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Ethics and scientific publication

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Benos, Dale J., Jorge Fabres, John Farmer, Jessica P. Gutierrez, Kristin Hennessy, David Kosek, Joo Hyoung Lee, Dragos Olteanu, Tara Russell, Faheem Shaikh, and Kai Wang. Ethics and scientific publication. *Adv Physiol Educ* 29: 59–74, 2005; doi:10.1152/advan.00056.2004.—This article summarizes the major categories of ethical violations encountered during submission, review, and publication of scientific articles. We discuss data fabrication and falsification, plagiarism, redundant and duplicate publication, conflict of interest, authorship, animal and human welfare, and reviewer responsibility. In each section, pertinent historical background and citation of relevant regulations and statutes are provided. Furthermore, a specific case(s) derived from actual situations is(are) presented. These cases were chosen to highlight the complexities that investigators and journals must face when dealing with ethical issues. A series of discussion questions follow each case. It is our hope that by increasing education and awareness of ethical matters relevant to scientific investigation and publication, deviations from appropriate conduct will be reduced.

plagiarism; redundant; falsification; conflict of interest; fabrication

PUBLICATION OF A RESEARCH article represents the final stage of a scientific project. It is the culmination of many months and sometimes years of meticulous planning, execution, and analyses of hundreds of experiments. In many cases, the funds supporting the project were derived from public monies. There is, therefore, the expectation that the work be conducted and reported honestly, objectively, and fairly. Yet, sometimes deviations from this ideal occur. Ethical breaches can be intentional, such as data fabrication, or can arise simply out of ignorance, e.g., inappropriate anesthetic use in animal experimentation. Nonetheless, in legal parlance, ignorance is not and cannot be an excuse. Thus it is incumbent on every investigator to be cognizant of all the ethical requirements for conducting scientific studies. Moreover, a scientist needs to develop a strong sense of ethical responsibility to apply at every stage of scientific inquiry. Straying from an ethical course during the conduct of an investigation undoubtedly manifests itself during the publication phase.

The purpose of this article is to provide a comprehensive discussion of ethical problems encountered during the publication process. We discuss common ethical breaches such as data fabrication and falsification, plagiarism, and redundant and duplicate publication. We discuss ethical issues that can arise because of conflict of interest, author conflicts, and human experimentation. We also present a brief discussion of animal welfare concerns, but because of the breadth, complexities, and controversies of animal experimentation issues, we

refer the reader to more in-depth literature on these important matters (42–44, 53). We conclude with a discussion of reviewer rights and responsibilities. In each section, we compile pertinent current regulations, include source documentation, and present a specific case or cases relating to the topic. These cases were modified from actual situations that have arisen during reviews of manuscripts submitted to the *American Journal of Physiology*, the *Journal of Applied Physiology*, and the *Journal of Neurophysiology* over the past decade. Each case is followed by a series of discussion questions. It is our hope that both investigators and students will use this article as an educational and reference tool. The Council of Science Editors (previously known as the Council of Biology Editors) has published a book dealing with ethical policies in scientific publications (9). The reader is also referred to the Committee on Publication Ethics (COPE) and World Association of Medical Editors web pages for other specific cases, and for a discussion of ethics as it relates to publication (16, 78).

SCIENTIFIC MISCONDUCT: WHAT'S THE PROBLEM?

The current Federal definition of scientific misconduct (and one that is used by most universities and publishers) is “. . . fabrication, falsification, or plagiarism in proposing, performing, or reviewing research or in reporting research results. . .” (73). Fabrication is defined as recording or presenting (in any format) fictitious data. Falsification is manipulating data or experimental procedures to produce a desired outcome or to avoid a complicating or inexplicable result. Plagiarism is using someone else's words, ideas, or results without attribution. In order for an action to be considered misconduct, it must be a “. . . serious deviation from accepted practices. . .” of the relevant research community, have been “. . . committed intentionally, or knowingly, or recklessly. . .”, and it must be “. . . proven by a preponderance of evidence. . .” (73). Research misconduct does not include legitimate differences of opinion. While it is always difficult to legislate appropriate standards of behavior, it was the intent and responsibility of the Federal Government to ensure that publicly funded research is above reproach. The first two regulations covering human and animal experimentation that were enacted by Congress were the 1974 National Research Act (PL 99–158) and the Animal Welfare Act (PL 89–544, 1986).

The issue of scientific misconduct in the United States attained public awareness in the 1980s with the emergence of several episodes of scientific improprieties (29, 31, 58, 60, 61, 71, 74). At the same time Congress became concerned that both the National Institutes of Health (NIH) and universities were not responding adequately to these charges and allegations. Consequently, Congress in 1985 passed the Health Research Extension Act (30, 50). This act, specifically section 493, required institutions seeking federal research funding

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grants to establish an administrative process to deal with scientific misconduct in a formal way. This legislation underwent revision and was entitled, Responsibilities of Awardee and Applicant Institutions for Dealing With and Reporting Possible Misconduct in Science (54FR 32446) when it was ratified into the *Federal Register* August 8, 1989. The regulation was codified in the *Code of Federal Regulations* (CFR) at 42 CFR Part 50 Subpart A.¹ In essence, an institution must have procedures in operation that designate an individual or individuals to assess allegations of misconduct, to conduct inquiries and formal investigations of allegations, a person designated to adjudicate the findings of the inquiry and investigative committees, and a mechanism for reporting to the Office of Research Integrity (ORI).

Before 1986, the funding agencies themselves (or, in the case of NIH, the individual institutes) were responsible for performing the regulatory functions established by the aforementioned CFR. After that time, the NIH Institutional Liaison Office received and responded to allegations of scientific misconduct. In 1989, the Public Health Service (PHS) created the Office of Scientific Integrity located within the NIH Director's office and the Office of Scientific Integrity Review located within the Office of the Assistant Secretary for Health (73). In June of 1993, the NIH Revitalization Act was signed by President Bill Clinton establishing the ORI as an independent entity within the Department of Health & Human Services (73). The ORI is located within the Office of the Secretary of Health & Human Services in the Office of Public Health & Science, which is run by the Assistant Secretary for Health (73).

One of the more serious sanctions that a journal can impose on its authors is to inform his/her home institution of a publication infraction. Once an institution is informed, it is required by statute to begin an inquiry into the matter, if that allegation involves Federal funding (42CFR Part 50; Ref. 59). If NIH funding or animal or clinical trials are involved, these may be frozen or suspended until a resolution is achieved. Regardless of outcome, the process is quite stressful and unpleasant for the accused. In addition, the scientists who serve on institutional investigational committees also pay a price. These scientists lose time from their research, are not compensated for this service, and potentially incur the wrath of their colleagues, not to mention possible civil lawsuits (27). Nevertheless, it is a scientist's duty to serve on such boards. Because science is a profession, it is essential that scientists themselves self-evaluate and establish policies and procedures to self-regulate and correct any wrongdoing. Only in this way will public trust in the enterprise be maintained.

¹The CFR is a compilation of all the regulations issued by all of the agencies of the United States Federal Government. The *United States Code* (USC) is the compilation of all permanent laws of the United States. Laws and regulations are different. Only Congress can enact laws. Federal agencies issue regulations to enforce and ensure compliance with laws. The USC is published every 6 yr by the Office of the Law Revision Counsel of the United States House of Representatives. The CFR is amended as needed. These agency-approved amendments, or proposed amendments, appear in the *Federal Register*, which is published daily. The *Federal Register* also publishes notices of the Federal agencies, executive orders, and other executive branch documents. Federal regulations may have the force of law and can be enforced by the government agencies but are not laws themselves. Regulations can only be developed by agencies if laws permit them to do so, i.e., there is an enabling statute. All three of these publications can be accessed and searched from the web site of the United States Government Printing Office (www.gpoaccess.gov).

Once an accusation of scientific misconduct has occurred, normally repositied directly to the university's Research Integrity Officer, the allegation is assessed to determine whether it warrants an inquiry. If so, then an inquiry committee is established to decide whether the allegation has substance and whether an investigation is warranted (56). It is possible that the inquiry could lead to an investigation, which is the formal development of a factual record, and the examination of that record leading to dismissal of the case or to a recommendation for a finding of research misconduct or other appropriate remedies (56). If the parties are judged guilty of scientific misconduct by the investigation committee, then adjudication occurs, usually by a high-ranking university official such as the provost or president, during which recommendations are reviewed and appropriate corrective or punitive actions determined (56). This discussion applies only to federally funded research, but most universities have procedures in place to deal with any allegations of misconduct.

