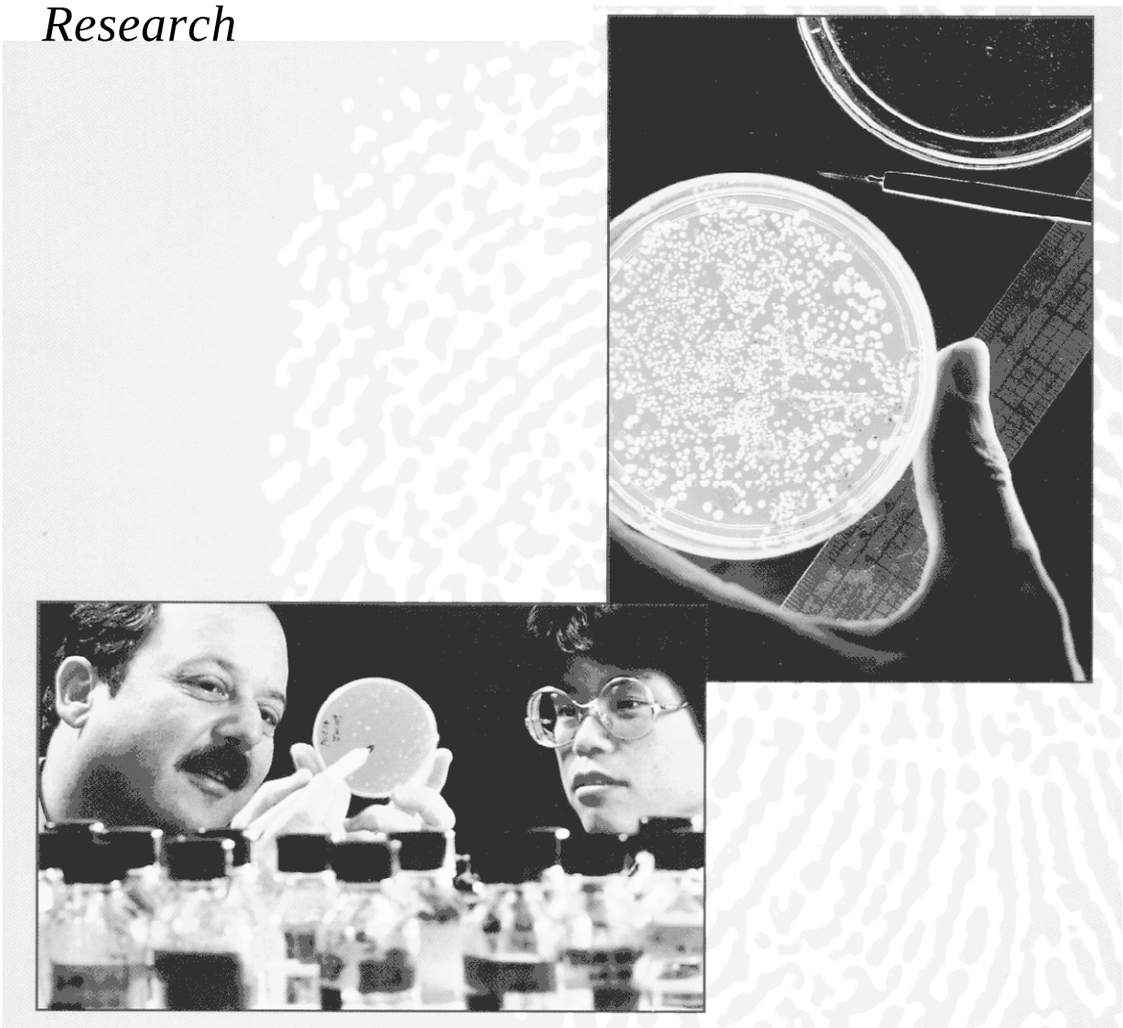
American Academy of Microbiology

Dynamic Issues in Scientific Integrity: Collaborative Research



Dynamic Issues in Scientific Integrity: Collaborative Research

a report from
The American Academy of Microbiology

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Preface

This report from the colloquium on "Dynamic Issues in Scientific Integrity: Collaborative Research" is published by the American Academy of Microbiology which provides summary statements on timely and important issues for scientists, governmental agencies, industry, and the public. The Academy focuses on issues that have broad implications for society. This colloquium convened **12** individuals who have significant experience with the issues under consideration. The colloquium was supported by the National Science Foundation and the American Society for Microbiology.

