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All abbreviations should be explicitly defined at first usage. However, internationally accepted abbreviations do not need to be defined. Please consult the list of accepted abbreviations for our journals (<http://www.the-aps.org/publications/journals/abbrv.pdf>). For word usage, symbols, etc., authors are referred to *Scientific Style and Format: The CBE Manual for Authors, Editors, and Publishers* (6th ed., 1994). For chemical and biochemical terms and abbreviations, consult the recommendations of the IUPAC-IUB Combined Commission on Biochemical Nomenclature. Online resources can be found at <http://www.iupac.org>. Isotope specification must conform to the IUPAC system. Authors are referred to the following articles for style in specialized fields: "Glossary on respiration and gas exchange" (*J Appl Physiol* 34: 549–558, 1973); and "Glossary of terms for thermal physiology" (*J Appl Physiol* 35: 941–961, 1973).

Special Symbols

For special characters not available on the standard 104-key keyboard (e.g., Greek characters, mathematical symbols, figure symbols), use the "Insert Symbol" function in Microsoft Word; do **not** use math font or image files (e.g., GIF) within the text for special characters or text constructions.

Spelling and Editorial Style

Authors should follow *Webster's Third New International Dictionary* or *Merriam-Webster's Collegiate Dictionary*, 11th edition, for spelling and compounding. The APS Journals use American English rules for spelling.

All manuscripts will be edited by highly trained professional copy editors, according to the APS house style and guidelines.

Trade Names

Proprietary (trademarked) names should be capitalized, with the spelling carefully checked. The generic name or generic descriptor should accompany the trade name the first time it appears.

Genes and Proteins

When reporting studies on genes and proteins, be sure to follow the established style conventions of the genetics community for properly expressing gene vs. protein symbols and names.

Cell Lines and Reagents

The source of cells utilized (species, sex, strain, race, age of donor, whether primary or established) should be clearly indicated. The source of reagents should be stated (name, city, and state within parentheses) when first cited. If tests to rule out the presence of mycoplasma contamination were not performed, this fact should be clearly stated. Other data relating to unique biological, biochemical, and/or immunological markers should also be included if available, with their source identified. Publication of results is based on the principle that results must be independently verifiable. Authors are expected to make unique reagents available to qualified investigators either directly or through a recognized distributor. See also *Unique Materials and Data Banks* (above) and *Ethical Policies and Procedures* (appearing at the end of this document) for other requirements.

Manuscript Sections

Title Page

All submissions must contain a title page. The title page must contain the full title of the article; author(s) name(s); all departments and institutions in which the work was done; an abbreviated title for the running head; and the corresponding author's name, e-mail address, and physical address for correspondence. Only one author may be designated as the corresponding author.

Title

Make the title informative. Avoid unnecessary words like "Studies in" The title must not exceed 160 characters, including spaces between words.

Authors

List all authors' names and their first names or initials exactly as they should be known, **in the order of importance of their contribution to the study**. Do not include any specific titles (e.g., PhD, MD, and Prof. are not needed). "Group authorship" is allowed, with the name of a group (such as a consortium or program) to be listed as an author, with members of the group listed in the Acknowledgments section; however, the Program Director of the named group must be the one who signs for the group when the group's "author" signature is needed, i.e., on a Mandatory Submission Form or a Change of Authorship Form.

Authors who publish in APS Journals may now present their names in non-Latin characters (in their native writing system) alongside the standard English transliteration of their name in the main author line of the published article; for example, "Ta-Ming Wang (王大明)". We will accept any non-Latin languages that have standard Unicode characters (<http://www.unicode.org>) designated for the native characters. For authors that choose this option, please only provide the native expression for the original written form of the transliterated **name**; that is, do not include any associated degree, rank, or title information in the native format. This feature is meant for the person's name only, not for ancillary information regarding academic achievement or institutional affiliation. To take advantage of this new feature, please insert the native expression of your name alongside the English transliteration in the main title page of your manuscript submission.

Affiliation

List all departments and institutions in which the work was done, with city and state or country. Identify each author's affiliation by superscript numbers matched to the appropriate institution. Affiliation must reflect the organization(s) supporting the author(s) while the work was done. This may differ from the current affiliations of the author(s), which will be listed in such cases in the Acknowledgments section as the present addresses of the authors.

Running head

The running head is an abbreviated version of the title, which will appear at the top of every page subsequent to the first page. Running heads must not exceed 60 characters including spaces between words.

Contact information

Only one author may be designated as the corresponding author. A full address for correspondence will be published and must be included, **with a current, valid e-mail address** for the corresponding author. The address of the sole corresponding author (there must be only one corresponding author) will appear on the first page of the article, if the article is accepted for publication. Please note that a valid e-mail address is essential to participate in the APS electronic proofing service. Also, provide phone and fax numbers for use while your article is in production. If the contact information to be used during production differs from that to be included in the final article, indicate this explicitly. To contact APS during the submission and peer review and/or during production after acceptance, go to the APS website (<http://www.the-aps.org>) and choose the appropriate journal's web page.

Abstract

An informative one-paragraph abstract of not more than 250 words must accompany each manuscript. It must state concisely what was done and why (including species and state of anesthesia), what was found (in terms of data, if space allows), and what was concluded.

Keywords

Include three to five words or short phrases, relevant to the article, that do not appear in the title or running head.

Introduction

Provide a brief overview of the scope and relevance of the study, especially with regard to previous advancements in related fields.