The final legal definition of scientific misconduct was published in the *Federal Register* on December 6, 2000 (22), although proposed changes to this definition are being considered (22). These proposed changes include 1) changing the terminology, i.e., "scientific" misconduct would become "research" misconduct; 2) expanding misconduct to include both grant and contract research; 3) expanding the scope of plagiarism to encompass activities related to funding requests and scientific publications; 4) use the term "performing" instead of "conducting" research, which would expand misconduct to encompass reviewing of research; 5) replacing the term "serious deviation" from accepted practices to "significant departure"; and 6) dropping the phrase "other practices." As indicated above, extramural institutions and intramural programs have primary responsibility for responding to allegations of scientific misconduct. The Office of the Inspector General conducts initial fact-finding inquiries in cases of scientific misconduct, whereas the ORI provides investigational oversight and has discretionary ruling power. All extramural institutions requesting federal PHS funding must provide training in the responsible conduct of research to employees, faculty, students, and postdoctoral students (39). In addition, training must be provided to those who contribute work to PHS-funded projects, even if the institution does not receive PHS funding.

Between 1974 and 1981, only 12 cases of alleged scientific misconduct in the United States were reported (60). However, recent years have seen an exponential increase in alleged cases (Fig. 1; Ref. 57). This increase in reporting alleged scientific misconduct to ORI paralleled the same increase in alleged scientific and publication improprieties seen in many biomedical journals, including those of the American Physiological Society (APS). For example, Fig. 2 shows the yearly increase in ethical cases handled by the publications program of the APS between 1996 and 2004. Over this time span, on average 30 new cases per year were opened. It is important to emphasize that this number still represents only a small fraction of the total number of manuscripts that flow through the system. Nonetheless, even one incident is too many. The cost of such ethical issues is high to both the authors and the journal and to biomedical science in general.

The nature of the ethical problems reported to the ORI is evenly distributed among fabrication, falsification, and plagiarism. For example, for the 103 new allegations of scientific

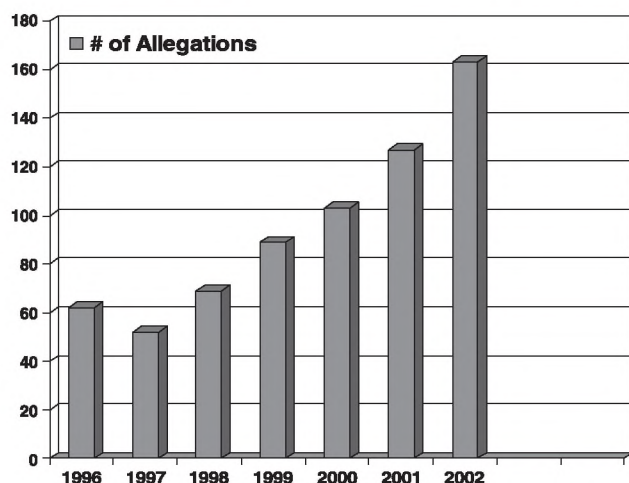


Fig. 1. Total number of new allegations of scientific misconduct reported to Office of Research Integrity (ORI) (Data obtained from Ref. 60).

misconduct reported to the ORI in 2000, 24 involved falsifications of data, 37 involved data fabrication, 19 involved plagiarisms, and 23 were in other categories (59). For the APS journals between 1996 and 2004, redundant publication (i.e., attempts to republish data that have already been published) was the most frequent (24%) infraction (see Fig. 3). It is important for authors and reviewers alike to be aware of what constitutes misconduct in publication. In this way, the sanctity of the process can be preserved, and authors can be spared much anguish. Honesty, objectivity, and fairness are the virtues essential for conducting, reporting, and evaluating research. In this way, our scientific colleagues, the paying public, our appointed and elected government officials and members of Congress, and most importantly, we as individual scientists can be assured that the products of our labors are true and beyond reproach.

DATA FABRICATION AND FALSIFICATION

Data fabrication and falsification are perhaps the most obvious and egregious examples of scientific misconduct. Falsification or fabrication of data represented over half of the new allegations reported to the ORI in 2002 (57). According to the ORI, "Falsification of data encompasses fabrication, to deceptive selective reporting of findings and omission of conflicting data, or willful suppression and/or distortion of data." (55). This can include anything from throwing out an unwanted piece of data to just making it up. Data falsification is problematic for many reasons. First and foremost, it dilutes the integrity of other scientific research, both from that author(s) and from others in the field. Second, if left undiscovered, it could waste other researcher's time and energies attempting to replicate or build on the data presented in a falsified paper. Third, it jeopardizes the public trust in the scientific enterprise.

Data falsification/fabrication can have consequences more disastrous than these. The Alliance for Human Research Protection points out that "... scientific misconduct is a big problem undermining the integrity of the scientific literature. Data falsification leads others to erroneous conclusions that may have adverse consequences for patients in clinical research and clinical practice." (69). If an investigator were to falsify findings on a potentially new clinical therapy or a paradigm-

shifting disease management program, the impact on a patient could be life threatening at the worst or, at a minimum, psychologically devastating.

It is obvious from the reports of ORI that the falsification/fabrication of data is rising. Each member of the scientific community must ensure that he/she faithfully and accurately obtains, represents, and reports experimental data. It is only in this way that the integrity of the scientific enterprise can be maintained.

Case study. A manuscript has been submitted to a journal. After being sent out for peer review, one of the reviewers contacted the editor and said that she had reviewed the manuscript previously for another journal. What concerned her about the manuscript was that, in the submission to the other journal, a time course experiment was shown in which intracellular calcium was measured by fura-2. The external solution was said to be NaCl in the original submission. However, the identical figure is in this manuscript, only with the external solution being stated to contain LiCl. In the reviewer's original review, she had made the major comment that the experiment should be rerun with LiCl. What should be done?

Questions for discussion:

1. How would you go about checking whether or not this author actually had rerun the experiment?
2. How would you ensure that all authors knew of the ethical breach, if that was determined to be the case?
3. What sanctions would you, as a member of a publications committee, suggest for these authors if they were deemed guilty?
4. Would your recommendation apply to all of the authors, or only to those who knew of the ethical misconduct?
5. What about the integrity of the reviewer? In order for the reviewer to remember such experimental detail, it is likely that he/she retained a copy of the original confidential submission, an action contraindicated by most journals.

PLAGIARISM

The ORI estimates ~25% of the total allegations it has received concern plagiarism (45). A surprising number of

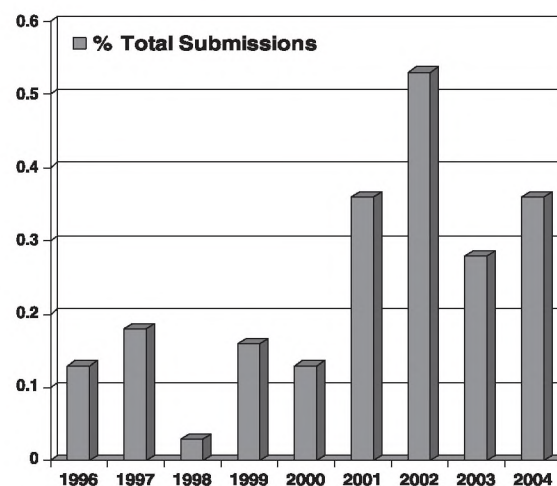
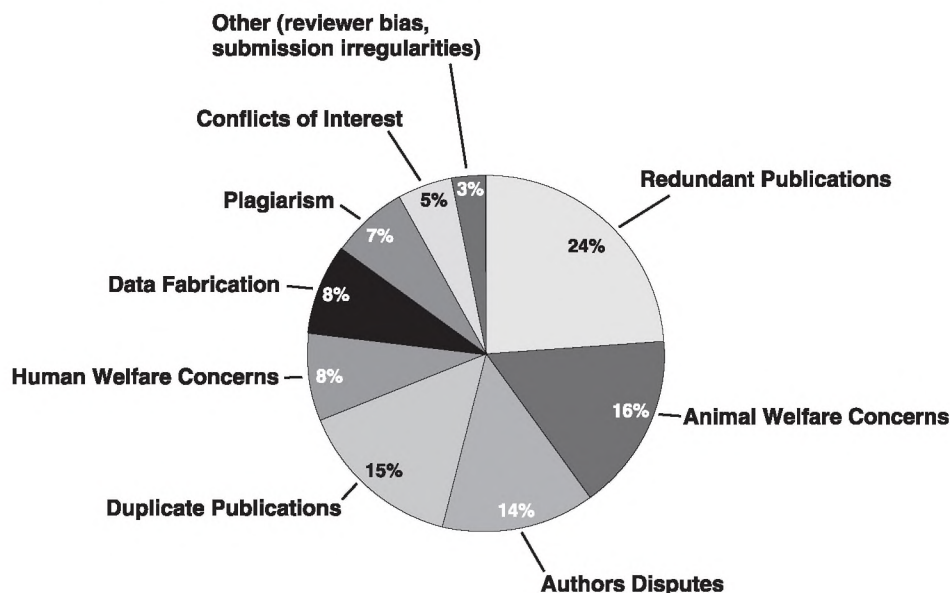


Fig. 2. Total number (expressed as a percentage of total yearly submissions) of ethical cases handled by the publications program of the American Physiological Society (APS).