This white paper includes an in-depth analysis of the issues and recommendations to individuals involved in teaching courses in scientific integrity, to the broad microbiology community, to policy makers who have concerns about collaborative scientific research, and to the lay public. Scientific societies, as well as academic institutions, have sponsored workshops and forums that have addressed the entire spectrum of issues in scientific integrity. These meetings have provided the opportunity to describe the relevant issues, but have provided little analysis and guidance. The American Academy of Microbiology has focused on a very specific area—collaborative scientific research—in order to explore and develop the issues in depth. This report will be of maximum use to scientists and to instructors in defining, refining, and developing their courses in scientific integrity. It will serve as well to assist the lay public in understanding the complexity of the issues surrounding collaborative scientific research.

Specifically, issues addressed during the colloquium included the following:

- defining contributions
- defining authorship
- defining responsibilities of individual researchers involved in collaborative relationships
- defining intellectual property ownership
- defining accountability
- monitoring

The American Academy of Microbiology thanks Frank Macrina, Susan Gottesman, Bernard Sagik, and Keith Yamamoto for organizing and conducting an excellent meeting. Academy staff worked hard to ensure the success of the colloquium. Most of all, the Academy is grateful to the colloquium participants who generously gave of their time and ideas to this important project.

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The Report

INTRODUCTION

Collaboration in scientific research has grown dramatically in this century. Collaborative research can increase the ability of scientists to make significant advances in their fields in general and in their own research programs specifically. Because of the specialization and sophistication of modern research methods, collaborations become necessary whenever researchers wish to take their research programs in new directions or realize the practical benefits of joint endeavors. Interdisciplinary collaborations may also open up entirely new areas of research. Advances in communication technologies augment opportunities for research interactions. Especially in the biomedical, agricultural, and natural sciences, research often mobilizes intellectual and technical resources in ways that lead to scientific discovery of direct benefit to society.

The study of the human genome exemplifies the power of collaborative research. Basic research on gene structure, location, replication, and repair can be related to general problems of disease etiology through cooperative efforts. The coupling of epidemiologic observations with biochemical and genetic data through collaborative research can accelerate progress. The resulting molecular understanding of disease allows the rapid development of novel diagnostic, therapeutic, or preventative applications.

The recent discovery of a class of colon cancer genes provides a cogent example. Geneticists and molecular biologists who were studying inherited colon cancer discovered a high incidence of DNA instability in certain patients. Microbial geneticists and biochemists made connections between this observation and the molecular events that accompany DNA repair in bacteria and yeasts. Collaborative studies among all these scientific groups resulted in an explosion of information about the molecular background for a common form of cancer. Knowledge of the genetic basis of and biochemical pathway for the repair of DNA in single–cell organisms laid the critical foundation. Bacterial and yeast DNA repair genes provided clues to the function of eucaryotic homologs, leading to an understanding of the etiology and pathogenesis of this cancer. Chromosomal mapping and determination of the nucleotide sequences of these homologs then set the stage for analysis of the genes of affected patients. The results demonstrated that mutations in these genes were clearly associated with colorectal cancer. One summary of this story is found in a review by Modrich (Modrich, P. 1994. Mismatch repair, genetic stability, and cancer. Science 266:1959–1960).

There are different levels of collaboration, ranging from temporary arrangements that "stitch" together individual contributions to longer–term ventures in which researchers from different laboratories target a specific problem to projects that eventually lead to the merger of groups that are focused on large, multidisciplinary problems. Flexibility is important because roles and responsibilities in collaborations often evolve over time. Collaborations involving scientists from disparate fields of study can be especially complicated, because the parties may not have common vocabularies, compatible working styles, or shared assumptions about the collaboration. These complexities can be increased when the scientists are working in different countries. Interdisciplinary and international collaborations place special responsibilities and obligations upon the participants.

