorectal cancer prevention, screening, diagnostic evaluation, and treatment.
- Development of mechanisms to track NCI funding of PRG recommendations.

RESEARCH PRIORITIES

Research Priority 1: Develop conceptual models and methods that relate to the efficacy, effectiveness, and cost-effectiveness of intervention strategies, including those that increase the use of effective colorectal cancer prevention, screening, diagnostic evaluation, and treatment modalities, as well as those that enhance the quality of care.

- Develop explanatory models that can be used to explain decision-making about, and the utilization of, colorectal cancer prevention, screening, diagnostic evaluation, and treatment modalities. The models should address issues related to the utilization of single and multiple modalities that can serve to reduce the cancer burden (e.g., fecal occult blood testing, endoscopy, imaging).
- Design reliable, valid, and generalizable methods for measuring risk (e.g., genetic and lifestyle factors), behavioral determinants (e.g., demographic background, medical history, and psychosocial and cultural characteristics), behaviors (e.g., periodic screening and follow-up, decision making), quality of care (e.g., use of state-of-the-art procedures, timely provision of care), and outcomes (e.g., vital status, quality of life).
- Develop intervention approaches to facilitate the informed utilization of prevention, screening, diagnostic evaluation, and treatment modalities. These approaches should reflect advances in model development and measurement and should be applicable in diverse populations and settings.

- Identify gaps in knowledge about barriers to and facilitators of screening, particularly those related to special and underserved populations.

Research Priority 2: Characterize variations in patterns of colorectal cancer prevention, screening, diagnostic evaluation, and treatment, including quality of care, for populations, among providers, and in health care systems.

- Identify the determinants of variation for the general population, at-risk groups, providers, and health care systems.
- Measure and monitor the impact of colorectal cancer prevention, screening, diagnostic evaluation, and treatment patterns on health-related outcomes (e.g., morbidity, mortality, survival, and quality of life).
- Generate needed knowledge and methods related to the general population, at-risk groups, and special and underserved populations.

Research Priority 3: Develop and evaluate strategies for (a) improving access to screening, diagnostic evaluation, treatment, and clinical trials and (b) increasing participation in clinical trials of colorectal cancer prevention, screening, diagnostic evaluation, and treatment.

- Identify gaps in knowledge about barriers to and facilitators of access to colorectal cancer prevention, screening, diagnostic evaluation, treatment, and clinical trials.
- Develop effective methods for increasing access to colorectal cancer prevention, screening, diagnostic evaluation, treatment, and clinical trials.
- Identify the determinants of participation in clinical trials, such as characteristics of at-risk individuals, providers, and health care systems.
- Develop and evaluate strategies to improve recruitment and retention in clinical trials.
- Generate needed knowledge and methods related to at-risk groups and special and underserved populations.

Research Priority 4: Develop and test strategies for increasing the availability of effective colorectal cancer screening, diagnostic evaluation, and treatment methods and opportunities for participation in clinical trials in health care systems.

- Identify structural and organizational determinants (e.g., manpower, financing arrangements, capacity, health policy) that affect the availability of effective colorectal cancer screening, diagnostic evaluation, and treatment and opportunities for participation in clinical trials.
- Develop strategies to optimize the availability of effective colorectal cancer screening, diagnostic evaluation, and treatment methods and clinical trials opportunities.
- Assess the impact of defined strategies related to increasing the availability of these health care services.
- Implement effective strategies for increasing availability.