Fig. 3. Distribution of ethical issues in APS publications (1996 through March 2004).



plagiarism allegations turn out to be misunderstandings of exactly what constitutes plagiarism or proper citation procedure (45). Dr. Mark Wiser of Tulane University (New Orleans, LA) has suggested applying five criteria to evaluate the seriousness of plagiarism allegations (45). These five criteria are 1) What was the extent of the plagiarism? 2) Was the intent malicious? 3) Has the author previously engaged in plagiarism? 4) What is the position and training of the author? and 5) Was the source material original or did the plagiarism occur from notes?

The ORI considers plagiarism as "...the theft or misappropriation of intellectual property. . ." or "...the substantial unattributed textual copying of another's work. The theft or misappropriation of intellectual property includes the unauthorized use of ideas or unique methods obtained by a privileged communication, such as a grant or manuscript review. Substantial unattributed textual copying of another's work means the unattributed verbatim or nearly verbatim copying of sentences or paragraphs which materially mislead the ordinary reader regarding the contributions of the author." (60).

The current trend in the regulatory procedural scheme of dealing with plagiarism is not uniform among scientific journals. Obviously, education of graduate students, postdoctoral fellows, and faculty is necessary to instill a set standard of scientific research conduct. Dr. Miguel Roig, St. Johns University (New York, NY), has proffered a sound and thorough set of guidelines dealing with the finer points of plagiarism and writing practices that may not pass ethical muster (68). These guidelines include 1) always acknowledge explicitly the originator of ideas and the contribution of another, regardless of whether it was paraphrased, summarized, or used directly; 2) any verbatim text taken from another author must be enclosed in quotation marks (68); 3) when paraphrasing, make sure you understand completely the text and use your own words; and 4) provide a reference when you are not sure that the fact or idea you are using is common knowledge.

There are a number of different computer programs available to detect commonality of language between different written works (see Ref. 33). These programs do not detect

identity of ideas, only of language. Yet, duplication of words and phrases, however brief, may be indicative of plagiarism (34).

The cost of plagiarism can be high for all the parties involved in the initiation, investigation, appeal, and resolution of the allegation. Obviously, in a reputation-driven field such as the biological sciences, even the allegation of plagiarism can seriously damage a scientist's career. A recent example of plagiarism and its associated cost was published in *Nature*, in January of 2004 (29). Yung Park, a visiting materials scientist at Cambridge University (Cambridge, United Kingdom) published eight plagiarized articles between 1997 and 2001. A disturbing anecdote is that of these eight papers, four were retracted from the journals, but the remaining four were not (29). Fortunately, the total number of plagiarism incidents in the United States is low compared with the total number of peer-reviewed journal submissions, but reports of plagiarism have increased every year since 1998 (27). This fact may reflect increased reviewer and editorial vigilance, increased misconduct, or both. Whatever the reason, it is important that students, fellows, and faculty understand precisely what constitutes plagiarism and how to reference items and statements appropriately.

Case study 1. A scientist has submitted a manuscript to a journal for publication. Three reviewers reviewed the manuscript. One reviewer claims plagiarism has occurred and cites three examples of paragraphs in the submitted paper that have been copied verbatim or substantively from other works. The journal editor rejects the manuscript for other reasons, but fails to mention in his cover letter to the manuscript author the alleged plagiarism. In fact, the editor encourages the author to revise and resubmit his manuscript elsewhere. A coauthor, on reading the reviews, immediately contacts her departmental chair and journal editor about this incident, and states that indeed the cited examples were plagiarized, unknown to her, because they were added to the final version (which she did not see just before submission). What should be done?

Questions for discussion:

1. What are the responsibilities of all of the parties involved?
2. What type of communication with the author or authors is necessary and who must approve the communication and have access to it?
3. What explanations would be acceptable to a publications committee, and if no acceptable explanation is provided, what recourse does the committee have?
4. If the author is found guilty of the allegation, what punishment is fitting? What do you see as possible mitigating factors in the decision?
5. Because the departmental chair has already been notified, what should the interface between the institution and publication committee be?
6. What strategies might an editor or publications committee implement to increase detection and expedite handling of plagiarism allegations?

Case study 2. A review article written by a prominent researcher was published in a high-profile journal. A reader writes to that journal's publication committee stating that large portions of the review article contained verbatim sentences and complete paragraphs of a book chapter published some years earlier. Neither of the two authors of the book chapter was the author of the review article. The book chapter was not referenced in the review article. When contacted, the author produced a copy of a newly revised version of that book chapter in which he is now included as a third author. What should be done?

Questions for discussion:

1. Is this self-plagiarism? If so, is self-plagiarism permissible?
2. How might plagiarism or even appearances of plagiarism jeopardize the reputation of an author or authors?
3. How should the author's home institution handle situations such as this?

REDUNDANT PUBLICATION

Redundant publications constitute a special type of plagiarism. Redundant publication is sometimes equated to duplicate publication. Here we define redundant (or repetitive) publication as the publication of copyrighted material with additional new or unpublished data (25). Thus we mean by redundant publication the republishing of a part or parts of an already published article, not the entire article. There are a number of reasons why redundant publication is unethical (32). First, it may infringe international copyright law. Second, duplication of data with additional new data wastes the valuable time of expert peer reviewers. Third, it needlessly expands the already extensive body of published literature. Fourth, it confounds scientific communication by dividing rather than combining closely related data from a single group. Fifth, it may unduly overemphasize the importance of the findings by having them appear more than once. Sixth, it may interfere with subsequent meta-analysis by apparently boosting patient or experimental numbers.

COPE has made some specific recommendations with regard to redundant publication: 1) published studies do not need to be repeated unless further confirmation is required; 2) previous publication of an abstract during the proceedings of meetings does not preclude subsequent submission for publication, but

full disclosure should be made at the time of submission; 3) republication of or data contained in an article previously published in another language is acceptable, provided that there is full and prominent disclosure of its original source at the time of submission; and 4) at the time of submission, authors should disclose details of related papers, even if in a different language, and similar papers in press. In fact, many journals require copies of those related manuscripts at the time of submission. The point to be made here is that authors should not attempt to republish data that has already appeared in a journal. If an author considers those previously published data essential, he/she should repeat the experiment or part of an experiment and include new data, even if that experiment has already been published.

Case study 1. An associate editor, during the review of a manuscript, related to the editor a concern raised by one reviewer that certain data in the submitted paper (2 panels of a 6-panel figure) appeared in an earlier publication (different journal) from the senior author's laboratory. In the text and in the figure legend, the authors refer the reader to the earlier publication. What should be done?

Questions for discussion:

1. What explanations from the author are acceptable?
2. If the author used the data from the two published panels in the text instead of reproducing the panels themselves, is the practice acceptable?
3. If it were determined that the same data were used, what action should be taken?

Case study 2. A manuscript was submitted to your journal. During review, one of the referees noticed that the mean arterial blood pressure, total body weight, and glomerular filtration rate on sham-operated male and female rats appeared identical to data included in an article published in another journal by the same authors a year earlier. The similarity extended to the same number of animals used and the same error on each of the aforementioned data. When queried, the author became irritated and asked, "Why shouldn't these data be identical? These are the same animal groups." He went on to argue that the point of the two articles were different. What should be done?

Questions for discussion:

1. Should these control data be deleted from the submitted manuscript?
2. Would it be permissible to republish data if new experiments were added (under the identical conditions) in the second manuscript?
3. Would it be permissible to republish data in a second paper submitted to a journal with an entirely different readership than the first?
4. What are the scientific benefits of republishing data? What are the shortcomings?

DUPLICATE PUBLICATION

Duplicate publication is defined as the publication of an article that is identical or overlaps substantially with an article already published elsewhere, with or without acknowledgment (11, 36). It can be classified as self-plagiarism. It is also a subset of redundant publication in that two papers share the

same hypothesis, results, and conclusions (15). In some cases, the same authors are arranged in a different sequence (3).

Why do scientists attempt to republish the same article? One reason may be the perception that to survive in the highly competitive biomedical science field, individuals are required to achieve voluminous curriculum vitae. There is some truth in the contention that the number (rather than the quality) of publication is an important factor for promotion and academic advancement and as a measure of productivity in assessing grant applications (1). Another, more justifiable reason, at least before the advent of the world wide web, is the authors desire to reach readers that would not necessarily be familiar with the particular journal in which the article was first published (for example, if the article was published in Chinese in a relatively inaccessible journal). An author must secure the permission of both journals before even attempting to republish the same paper.