Interdisciplinary collaborations regularly involve work on topics that appear very different from different disciplinary perspectives, and participants should be prepared to recognize the distinct problems with which their colleagues must grapple. If the collaboration is to be fruitful, the researchers must be prepared to understand the implications that the problems and solutions of one discipline hold for the problems and solutions of the other and to address the problems appropriate to their own discipline. For example, collaborators must recognize the criteria that colleagues from other disciplines use to establish what has occurred in a given process. In the case of a collaboration between molecular biologists and chemical engineers to scale up a process for making a therapeutic protein, the biologist's criteria for when the process has reached a certain stage may be a color change in the solution. Qualitative criteria such as color change may serve well for the concentrations, quantities, and glass containers with which the biologist works in a laboratory. However, that color change will not be a useful indicator for a process taking place at greater concentrations or in stainless steel vats in a factory operation, and it will have to be replaced with precise specifications of quantitative measures such as dissolved oxygen concentration, pH, and residual sugar concentration. To select parameters, for example, the change in concentration necessary to manufacture the protein cost-effectively in quantity, engineers must understand the underlying physical and chemical mechanisms in the biological process.

Suppose that the biologist has a yield of 2 g of the therapeutic protein /liter of solution. To produce a sufficient quantity of the protein efficiently, the engineer must typically increase the concentration, say to 50 g/liter. At this concentration, new problems must be considered, such as supplying sufficient nutrients to the cell producing the protein. Large concentrations of nutrients may inhibit the synthesis of the therapeutic protein or cause the death of the cell. Feeding of the cell therefore must be carefully monitored in the scaled–up process. Furthermore, concentrations which vary only a little in the biologist's work may vary much more widely in a scaled–up operation. For example, concentrations of selective antibiotics used to maintain plasmid vectors may vary in small– vs. large–scale cultures. Such differences between the problems that collaborators in different disciplines address and the variables they must consider should be appreciated when a collaboration is begun and be discussed throughout the effort.

The issues described below have much in common with those seen in collaborations between mentors and trainees or between peers in the same laboratory, but the special nature of these relationships and the obligations of the mentor in guiding the process raise issues beyond those addressed in this document.

PRINCIPLES AND ISSUES

The overriding principles in science are that methods, data, and observations must be reported honestly and that sources of contributions must be acknowledged. These principles apply equally to individual and collaborative endeavors. Joint efforts, however, present some circumstances and issues that do not necessarily arise in other settings. All collaborations-working arrangements between and among scientists—require communication and a well–founded trust. There are no rigid prescriptions or rules that will ensure a uniquely correct outcome in every situation; the principles of science and the guidelines below should be used together to develop successful and productive collaborations.

Major issues for collaborators include:

- agreeing upon the goal of the collaboration, including expectations for outcomes or products;
- establishing and maintaining effective communication and making assumptions as clear as possible;
- defining the expected contributions each participant can make;
- allocating responsibilities;
- estimating an initial time frame for the collaboration;
- articulating the legal obligations of each party, especially with respect to intellectual property requirements and regulatory compliance;
- specifying the process and criteria by which authorship and credit will be assigned; and
- recognizing accountability to research institutions, funding agencies, the profession, and the public.

While the timing of discussion of these issues may vary-they may be discussed in advance of the collaboration or as they arise—these are topics that the collaborators will likely need to consider at some point during the project; early discussion will often prevent misunderstanding.

RESPONSIBILITY AND ACCOUNTABILITY

Data and Methods. Collaborative efforts are no different from other research endeavors with respect to the responsibilities of authors to be thorough, honest, and forthcoming. However, they do add complexities in that every author may not have direct access to or control over all relevant aspects of the collaboration.

Sharing. Collaborators must agree how data and materials will be shared. Some collaborators pool all their assets; others make very limited and explicit arrangements for defined purposes. Although raising such matters can be awkward, it is preferable to making assumptions. Expectations should be stated prior to or, if needed, during the collaboration.

Two labs collaborate to clone a transcription factor. Lab A has purified the protein and prepared antibodies; lab B will screen an expression library to identify the clone. Clearly, lab B will receive a portion of the highly specific monoclinal antibody available and the resulting DNA clone will be shared. Will lab B also receive the hybridoma cell line? In a similar vein, consider a case in which lab C has recovered and sequenced a cDNA that appears to encode a new member of a protease family. They collaborate with lab D, experts in that protein family, sending in vitro–translated protein for characterization. Should lab D also expect access to the cloned cDNA?

Cases like these often arise. Sometimes the same answer seems clear to both parties; frequently it does not. The resolution has obvious bearing on the abilities of the individual labs not only to replicate portions of each other's work, but also to undertake independent work on proprietary materials at the conclusion of the collaboration. The only safe course is to discuss and settle these issues as soon as they can be foreseen.