Appendix A: Other Priorities Identified by the Colorectal Cancer PRG

Fundamental Research

- Establish an organized program of psychosocial research into patient participation in unconventional treatment methods and their satisfaction with care.
- Conduct studies of the developmental biology of the intestinal tract, with an emphasis on the colon.
- Develop an in-depth definition of the human colorectal carcinogenesis field effect.
- Support fundamental research into complementary and alternative treatment modalities.
- Conduct studies of groups—including Native Americans, Hispanics, and Filipinos—whose risk of colorectal cancer is lower than that of whites might further understanding of etiologic or protective factors specific to these populations. It is possible that colon cancer rates in these groups will increase over time, as has happened in other populations (e.g., the Japanese) that move from low-risk countries to Western societies.
- Rates of death from colorectal cancer among African Americans have not declined as have those of whites in recent years. To understand the reasons for this discrepancy, more studies need to be conducted specifically among African Americans.
- Because colorectal cancer takes decades to develop, the role of risk factors at all stages in the carcinogenesis pathway needs to be explored. Investigations of children and adolescents might help in identifying etiologic factors that operate early in the carcinogenesis sequence. Knowledge is currently lacking about lifestyle factors other than tobacco exposure that may be particularly relevant very early in the evolution of colorectal cancer.
- Study lifestyle effects in special populations.
- The colorectum is not a single, uniform organ, nor are colorectal neoplasias all identical. In future studies, separate consideration should be given to neoplasms stratified by colorectal subsite and by histological features and molecular markers of the tumors. Specifically, those characteristics that enhance malignant progression should be important factors to define tumor subtypes for stratified analysis.

Translational Research

- Include unconventional agents in drug discovery programs and support investigators with expertise in studying the interface between complementary and alternative therapies and conventional medical care.
- Develop mechanistically driven translational research components of colorectal cancer prevention trials.
- Provide funding of nutritional and chemopreventive agent studies through program projects, the Specialized Programs of Research Excellence program, and Clinical Research Prevention Units.
- Develop and test mechanisms for assessing, monitoring, and measuring quality of medical care in terminally ill patients.

Clinical Research

- Investigate the extent to which informed consent to participate in research or clinical trials is truly "informed."
- Evaluate older patients' comprehension of the informed consent process and their level of and desire for engagement in the treatment decision-making process.
- Expand research on patient decision-making to include older adults and underserved groups.
- Develop a methodology for defining screening versus diagnostic tests. Explore the impact of risk notification on subsequent screening and surveillance behaviors of those at increased risk for illness.
- Conduct research addressing how to identify individuals and populations at increased risk for colorectal cancer and how to enhance their participation in and adherence to screening recommendations.
- Conduct research to determine which complementary and alternative treatment methods and interventions are used in colorectal cancer treatment and which are effective.
- Conduct prospective clinical trials to evaluate the effectiveness of complementary and alternative remedies used to treat colorectal cancer.
- Conduct prospective trials to evaluate the effect of dietary changes on colorectal cancer patients' duration of remission or survival.
- The study of factors that might affect colorectal cancer survival after diagnosis is greatly needed. Little is now known about whether modifications in environmental or lifestyle factors have an impact on the behavior and prognosis of colorectal cancer after initial treatment.

Institutional Issues

- Create a NIH office to provide oversight and information on over-the-counter remedies.
- Engage critical scientific disciplines and provide multi-institutional resources for integrated research development of the prevention field.
- Establish a vertically integrated infrastructure to support collaborative research on molecular nutrition and genetics, leading to clinical trials in colorectal cancer prevention.
- Increase collaborations with the NIH Center for Complementary and Alternative Medicine to develop a research-based database on the popular appeal, use, and efficacy of complementary and alternative therapies.
- Establish a network of behavioral and psychosocial investigators and develop collaborations among NCI cancer centers, Community Clinical Oncology Programs (CCOP), the American Cancer Society, and other relevant organizations.
- Dedicate funding for interdisciplinary chemoprevention training (career development) for clinical investigators.

Appendix B: Estimated NCI Support of Colorectal Cancer Research, 1999

Scientific Topic Area	*Approximate Level of Support*	*Estimated No. Projects*
Biology	**$ 29,000,000**	**140**
Etiology	**$ 25,000,000**	**100**
Prevention	**$ 25,000,000**	**90**
Early Detection, Diagnosis, and Prognosis	**$ 21,000,000**	**80**
Treatment	**$ 37,000,000**	**200**
Cancer Control, Survivorship, Outcomes	**$ 14,000,000**	**60**
Scientific Model Systems	**$ 2,000,000**	**10**
TOTAL	**$ 153,000,000**	**680**

Appendix C: Colorectal Cancer Progress Review Group Roster

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April 2000 **T618**