Why is duplicate publication considered misconduct? Aside from the obvious attempt to inflate one's own publication record, duplication (and redundant) publication has the potential to skew the evidence base (65). If the same data were counted twice (or more), the outcomes of meta-analysis used to establish the best practice would be invalid. For instance, Tramer et al. (75) performed a systematic search of all published full reports of randomized controlled trials to investigate the effect of a drug, ondansetron, on postoperative emesis. They found that 17% of published reports of trials of the drug were duplicates and 28% of the patient data were duplicated. This led to an overestimation of this drug's efficacy by 23%. It should be evident from this one example that duplicate publication is a threat for scientists conducting systematic reviews and, more importantly, biases the conclusions on drug efficacy and safety (63).

Guidelines on good publication practice state that the authors can only submit their manuscript to a single journal at a time. Authors may resubmit the same or a revised version to another journal only if the first journal makes the decision not to publish it, or it is withdrawn by the author. In spite of this universally accepted criterion, double submission still occurs and continues to be a real problem for scientific journals.

Most journals do not wish to receive articles on work that has already been reported in a published article or is contained in another manuscript that has been submitted or accepted for publication elsewhere, either in print or in electronic format. The submitted manuscripts and data contained within must be original. Almost all journals have similar guidelines concerning redundant publications. The American Physiological Society Ethical Policies state that "... the journals of the APS only accept research papers that are original work, no part of which has been submitted for publication elsewhere except as a brief (i.e., <400 words) abstract. When submitting a manuscript, the corresponding author should include copies of related manuscripts submitted or in press elsewhere." (5).

The APS will not normally consider articles first published in a non-English language, unless the circumstances are extraordinary. Nonetheless, some journals permit secondary publication of an article in the same or in another language, especially in other countries. This practice may be justifiable and beneficial provided that all of the following conditions are met: 1) the author has received approval from the editors of both journals; the editor concerned with secondary publication

must have a photocopy, reprint, or manuscript of the primary version; 2) the priority of the primary publication is respected by a publication interval of at least 1 wk (unless specially negotiated otherwise by both editors); 3) the paper for secondary publication is intended for a different group of readers (an abbreviated version could be sufficient); 4) the secondary version reflects faithfully the data and interpretations of the primary version; 5) a footnote of the title page of the secondary version informs readers, peers, and documenting agencies that the paper has been published in whole or in part and states the primary reference (a suitable footnote might read as follows: "This article was first published in the [title of journal, with full reference]."); and 6) permission of such secondary publication should be free of charge (62).

With the availability of computerized medical databases, including databases of dissertations, scientific proceedings, and research articles, such as PubMed or HighWire Press, it becomes much more difficult for authors to duplicate previously published work (1). Once a duplicate publication is discovered and reported by peer reviewers, journals can promptly reject the submitted papers, or retract the article if it has been published. If the editor was not aware of the violations and the article has already been published, then a notice of duplicate publication will be published with or without the author's explanation or approval. The notice is cited in PubMed, which can have serious impact on the reputation of the author(s) (36). The journal editor may choose to send the information to other journals, or to the head of the authors' institutions. Time-limited sanctions, including a ban from publishing in those journals, can be imposed. The editors of both journals may join to condemn publicly this unethical behavior and organize committees to help each other in the investigation of such cases. In some cases, authors may have to confront a civil suit for international copyright law violation (1).

Case study 1. A manuscript has been sent to your journal. It was sent to two peer reviewers, both of whom recommend acceptance. However, after one of these two reviewers posted his review, he discovered the authors have just published another very closely related paper in another journal, which apparently was submitted at the same time as the one they sent to your journal. Basically, both papers examined mechanisms of apoptosis in isolated cells and reached the same conclusions as to mechanism. In actuality, the paper that was published was more interesting and definitive because it was more clinically relevant to the disease being studied. The reviewer, who pointed out this previously published article, also noted the authors did not cross reference nor allude to the existence of the other article at the time of the initial submission. A perusal of both manuscripts reveals that the same number of figures is present, but in the first manuscript, the apoptotic stimulus was a bacterium and in the second it was a specific cytokine. The organizations of both papers are very similar. What should be done?

Questions for discussion:

1. What are the actions that should be taken by editors?
2. What if the author responds indignantly stating that the main focus and message of each paper were basically different?
3. What if one of the authors says that he or she had been unaware of the submission of the other article?

4. What if the authors emphasize the difference between two apoptotic stimuli and suggest that bacterial LPS mentioned in the first paper may induce other apoptotic mechanisms, but the specific cytokine mentioned in the second paper may not?
5. What is the best way for the authors and journals to resolve this matter?

Case study 2. A manuscript was submitted to your journal. It had a single author from a country other than the United States. During the review process, one of the reviewers contacted the handling editor, telling her that he remembered recently reviewing a similar paper for another journal. That paper, however, had multiple authors and a different title, but the contents were virtually identical. When you (as Publication Committee Chair) contacted the editor of the other journal, you learned that the two papers were indeed identical except for the author list and title. What should be done?

Questions for discussion:

1. Should a letter be sent to only the author of the current submission or all of the authors from the previous submission notifying them about and asking for an explanation for the duplicate submission?
2. What are some of the explanations for the duplicate submission that would be acceptable? What are not acceptable explanations from the author?
3. If the explanations given are acceptable, what actions, if any, should be taken against the author? Should these apply to all the authors or just the one who is the author of the current submission? What are some actions that one should take if the explanations given are not acceptable?
4. What action would you recommend concerning an author who has a history of duplicate submissions? How far can a journal go?

CONFLICT OF INTEREST

University employees who fulfill professional obligations objectively sometimes face an unpleasant but unavoidable situation when a conflict exists between their official responsibilities and their private interests. A person who finds him/herself in such a situation may knowingly or unknowingly make questionable decisions. Such conflicting situations arise not only because of money but also because of factors like political affiliation, religious conviction, and personal relationships. The consequences of such decisions or actions take on another dimension when the scientists in question are people in leadership or supervisory positions. Even a perception of bias can be just as damaging as the real thing.

In scientific research and publishing, maintaining objectivity is vital to uphold public confidence in the integrity of the research process and the reputation of the home institution and journal (54). An unacknowledged conflict can erode this confidence and threaten the integrity of otherwise solid research. The author of a manuscript is expected to be objective in presenting his/her findings, and the editors and reviewers also have to be objective in evaluating them. When such people in positions of trust hold competing interests that can result in bias or improper decisions, the information reaching the scientific community and the general public could be distorted and potentially devastating.

Conflicts of interest, either individual or institutional, can be real or perceived. Recognizing the potential for conflicts of interest is usually easy, but it can be extremely difficult to determine whether a conflict actually exists if not fully disclosed. This is important because what is not transparent could be perceived to be biased or corrupt. What is important is to acknowledge potential conflicts so that they can be dealt with appropriately. Doing otherwise reflects insensitivity to the issue, and may indicate that the author indeed has something to hide.

The Bayh-Dole Act, passed into law in 1980 (17), permitted and encouraged the commercialization of federal government-supported research by allowing the patenting of results of research carried out using government funds. Universities and individual scientists could own the rights to these patents. This action encouraged universities and researchers to develop their inventions into marketable products. This act also accelerated the interactions of academia with industry and biotech companies. In 1995, NIH policy changes did away with many of the restrictions on its own employees with respect to outside consulting in an attempt to attract highly qualified and respected researchers into its fold. This action included removing the limits on the dollar amount that NIH employees could earn or the time that they could invest in outside activities, provided it did not interfere with their work at NIH. Employees could now accept stocks and stock options besides money in return for their services. To provide specific guidelines for these activities, the PHS promulgated regulations that institutions that apply for research funding from the PHS could follow. NIH requires grantees and investigators to comply with the requirements of Code 42 of Federal Regulations Part 50, Subpart F, Responsibility of Applicants for Promoting Objectivity in Research for Which PHS Funding is Sought (51). In fact, at most (if not all) universities, key personnel on a research funding application must sign a Conflict of Interest form.

The intent of the regulation is to promote "...objectivity in research by establishing standards to ensure there is no reasonable expectation that the design, conduct, or reporting of research funded under PHS grants or cooperative agreements will be biased by any conflicting financial interest of an investigator. . ." (10, 26, 47, 48, 72). The important issue is that the individual scientist fully discloses any source of income outside of his/her normal employment. In Alabama, for example, any state employee whose salary exceeds \$50,000 per annum must file a yearly disclosure form to the State Ethics Commission. Nonetheless, the road is still rocky. In the September 24, 2004, edition of the *Washington Post*, an article by Rick Weiss appeared highlighting the current turmoil at NIH concerning conflicts of interest (77). NIH has effectively banned (for at least one year) any of its intramural scientists from collaborating with pharmaceutical or biotech companies. Even existing collaborations must be terminated. This action was prompted by the discovery of numerous improprieties with regard to nontransparency of conflict of intent issues (23, 40, 46).