Authorship. Authors receive credit for their contribution to research and accept responsibility for the accuracy and integrity of their publications. While allocation and order of authorship are matters to be settled among collaborators, there is a significant public interest in equitable and accurate assignment of credit. It follows that authorship must not be considered as a form of remuneration, a privilege of status, or even a reward for contributions which are only of a technical nature. Collaborators may differ in their evaluations of different kinds of contributions; this may require negotiation and compromise, but it is improper to award authorship to individuals who can take no significant responsibility for the published work. In the absence of specific indications to the contrary, readers will assume that the authors of a publication are jointly responsible for the work described. Authors may wish to forestall this assumption by specifying the nature of their individual contributions.

We urge journals to support authors' efforts to specify the contributions and responsibilities of the laboratories that contributed to the work. Interdisciplinary collaborations in which expertise from different fields and / or backgrounds is brought together increase the need for such specifications beyond the normal imperatives.

In 1943, Salvador Luria and Max Delbruck, in their famous paper demonstrating the preexistence of mutant bacteria in a population (Luria, S., and M. Delbruck. 1943. Mutations of bacteria from virus sensitivity to virus resistance. Genet***ics*** 28:491–51 1), found it useful to add the following footnote: "Theory by M.D., experiments by S. E. L." While specific attribution of thought and experiment is probably not a wise idea for most papers, publications increasingly may represent the contributions of researchers in multiple fields, multiple institutions, and multiple countries. In cases in which, for instance, one laboratory has carried out an NMR analysis of a protein, a second group has contributed a genetic analysis of the same protein, and a third group has provided a theoretical analysis of the implications of the work, the choice of corresponding author may be relatively arbitrary. Scientists requesting materials or clarifications from the corresponding author may find themselves redirected to the appropriate laboratoy. Specification of some degree of split responsibility in the paper itself also acknowledges the reality that, in interdisciplinary and interlaboratoycollaborations, errors made by one group are not al ways detectable by the collaborators.

Confidentiality. Colleagues may have very different expectations about how long information will be kept confidential. Scientists differ in their preferences for discussing research progress. Researchers may not fully understand the effect of a disclosure on collaborators in another field. Finally, legal restrictions may sometimes apply. When and how information will be released are items that should be addressed and resolved among collaborators.

Compliance. Individuals are responsible for compliance with all applicable regulations governing their research. Nonetheless, collaborators should know that the failure of anyone associated with the project to comply with regulations may carry consequences for all of the scientists involved in the study.

Certain aspects of research in the biomedical and natural sciences are governed by federal and state laws, policies, or regulations. Examples include the use of humans and animals in experimentation, the use of radioisotopes, and the transfer of certain types of infectious agents. Regulations also apply to the use of certain hazardous substances and the disclosure of potential risks of such usage to coworkers. Consider a collaboration between a basic scientist and a clinical researcher located at different institutions. The clinical researcher is providing serum samples from patients who have a specific bacterial infection. These serum samples are shipped by express courier to the laboratory of the basic scientist, where they are immunologically analyzed. For such a collaboration, an approved human use protocol must be in place at the clinical researcher's institution, which would include a provision for seeking and obtaining informed consent from all patients participating in the project. If approval was not obtained, use of the serum samples in laboratory studies would be inappropriate. Discovery of a failure to comply with relevant regulations might necessitate the destruction of the clinical materials and prohibition of the use of any existing data generated in the basic scientist's lab.

In addition, rules governing the use of biohazardous materials might apply to the analyses of the serum samples in the basic scientist's lab. The scientist would be responsible for informing all coworkers of the potential biohazards of dealing with materials of human origin and for instructing them in the handling, storage, and disposal of the samples. An accident in the basic scientist's lab involving the serum specimens might leave both collaborative parties open to sanctions and even legal actions under certain circumstances. Thus, in such a scenario, although regulations may at first inspection be associated with only one party of the collaboration, failure to comply may have implications for or effects on all members of the joint effort.

Many research institutions and journals require that scientists disclose the sources of their financial support. Because there may be sensitivity about some sources of funds, collaborators should as a matter of course inform each other about all funding for joint projects. Prompt and full disclosure of other financial support helps to avoid misunderstanding and suspicion of bias.

If there is an allegation of irregularities in a joint study, scientists should immediately inform all other members of the team and the appropriate authorities in their research institutions and funding agencies. There is no substitute for a thorough, cooperative review of all research materials, methods, calculations, results, and conclusions. Prudence dictates that manuscripts in the process of publication should be withdrawn if any coauthor thinks the allegation has merit. In any case, journal editors should be notified so that their judgement can be fully informed.