The fact that conflicts also exist within journals is not difficult to appreciate. Many journals, especially clinical journals, depend heavily on advertising (see Ref. 41). Review articles that acknowledge sponsorship by industry may possibly draw conclusions that are favorable to the industry. This concern led the *New England Journal of Medicine* to prohibit authors from writing review articles if they held a financial

interest in a company. Even if they divested all financial ties to industry, there would still be a two-year hiatus from writing review articles about research involving companies from which support was received. This prohibition has recently been rescinded primarily because of the difficulty of finding authors that were completely free of industry ties (6, 54).

Under the final rule on "Objectivity in Research" in the CFR, investigators are required to disclose a listing of "significant financial interests" that would reasonably appear to influence the research proposed for funding by the PHS. "Financial interest" means anything of monetary value, including, but not limited to, the following: 1) salary or other payments for services (consulting fees or honoraria); 2) equity interests (stocks, stock options, or other ownership interests); and 3) intellectual property rights (patents, copyrights, and royalties from such rights). Davidoff et al. (18) wrote a concise summary of conflict of interest policies for clinical journals.

An investigator's financial interest in an external entity is considered to be "significant" and must be disclosed if it exceeds either one of the following: 1) \$10,000 per annum for any combination of salary, payments for services, equity, and income from intellectual property rights; or 2) 5% ownership interest.

Examples of how financial conflicts of interest might be addressed include 1) public disclosure of significant financial interests; 2) monitoring of research by independent reviewers; 3) modification of the research plan; 4) disqualification from participation in all or a portion of the research funded by PHS; 5) divestiture of significant financial interests; or 6) severance of relationships that create actual or potential conflicts.

Under a renewed effort to address the issue, it has been recommended recently by a Blue Ribbon Panel that reviewed the current NIH conflict of interest policies that employees in a position to influence the financial interests of an outside entity such as a current or possible future recipient of an NIH grant or contract should neither receive financial benefits from that organization nor have significant financial interests in it (48). From our perspective, the rule of thumb to follow is this: it is better to disclose a potential conflict than not. In this way, information is available to the reader so that he/she can better judge whether the author's objectivity has been compromised. The fact that an author disclosed such information sends a positive message that he/she has nothing to hide. We also think that a \$10,000 per year threshold for reporting is too high and too rigid. Perhaps an additional \$9,000 check for consulting work may not influence unduly an independently wealthy scientist, but an extra \$1,000 (or maybe even \$100) to a graduate student, a newly appointed assistant professor, or even a full professor may make a significant difference in their income.

Case study 1. A paper has been submitted to a journal, and after two rounds of thorough scientific review, is accepted for publication. Just hours before web posting of this manuscript, the editor received a panicked call from the communicating author who said that a problem had arisen. A major drug company that had sponsored the research disputed the authors' right to submit the manuscript because the authors and the company signed a contract specifically stating that the company must agree with the contents of the manuscript before submission. The company did not agree with the authors' conclusions. The company made it clear to the authors that it

was prepared to bring legal action against them and the journal if the paper was not immediately withdrawn. What should be done?

Questions for discussion:

1. Is it appropriate for the drug company to bring legal action against the authors and the journal?
2. In case the drug company disagrees with the content of the paper and exercises its legal right to prevent the paper from being published, would it be justified to hold back information from the scientific community and the general public, given that the editors of the journal have deemed the contents of the paper novel, significant, and hence publishable?
3. Who should bear responsibility for such miscommunication between the authors and the sponsoring agency?
4. What should a journal's stance be on industry-sponsored research?
5. Should findings of sponsored research always be viewed with distrust as being biased towards the funding agency?

Case study 2. The Director of Publications receives a letter from an irate reader complaining that the journal did not publish a financial disclosure from an author of a review article that was published 6 mo earlier. At the time, the journal did not have a policy on conflict of interest that covered review articles. This reader was not dissuaded by any argument. He/she continued to write, demanding that "...an honest disclosure of competing financial interest..." of the authors be acknowledged in print. The author's response was that this individual had been harassing him over this issue for years, mainly because of a personal scientific vendetta. The author has, in the past, freely disclosed his finances if asked, but feels in this case that it is not appropriate, given the policies of the journal at the time. What should be done?

Questions for discussion:

1. Should the journal publish a retrospective disclosure?
2. What are appropriate journal policies concerning conflict of interest disclosures?

AUTHORSHIP ISSUES

Being an author on a scientific manuscript is a privilege and one of the more satisfying experiences of a scientist. Not only does being an author signify a personal contribution to knowledge thus imparting respect and pride, but it is also used as a measure for promotions and tenure. These aspects, however, are only half of the authorship equation. Being the author of a scientific manuscript also entails responsibility. It is this amalgam of credit and responsibility that forms the precious foundation for the esteemed moniker of "author."

Every scientist has his/her own conception of what is required to be an author. However, often these ideas differ among participants in a research project. Disputes and personality conflicts can arise during an investigation that may cause discord and disagreement over who qualifies for authorship. There are general guidelines put forth by entities such as the NIH and The Council of Science Editors. But, as helpful as they are, they are just guidelines. These helpful guidelines appear definitive, but, like a smoky advertisement written from a vapor trail of a plane, they can quickly fade into bits of

useless literary dust when released into the everyday environment of the lab.

The suggested guidelines, however, do give us a solid foundation from which to start. One definition of an author, in a broad sense, is "...[one who is] generally considered to be someone who has made substantive intellectual contributions to a published study. . ." (19, 20). The International Committee of Medical Journal Editors (ICMJE), a recognized organization on ethical issues pertaining to the biomedical research community, defines authorship in the following way: "Authorship credit should be based on: 1) substantial contributions to conception and design, or acquisition of data, or analysis and interpretation of data; 2) drafting the article or revising it critically for important intellectual content; and 3) final approval of the version to be published. An author should meet conditions 1, 2, and 3." (36)

The NIH gives similar criteria in their "Guidelines for the Conduct of Research" in the Intramural Research Programs at NIH. They suggest that those persons designated as authors should make a significant contribution to the conceptualization, design, execution, and/or interpretation of the study, and that they are willing to accept responsibility for the study (49). The NIH also expands on the duties of the first author. The first author should coordinate the completion and submission of the manuscript and attend to all rules of submission. He/she should also be responsible for all communication regarding the manuscript (with the journal and reviewers). This person should also make sure that the contributions of all those involved in the study are appropriately recognized. Importantly, he/she must ensure that each coauthor has reviewed and approved the paper for submission at all points in the process (49). When a large, multicenter group is involved, as is increasingly the case, then the ICMJE suggests that all the individuals involved meet the criteria for authorship, but that the group designates certain individuals that are responsible for the work as a whole. The ICMJE also comments on what criteria *do not* make one qualified for full authorship. These include acquisition of funding (alone), collection of data (alone), or general supervision of the research group (alone). They also specifically state that "...[e]ach author should have participated sufficiently in the work to take public responsibility for appropriate portions of the content. . ." (36).

If an individual does not meet these qualifications for authorship, but they are still involved in the study, then they are relegated to the acknowledgements section. Such individuals, for example, would include those who provide technical help only, writing assistance, or the chair of the department who provides only general support. The ICMJE also suggests, and it is good practice, that all persons acknowledged must give written permission (36). The NIH describes the acknowledged as those individuals who do not meet the criteria for authorship, but who have given advice, provided space, financial assistance, "occasional analyses," or patient material (49).

The vagueness of authorship criteria and the common practice of honorary or guest authorship (i.e., lists of noncontributing persons as authors simply for political or personal reasons) has led Drummond Rennie, Deputy Editor of the *Journal of the American Medical Association* (JAMA), to say: "There is abundant evidence that the concept of authorship, when applied to co-investigators in biomedical research, is inadequate and the system is truly broken" (66). Some of the

suggestions that have been made include teaching scientists about the importance of authorship and about the weight it carries. In the past, the *Journal of Physiology (London)* listed authors in alphabetical order in an attempt to eliminate the weight that authorship order carries. The problem with this approach is that this is not a uniform practice, and, regardless of intent, the first and last authors are the most critical. Another solution is for all journals to enforce the above listed guidelines. Drummond Rennie considers the problem as being a disconnection between credit and responsibility. As such, he proposed to reconnect these two critical aspects of authorship by suggesting contributorship (66, 67, 80). In this case, each "contributor" to an article is required to list their explicit role in the project. One person is designated as the "guarantor" of the article, i.e., the person accountable for the veracity of the data and the ethical conduct of all aspects of the work. Several journals, including JAMA, *Proceedings of the National Academy of Sciences of the United States of America*, *Nature*, and the *British Medical Journal*, have adopted this policy.

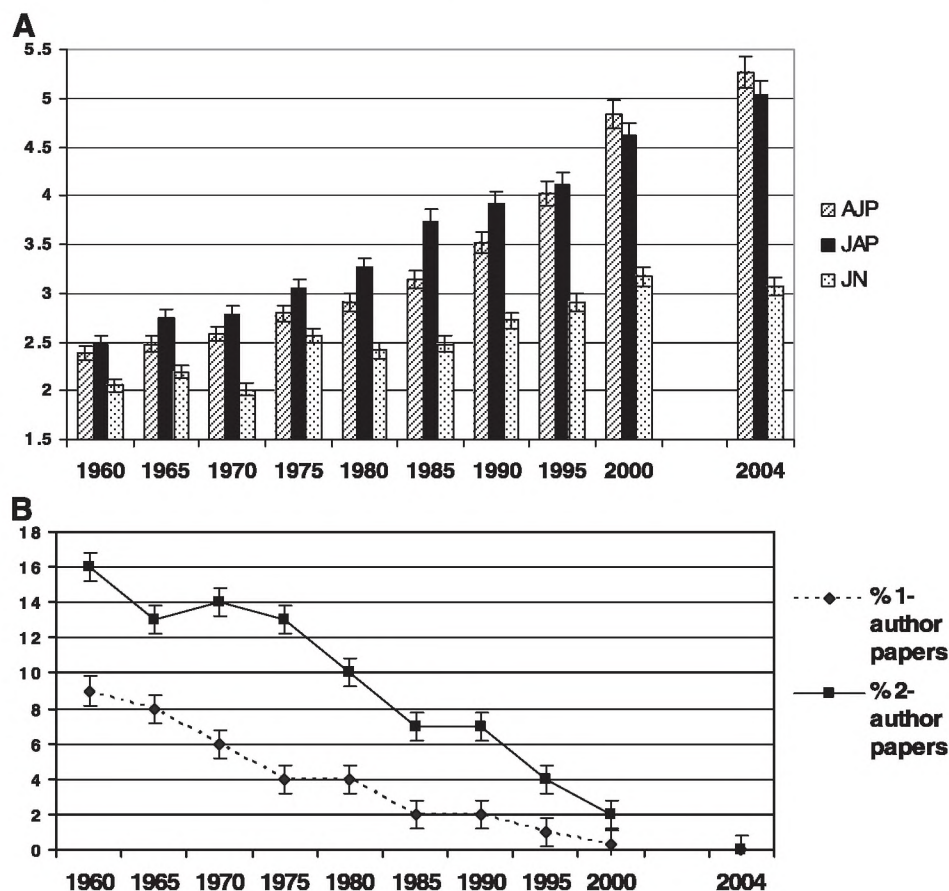
As long as people are doing science, people rightfully desire credit for their efforts. Authorship will remain an integral part of the science career, as well it should. Partitioning credit as well as responsibility is a critical part of the scientific process. Authorship issues are increasing, primarily because the average number of authors per research article has been steadily rising over the years. More authors mean more interpersonal interactions and more potential for problems if communication is not adequate. For example, for the publications of the APS, the average number of authors per article increased between 1960 and 2004 from 2.4, 2.5, and 2.0 to 5.3, 5.0, and 3.1 for *American Journal of Physiology-Consolidated*, the *Journal of Applied Physiology*, and *Journal of Neurophysiology*, respectively (Fig. 4A). During the same time interval, the percentage of articles published by the APS that were single- or dual-authored decreased from 9 and 13% (single- and dual-authored articles in 1960) to 0.03 and 0.002% (in 2004), respectively (Fig. 4B). The best advice is to discuss authorship issues at the onset of a study, as well as during, particularly if new investigators join, or original ones leave, the research project. In our opinion, it is always better to err on the side of generosity.

Case study 1. A manuscript was submitted to a journal. There were three authors: the first author was a postdoctoral fellow working with the senior (third) author, and the second author was a technician in the same laboratory. All three individuals signed a mandatory submission form, a requirement of that journal, attesting that they each contributed to the work. The paper was reviewed favorably. The only comment made was to remove one figure. The authors complied with this request. However, when the revised manuscript was resubmitted, the technician's name had been dropped from the list of authors. Both the postdoctoral fellow and the senior author signed a Change of Authorship form, but the technician refused to sign. The senior author argued that the only contribution the technician made was performing the experiment in the figure that the reviewers' asked to be removed. What should be done?

Questions for discussion:

1. What responsibilities do the first author and senior author hold in designating credit for this manuscript?
2. Could the journal publish the manuscript without the technician signing the Change of Authorship form?

Fig. 4. A: average number of authors per article published in the research journals of APS from 1960–2004. B: percentage of the total number of published articles in the *American Journal of Physiology-Consolidated* (AJP), *Journal of Applied Physiology* (JAP), and *Journal of Neurophysiology* (JN) authored by either one (▲) or two (■) persons from 1960–2004.



- How would you have handled the situation if you were the senior author?
- Would it matter if the technician was from a different lab than the first and senior authors? (i.e., would the senior author hold more or less “weight”?)

Case study 2. One of the authors of an accepted article (posted on the web, but not yet appearing in the print journal) wrote to the editor demanding that publication of that same article be stopped (and the posted version removed from the web site) until a disagreement between her and the other two authors of the paper was resolved. According to the disgruntled author, after the paper was accepted, the lead author made himself (a postdoctoral fellow) the corresponding author without informing the other two authors. No change of authorship form was signed (the order of the authors was unchanged throughout the review process). A perusal of the submission history revealed that the person(s) designated as corresponding author changed as many times as there were revisions. What should be done?

Questions for discussion:

- Is this an authorship issue?
- What is a corresponding author?
- Can (or should) more than one person be designated as corresponding author?
- How should the journal handle this case?

ANIMAL WELFARE CONCERNS

Animals continue to be integral to biomedical research (37). It is essential that scientists do everything possible to promote

and ensure the humane care and treatment of animals used in research and teaching. The use of animals in such venues has contributed much to advance scientific and medical knowledge. Yet, there are those who oppose animal experimentation regardless of outcome. The reader is referred to several lucid articles discussing this controversial topic (42–44, 53). The APS has long been both a proponent of the use of animals in research and an avid formulator and supporter of strong principles guiding the use of animals. In fact, the sixth president of the APS, Walter B. Cannon, first proposed APS’s “Guiding Principles to the Care and Use of Animals” in 1909 (4). These principles, namely, that animals to be used in the laboratory must be acquired lawfully, must be properly fed and sheltered, and under no circumstances must they be subjected to unnecessary pain or discomfort, are inherent to every statement by virtually every governmental agency or regulatory body. Moreover, animal use in a laboratory or teaching setting must be in compliance with the regulations stipulated by the Institute for Laboratory Animal Research (35). Oversight for compliance with federal regulations is provided by the United States Department of Health and Human Services (DHHS). Institutions can voluntarily participate in an accreditation program administered by the Association for Assessment and Accreditation of Laboratory Care International. The Office for Laboratory Animal Welfare (OLAW; 52) is the DHHS agency charged with ensuring that institutions that receive federal funds are in compliance with the PHS Policy on the Humane Care and Use of Laboratory Animals (64). The OLAW does not defer any authority to accreditation agencies, however.

Furthermore, each institution where animal research is conducted has a staff of licensed veterinarians and trained animal caretakers to make sure that all regulations are followed. Each animal protocol must be reviewed and approved by the Institutional Animal Care and Use Committee (IACUC) before animals can even be purchased. An explicit statement to that effect must be included in every manuscript submitted to an APS journal, and should be included in manuscripts submitted to other journals as well.

The Animal Welfare Act became law in the United States in 1966. It was the first but not the only Federal Law that regulates the care and use of animals in research. This law was last amended in 2002 with congressional approval of the Helms Amendment, and is found in the CFR, Title 9, Chapter 1, Subchapter A (9CFR). It is also found in the *United States Code* (USC), Title 7, Sections 2131 to 2156. The Animal Welfare Act falls under the purview of the United States Department of Agriculture (USDA). The Animal Welfare Act did not specifically apply to rats, mice, and birds (together constituting 95% of the 20 million animals used each year in teaching and research in the United States), although the same principles that govern the care and treatment of other species have been uniformly applied to these animals by institutions and scientific societies and publishers. The USDA, under pressure from animal rights groups, proposed regulations that would not exempt rats, mice, and birds. This action in turn was opposed by the research community on the basis that these new regulations would unduly increase both the cost and administrative burden of using such animals without affecting humane care and treatment. Congress agreed, and amended the Animal Welfare Act in 2002 with the passage of the Helms Amendment, which specifically exempts rodents and birds from USDA oversight with regard to use in research (7, 8, 14, 28).

Most recently (June 4, 2004), the USDA has published advance notice for comment of proposed rule changes for Animal Welfare Act standards for rats, mice, and birds not bred specifically for research (8, 14). Regulatory standards and laws notwithstanding, it is imperative that all scientists conduct their experiments with the highest regard for the well-being, comfort, and humane treatment of their animal subjects.