If misconduct is found to have occurred in published research, coauthors have individual and collective responsibility to correct the published record of their work. Preferably, all authors, after consultation, should submit a retraction with their names in the same order as in the original report and with a full and complete citation of the original article. Editors and reviewers of scientific journals relied on representations in the original manuscript; it cannot be assumed that they will automatically concur in the authors' recalculations. Authors must provide sufficient background material to allow the editors to make informed decisions about the compromised science.

Accountability. Scientists engaged in research have many constituencies to which they must be accountable, at various levels. Public funding carries special responsibilities, as does involvement with problems that may affect public health and/or the environment. In addition, participants in joint projects may have contractual and fiscal obligations that will affect the collaboration. Such obligations must be disclosed and accommodated.

Intellectual Property Issues. One of the special obligations of collaborators is to be informed about their legal responsibilities with respect to products of the joint research. Collaborators should tell each other about their individual responsibilities and be prepared to meet the requirements of their own institutions.

Most employers—universities and private corporations alike—require employees to assign ownership for inventions arising out of their research. Two factors distinguish university and corporate researchers with respect to intellectual property issues:

1) In many jurisdictions, publishing before applying for patent protection renders it impossible ever to secure a patent on the published material.

2) University-based inventors usually have more latitude to make decisions about whether to seek patent protection (and if so, in what jurisdictions) or whether to seek instead priority publication without such protection. Corporate researchers typically do not have the freedom to make these choices, and often their work is subject to a variety of constraints intended to protect the corporation's intellectual property, which can include confidentiality and nondisclosure requirements, laboratory notebook dating and signing protocols, and material use agreements that limit the ways in which certain samples can be analyzed, tested, incorporated into other materials, and/or shared.

When individuals working under different constraints and in different environments collaborate, their expectations and assumptions may be so divergent that it does not occur to the participants to discuss them. For example, a corporate researcher whose laboratory notebook is signed and witnessed every day and who meets periodically with lawyers to discuss what aspects of the work should lead to patent applications may not realize that a university researcher colleague could be preparing manuscripts for publication without such reviews and without realizing the effect it may have on the ability to secure patent protection.

Rewards. Collaborations yield products and rewards in various forms. It is not realistic to allocate credit in advance of the project because the work may lead in directions not originally anticipated. However, the participants should discuss explicitly how credit will be allocated and who will make the decisions. This applies especially under circumstances in which collaborators are from different sectors (i.e., industry and academia or different countries whose intellectual traditions may vary) and those in which legal considerations may intrude (i.e., patents and other issues of intellectual property protection). Outlets for presentation of the work, how public presentations will be made and by whom, and timing of the release of results should be discussed.

COLLABORATIONS BETWEEN INDUSTRY AND ACADEMIA

Collaborating across sectors amplifies the need for partners to define and understand the constraints under which each operates. The most obvious of these are restrictions on publication and requirements flowing from legal obligations of the participants, but more subtle issues can also arise in areas such as laboratory and institutional practices, for example, whether it is acceptable to delay in making public the results of dissertation research.

Scientists in industry and a university who are interested in initiating a joint project may encounter unanticipated hurdles. Although the issues raised by a collaboration between a scientist in industry and one in a university may also arise in collaborations between scientists in different universities, they are not usually addressed explicitly in advance. These are: how the decision to publish or not publish is made, how invention disclosures and patent applications are processed; and liability for any damages arising from the use or misuse of a material, software, or product.