Case Study 1. A manuscript was submitted to a journal in a response to a "Special Call for Papers." After it was peer-reviewed and accepted for publication, the handling editor raised a potential animal welfare concern (the three reviewers did not raise the concern in their reviews). The problem that concerned the editor involved an experiment that used cecal ligation in rabbits to induce sepsis. The investigators assessed cumulative mortality out to 10 days. The handling editor argued that mortality is not considered an acceptable experimental end point. According to the editor, an investigator is supposed to use a surrogate end point to identify animals that are terminal, but before they become moribund. The manuscript originated from a laboratory in the United States, and the paper stated that the protocol was done with IACUC approval. What should be done?

Questions for discussion:

1. Is death as acceptable experimental end point, or should animals be euthanized at the point when their health begins to decline?

2. Are IACUC review processes and standards uniform at universities within the United States?
3. How should a journal respond if an IACUC-equivalent approval was obtained for animal experiments conducted at a non-United States institution, but the protocol would not have passed review if United States standards were applied?
4. Can and should a journal refuse to publish a study if, according to the journal's opinion, animal treatment and use were inadequate, even if IACUC approval was obtained?

Case study 2. A manuscript was submitted to your journal. In this work the authors isolated a protein from the livers of black bears. In the Methods section, the authors stated that livers from 30 bears were used, and the bears were purchased from licensed trappers who hunted them for the fur. There was no indication of IACUC approval. What should be done?

Questions for discussion:

1. What if, on inquiry, the authors produced evidence of IACUC approval? What if no approval was secured?
2. Does a journal have the right not to publish the articles even if the work was judged to be scientifically sound?
3. Shouldn't investigators be permitted to use organs from animals that were hunted because the animals were killed anyway?

HUMAN USE CONCERNS

In the wake of war crimes witnessed during World War II, a set of 10 criteria was established to judge the actions of doctors and scientists who took part in studies conducted on concentration camp prisoners. These criteria, known as the Nuremberg Code, were the first to address ethical standards of human experimentation (2). According to this code, experiments on humans are permissible only if the results will benefit society, that the subjects involved in the study freely consent and are free to withdraw at any time, and that no harm or discomfort to the subject will result from the investigation. Since then, other guidelines have evolved that more clearly define human research that is ethically acceptable. The World Medical Association established the Declaration of Helsinki in 1964 in an effort to provide a global framework under which experimental work involving human subjects would be permitted (79), and has since been revised five times in efforts to maintain relevance to current science. The most recent revision took place in 2000, with amendments being made in 2002 and 2004 that further clarified language used within the Declaration to focus its intentions. The DHHS also adopted the standards of the Nuremberg Code and, in the mid-1970s, sought to define scientific ethics for this country. In July of 1974, the National Research Act became law, thereby establishing the Commission for the Protection of Human Subjects of Biomedical and Behavioral Research (64a).

Of the aims set forth by the commission, one in particular was to outline the essential ethical principles on which research involving human subjects should be based. The commission convened a task force, led by Kenneth J. Ryan of Harvard Medical School (Cambridge, MA), to examine in detail issues surrounding human experimentation. In 1979, this task force completed and published the Belmont Report (21). This report stipulated three basic principles that serve as the foundation of human biomedical and behavioral research. These principles

have been promulgated to guide investigators in the resolution of ethical issues surrounding their studies. All institutions receiving funds from DHHS to conduct or support research with human subjects are subject to regulatory requirements outlined in The Belmont Report.

Respect for Persons is the first of the three principles stipulated by the Belmont Report. It states that individuals should be treated as autonomous agents and that persons with diminished autonomy are entitled to protection (21). An autonomous person is one who is capable of deliberation about personal goals and can rationally make decisions for him/herself. Those who lack this capacity require protection.

The next basic principle, Beneficence, relies on the researcher to "do no harm." In other words, the study must maximize the possible benefits while minimizing all possible health risks (21). Persons should be treated in an ethical manner by respecting their decisions and protecting them from danger. Investigators are thereby charged with making efforts to secure the well-being of research subjects.

Third, the Belmont Report outlines Justice. Consideration of this principle resulted from the common practice in the 1800s and early 1900s of using the poor, the mentally deficient, or prisoners as research subjects, while affording the benefits of such research to the privileged. Therefore, scientists are required to evaluate whether their selection of research subjects has been made because of "...their easy availability, their compromised position, or their manipulability. . ." (21). Moreover, the benefits that derive from the research must be distributed to all persons regardless of class so that justice prevails.

The DHHS states that the application of these three basic principles entails certain requirements. First, subjects must give informed consent before participating in a study. Before the beginning of any experimentation, the subject is to be informed of the research procedure and its purpose, the risks and anticipated benefits of the study, and alternative procedures, if any. The subject should also be allowed the opportunity to ask questions as well as be given the freedom to withdraw without prejudice or fear of reprisal at any time from the research. Additional information concerning subject/investigator liability, the subject screening process, etc., has also to be delineated.

In some cases, it may be necessary to provide subjects with incomplete disclosure of the research. This is permissible only if incomplete disclosure is truly necessary to accomplish the goals of the study, there are no undisclosed risks to the subjects, and there is an appropriate process for debriefing subjects and distribution of results (21). It is also important to convey all information in an organized fashion, and to take time to relieve any confusion a subject may have concerning the study. When all necessary information is provided and the subject understands the benefits and drawbacks of the study, it becomes the subject's responsibility whether or not to give voluntary consent. Voluntary consent refers to a positive response toward partaking in a study that has not been coerced or influenced in any manner. All human subject protocols, including the actual informed consent document, must be reviewed and approved by a duly established Institutional Review Board (IRB). A requirement of publication in any of the APS journals is an explicit statement in the manuscript that such approval was obtained.

Before the commencement of any study, it is important to consider the target groups of subjects that will be included in the experimental process. Based on the experimental outline and intended benefits of the experiment, some populations may be unnecessary for inclusion, whereas others may be integral to the investigation. Of course, the inclusion of children and others considered not to be autonomous require special consideration and protection. The use or exclusion of one population over another must be accompanied by proper reasoning and be agreed on by the investigator's IRB.

In 1981, the regulations outlined by the Belmont Report were added to the CFR at Title 45, Part 46 (76). This particular portion of the CFR defines basic DHHS policy concerning the protection of human subjects; and as stated, "Applies to all research involving human subjects conducted, supported or otherwise subject to regulation by any Federal Department or Agency which takes appropriate administrative action to make the policy applicable to such research" (24). The CFR, like the Declaration of Helsinki, is continually critiqued and upgraded to maintain relevance to current scientific research.

Exemptions from this policy are those that can be seen as the least physically and psychologically invasive of studies conducted on human subjects. Research conducted in established or commonly accepted educational settings; studies involving the use of educational tests; research involving the collection or study of existing data, records, etc., taste and food quality evaluations and consumer acceptance; and the assessment of public benefit or studies aimed at causing beneficial changes to preexisting programs are all excluded from CFR 45.46 (24). However, these types of studies are subject to separate guidelines also found under the umbrella of the CFR. Importantly, the regulations outlined in the CFR have no effect on any local, state, or foreign laws or guidelines established to provide further protection of human subjects in scientific research (80). Use of these materials and protocols, including surveys, still require IRB approval.

Well-established outlets of scientific research such as the *American Journal of Physiology*, and the *New England Journal of Medicine* require that the research described in their publications adhere to the standards outlined by the Declaration of Helsinki and CFR Title 45, Part 46. Documented approval by an IRB, IACUC, or equivalent oversight committee is also a requirement for publication. Those submissions that do not contain such documentation are to be refused by reviewers. In the end, it still falls on the shoulders of those conducting human research to exhibit integrity, dignity, and justice to ensure that proper care is given to all who offer themselves to advance our understanding of the disease process.

Case study. During the review of a manuscript, one reviewer noticed that human cardiac tissue was obtained for microarray analysis from a patient during, according to the authors, a standard catheterization procedure used for diagnosis of a specific cardiac myopathy. The authors also stated in the manuscript that informed consent was obtained, and the entire study was reviewed and approved by their institution's IRB. However, the reviewer, who was a cardiologist, stated categorically that this procedure is not used for diagnosis; the condition is so well defined that its diagnosis is made by less invasive means. The authors' institution is in a European country. What should be done?

Questions for discussion:

1. Do these investigators have the same technology available to them as do their United States counterparts?
2. Would it make any difference if the study originated in a United States institution?
3. What should the first course of action of the journal be?
4. What should be done if the procedures violated the protocol approved by the IRB?