The results of collaborative research involving scientists in industry and in a university may be used to support applications for investigative or marketing permits for products regulated by the Food and Drug Administration or other federal agency. Such joint research comes under the provisions of "Good Laboratory Practices, " or GLP, which prescribes procedures for documenting, recording, reviewing, and retaining experimental protocols and findings in considerable detail. When a study is to be submitted to a federal regulatory agency, the industrial sponsor or collaborator is required to notify the academic collaborator that the research must be conducted in compliance with GLP. One of the provisions of GLP is that the laboratory of the academic collaborator may be inspected by authorized personnel from the regulatory agency. Studies for regulatory agencies shall be conducted according to written protocols, which are prepared in advance, reviewed, and signed by the designated study director, the sponsor, and the "quality assurance officer. " Protocols are subject to examination by both external federal inspectors and quality assurance officers. The contents of GLP protocols are more detailed than those usually found in laboratory notebooks of academic investigators conducting "discovery" or "basic" research. A laboratory conducting GLP studies is monitored by a quality assurance officer, who selectively observes the facilities and experiments and checks the equipment and records periodically. Academic scientists who are unfamiliar with quality assurance tend to consider this audit process an undesirable intrusion into their research. The final reports of a GLP study are signed by the principal scientists engaged in the work, the study director, and the quality assurance officer. The signature of the quality assurance officer acknowledges regulatory compliance of the studies. All records, including raw data, protocols, and final reports, are maintained in identified archives. The time that documentation must be retained varies, but it should be assumed to be a minimum of 5 years from the date of submission to a regulatory agency. Collaborations between academic and industrial scientists that involve GLP are three–way dialogs in which the quality assurance officer is an important participant. The issues pertaining to a successful collaboration between an industrial and an academic scientist are essentially the same as those described for academic collaborators. The primary difference lies in the requirements and procedures for documenting the research and findings.

Expectations and assumptions that should be addressed in cross–sector collaborations include:

- standard operating procedures in each researcher's environment;
- special obligations of confidentiality and restrictions on release of information that apply to each collaborator;
- understandings about sharing materials and resources;
- authorship and patenting issues;
- concerns unique to graduate students (thesis topics, etc.); and
- whether additional participants figure in the collaboration (e.g., lawyers, patent officers, marketing officers, sponsored research officials, etc.).

COLLABORATION AND PROFESSIONAL DEVELOPMENT

Institutions and review committees find it difficult to allocate appropriate credit for publications generated by faculty in collaborative research projects. Because independent work is the prevailing measure of scientific identity, junior faculty establishing their careers need to recognize the importance of balancing collaborative and independent work. In addition to the complexities associated with disentangling individuals' contributions to collaborative efforts, women and minorities can face systematic undervaluation of their contributions. Actions may range from subtle, unconscious behavior to deliberate discrimination.

These are formidable challenges, but the benefits of collaboration are so great that efforts to remove obstacles must be made. Especially in emerging fields, collaborations can facilitate novel research approaches; special recognition and credit should be allocated in such cases. The solution is for institutions to discover new ways to evaluate joint research realistically. Independence should not be equated with a requirement for noncollaborative research.

RECOMMENDED READINGS

Responsible ***Science: Ensuring the Integrity of the Research Process, Volume I. (1992).*** National Academy Press, ***2101*** Constitution Ave., N.W., P.O. Box 285, Washington, DC 20055 (197 pages). The work of a panel commissioned by the National Academy of Sciences, covering a wide range of the practical and theoretical issues germane to responsible conduct in the profession. Chapters 2 and 3 discuss issues regarding the principles and practices of research which are relevant to collaborative research.

Responsible Science: Ensuring the Integrity of the Research Process, Volume II. (1993). National Academy Press, 2101 Constitution Ave., N.W. P.O. Box 285, Washington, DC 20055 (275 pages). Volume II of work compiled by panel commissioned by the National Academy of Sciences. The emphasis of this volume is on background, policies, and guidelines in the practice of research. Verbatim documents used at a variety of institutions afford a look at specific issues that may impinge on collaborative research.

On Being a Scientist: Responsible Conduct in Research (2nd edition). National Academy Press, 2101 Constitution Ave., N.W., P.O. Box 285, Washington, DC 20055 (27 pages). A succinct guide to research practices, including several case studies for discussions.

The following books cover a variety of topics directly or indirectly relevant to collaborative research practices. Frequently, they offer case studies designed to stimulate discussion about problems and issues related to responsible scientific conduct.

Bulger, Ruth E., Elizabeth Heitman, and Stanley J. Reiser (Editors). 1993. ***The Ethical Dimensions of the Biological Sciences.*** Cambridge University Press, New York.

Macrina, Francis L. 1995. ***Scientific Integrity: An Introductory Text with Cases.*** American Society for Microbiology Press, Washington, D.C.

Penslar, Robin L. (Editor). 1995. ***Research Ethics: Cases & Materials.*** Indiana University Press, Bloomington.

Whitbeck, Caroline. 1995. ***Understanding Ethical Problems in Engineering Practice and Research.*** Cambridge University Press, New York.