REVIEWER RESPONSIBILITY

We conclude this article with a brief discussion of the ethics of peer review. Figure 5 summarizes the complete cycle of a scientific project from the perspective of manuscript submission and peer review. A reviewer of a manuscript fulfils an essential duty to his/her discipline, namely, to ensure that only the very best and solid science appears in the literature. A reviewer is considered by the journal editor to be an expert in the field or at least in some aspect of the work under consideration. Thus it should be considered an honor and a privilege to be asked to review manuscripts for a journal, not a bother or nuisance. Reviewing is contributing in a positive way. The review process of an article before publication is crucial and not simple. It involves the work of several people at different levels that finally will recommend whether a manuscript should be published. It is most often in this review phase of the publication process that untoward ethical issues are discovered. It is important to understand that journals vary in their practices, but usually the editor decides whether a submitted manuscript should be sent for review. If it satisfies the general requirements of that journal, the manuscript is transmitted to editorial board members or external scientists for review. The review process needs to be timely and fair for authors and for the reviewers. Journals specify a specific amount of time for reviewers to complete their evaluation. It is the editor's decision how many reviews are needed. The final decision regarding the ultimate disposition of a manuscript rests with the editor, not the reviewers (70).

Manuscript review can be divided into technical and ethical categories. Both of these aspects are concerned with adding value and quality to a manuscript. According to Benos et al. (12) the principal elements of a review are an evaluation of 1) the scientific quality of the work, 2) the clarity and logic of presentation, and 3) the ethical validity of the study. Prof. Y.

Epstein of the Sheba Medical Center in Israel wrote "The coin is two sided; it is not only the scientist who should adhere to high ethical principles but also the reviewer. . . ." (27). Unscrupulous, unethical reviewers can be a terrible burden on a journal or granting institution. Some reviewers can take advantage of their position to steal ideas, hinder other researchers' publications, deny funding to deserving researchers, and propel themselves to academic excellence and status. This does not mean that the process is corrupt; it means that all reviewers must maintain high integrity and ethical standards. This is why the review process usually does not rely on only one reviewer. The probability that one individual may dictate the outcome of a manuscript or grant is minimal. The system is designed so that more than one reviewer gives his/her informed opinion on the value and importance of a grant or manuscript. The author's work is taken very seriously, and the editor always has the final decision. It is the right and responsibility of all parties, authors and reviewers alike, to report suspected and actual ethical infractions and concerns to the editor.

Suggestions from authors as to who might or might not act as reviewers are often useful, but there is no obligation for editors to use those individuals. Confidentiality in the assessment of a manuscript must be maintained by expert reviewers, and this extends to reviewers' colleagues who may be asked (with the editor's permission) to give opinions on specific sections. The submitted manuscript should not be retained or copied by the reviewers. Reviewers and editors should not make any use of the data, arguments, or interpretations, unless they have the authors' permission before publication. Reviewers should provide speedy, accurate, courteous, unbiased, and justifiable reports. If reviewers suspect misconduct, they should write or call in confidence to the editor. The editor in turn must follow the established procedures for dealing with issues of misconduct and not investigate by him/herself. Journals should publish accurate descriptions of their peer review, selection, and appeals processes. Journals should also provide regular audits of their acceptance rates and publication times for self-evaluation purposes.

In summary, a reviewer is asked to provide an informed opinion about the suitability for publication of a manuscript. Reviewers' responsibilities include 1) evaluating the manuscript honestly, objectively, and critically; 2) disclosing (or avoiding) any real or perceived conflicts of interest with the work or the authors; 3) not engaging in plagiarism; 4) identifying to the editor areas of the manuscript in which the reviewer is not an expert; 5) writing reviews in a constructive, helpful fashion, and not being derogatory; 6) reviewing expeditiously; 7) maintaining confidentiality; and 8) reporting any suspected ethical breach to the handling editor.

Case study 1. The journal editor sent a paper to an outside referee to review. The editor's cover letter specifically stated that if the reviewer is unable to provide a review in the time frame specified, the reviewer may ask a colleague to assist. The senior author of that manuscript, by chance, was visiting the institution of the reviewer after the paper was submitted to the journal. During her visit, she was being escorted through the laboratory of the reviewer and noticed, in a reception area, multiple copies of her manuscript on a coffee table. She asked her escort (a graduate student of this laboratory) about the papers on the table. The graduate student, who was unaware that she was the author of the manuscript on the desk, stated

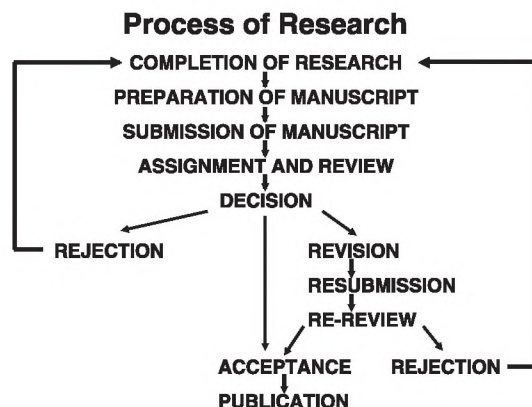


Fig. 5. Flow diagram of review and publication process for a manuscript submitted to a journal (adapted from Fig. 1 of Ref. 73).

that as part of the laboratory's Journal Club they do group reviews of manuscripts that the senior investigator has been asked to review. On returning to her own laboratory, she telephoned the editor with the complaint that her manuscript was circulated among her research competitors at another university. The editor, in turn, telephoned the reviewer who stated that he routinely asks his laboratory to review manuscripts as a group, primarily because of the teaching value of such an experience. The "review group" consists of graduate students, postdoctoral fellows, and junior faculty members. In general, the reviewer assembles all the comments into one review, signs the forms, and takes responsibility for the review. The reviewer felt that the procedure produces well-done reviews containing lots of constructive criticism.

Questions for discussion:

1. Is this review group permitted according to the editor's cover letter?
2. If the reviewer takes all the responsibility by signing the forms, can he discuss the articles with his review group?
3. Is the review valid?
4. What should the editor do with this reviewer?
5. Can the editor continue sending papers for review to this reviewer?

Case study 2. A paper was submitted to your journal. The review process was quite extensive, the paper having undergone several rounds of peer review. Part of the delay was caused by the authors not revising the paper in a timely fashion. The paper was also delayed by one of the reviewers in that very demanding revisions were required. After the paper was resubmitted a third time, the corresponding author wrote to the editor stating that she saw a similar paper that was just published on the web within the last week. The author asked a very specific question, "I have been wondering whether anyone in the [authorship] in the recently published paper was acting as a reviewer of our paper? Of course, that would raise an ethical issue because of the quite obvious conflict of interest. Although I do not pretend to know the identity of the referees, I feel justified to seek an answer to this question." On examination, the editor discovers that yes; indeed, one of the authors of the previously published paper was one of the three reviewers of the manuscript in question. Moreover, it was the same reviewer who demanded extensive revisions. What should be done?

Questions for discussion:

1. Who is responsible for the delay? The reviewer, the authors, or both.
2. What were the comments of other reviewers? Did they agree that the manuscript needed the changes recommended in the first submissions?
3. Did the reviewer intentionally delay the publication?
4. Should the reviewer inform the editor of a conflict of interest?
5. What action should be taken? Inform the author? Apology? Published statement? Publish the paper?
6. If there were misconduct, should the reviewer be dismissed from the review board of the journal and should there be a letter of reprimand?
7. Is there any plagiarism from the manuscript in the published paper (by the reviewer)?

CONCLUDING REMARKS

Walter B. Cannon in his book, *The Way of an Investigator* (13), remarked that a scientist, among other essential traits, "... must be ingenuously honest." A scientist "... must face facts as they arise in the course of experimental procedure, whether they are favorable to his idea or not." It is only in this way, from each of us, that the pillars of scientific integrity remain strong. In this article, we have summarized most of the common aberrations of scientific conduct that are encountered in the publication process. We emphasize that they are aberrations: by far and away, the vast majority of scientists and science is pure and true. This is precisely why any actions that may compromise this truth must be dealt with swiftly and fairly. The APS publications program has evolved procedures for handling accusations of ethical violations. These procedures are printed on the inside back cover of each issue of every journal that the Society publishes, as well as on the APS web site (<http://www.the-aps.org/publications/journals/apsethic.htm>). We think these procedures are sound, and should be adopted by every publisher. They ensure confidentiality, impartiality, multiple levels of adjudication, and above all fairness. They have been designed so that the accused is not assumed guilty of the alleged infraction, and that he/she has every opportunity to present his/her side of the story. These procedures have also been designed to preserve the validity of the scientific record and protect authors and journals alike from unscrupulous and unfounded allegations. Ultimately, however, sound science depends on sound scientists. It is imperative for all of us to be aware of potentially compromising ethical situations, and to continue our own education in proper experimental techniques and publication practices. It is only in this way that each of our individual excursions into scientific inquiry can forever contribute to the joy of formulating new knowledge.

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