Materials and Methods

Describe techniques, cell/animal models used, and lists of reagents, chemicals, and equipment, as well as the names of manufacturers and suppliers, including URLs for those supplies obtained online, so that your study can be most easily replicated by others. Also in this section, describe the statistical methods that were used to evaluate the data. If clinical trials were used, a statement of registration is required; also, for all investigations involving humans or animals, a statement of protocol approval from an IRB or IACUC, or an equivalent statement, must be included. **All animal or human studies must contain an explicit statement that the protocols were submitted to, and approved by, an institutional review board or committee or that the protocols were performed under a license obtained from such a committee, board, or governing office.** (see *Use of Humans and/or Animals in Experiments* above). See *Abbreviations, Symbols, and Terminology* (above) for style information.

Results

Provide the experimental data and results as well as the particular statistical significance of the data. APS has published an editorial on the use of statistics (<http://physiolgenomics.physiology.org/cgi/content/full/18/3/249>), and authors are encouraged to consult it.

Discussion

(Sometimes combined with the results in a section called "Results and Discussion"). Explain your interpretation of the data, especially compared with previously published material cited in the References.

Acknowledgments

The Acknowledgments section is where you may thank people indirectly involved with the research (e.g., technical assistance, gifts of samples, reagents, or cell lines, loans of equipment or laboratory space, comments or suggestions during the creation of the manuscript). However, it is important that anyone listed here know in advance of your acknowledgment of their contribution, as documented during the submission process.

Current addresses of authors (which may differ from those in the affiliation line) may be included here.

Do not include "promissory notes." APS Journal policy is against inclusion of implicit or explicit promises that future work will be published.

Do not include dedications (e.g., to persons living or deceased). Dedications of articles are not permitted.

Grants

List the grants, fellowships, and donations that funded (partially or completely) the research. However, industry-sponsored grants should be listed under *Disclosures*.

Disclosures

Authors are required at the time of submission to disclose to the APS Publications Office any potential conflict of interest, financial or otherwise. See the *Conflict of Interest* description above, or see the complete details of the APS *Ethical Policies* at <http://www.the-aps.org/publications/authorinfo>, which also appears at the end of this document. If the article is accepted for publication, information on the potential conflict of interest, or lack thereof, must be noted by the author in the manuscript file as a “Disclosures” statement following the Acknowledgments section of the paper.

Citing Unpublished Observations, Personal Communications and In Press Manuscripts

Submitted papers still in preparation or in peer review and/or any other unpublished materials, observations, or personal communications cannot be included in the reference list, which may only list published work. However, such material can be cited in the text, but at submission, authors will be required to confirm that all individuals acknowledged in the manuscript are aware that they are being acknowledged and approve of the manner and the context of the acknowledgement. This includes, but is not limited to the following circumstances:

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- to recognize additional individuals who helped in preparation of the manuscript
- for permission from a copyright holder to discuss information that is “in press” and not yet available, online or otherwise.

Reference List

Authors are responsible for accuracy of citations. References must be limited to directly pertinent **published** works or papers that have been **accepted for publication**. An abstract, properly identified as “Abstract”, may be cited only when it is the sole source.

Reference lists should be arranged alphabetically by author and numbered serially. The reference number should be placed in parentheses at the appropriate place in the text.

The examples given below are shown with numbers because that is the style for most APS Journals.

For an exhaustive set of examples for properly citing various types of publications, including articles published on the web, technical documents, congress proceedings, articles with errata/corrigenda, translations, and articles with large groups of authors, go to <http://www.the-aps.org/publications/authorinfo/examplerrefs.htm>.

The style of citation should be as follows, with journal name abbreviated as in Medline, PubMed, and Index Medicus. Appropriate templates for your citation management software are available from the respective company web sites.

Examples

Journal Articles

1. **Villalobos AR, Parmelee JT, Renfro JL.** Choline uptake across the ventricular membrane of neonate rat choroid plexus. *Am J Physiol Cell Physiol* 276: C1288–C1296, 1999.

Book References

1. **Pollock DM.** Endothelin receptor subtypes and tissue distribution. In: *Endothelin Molecular Biology, Physiology, and Pathology*, edited by Highsmith RF. Totowa, NJ: Humana, 1998.

APS Handbook of Physiology Series

1. **Kaufman MP, Forster HV.** Reflexes controlling circulatory, ventilatory, and airway responses to exercise. In: *Handbook of Physiology. Exercise: Regulation and Integration of Multiple Systems. Control of Respiratory and Cardiovascular Systems*. Bethesda, MD: Am. Physiol. Soc., 1996, sect. 12, pt. II, chap. 10, p. 381–447.

DOIs and Early Publication in Articles in Press

These articles may be cited and establish publication’s priority before they appear in final print and online forms. (Please note the required use of a “digital object identifier”—DOI—in this citation.)

1. **Scarafia LE, Winter A, Swinney DC.** Quantitative expression

analysis of the cellular specificity of HECT-domain ubiquitin E3 ligases. *Physiol Genomics* (April 26, 2001). doi:10.1152/physiolgenomics.00075.2001.

Note for reference lists in the Journal of Neurophysiology

Reference lists for the *Journal of Neurophysiology* should be arranged alphabetically by author. For in text citations, appropriate author name and year for each reference should be included in parentheses at the proper point in the text using the following style:

- One author (Brown 1982).
- Two authors (Brown and Smith 1982).
- Three or more authors (Brown et al. 1982).

If more than two references are cited by different authors, separate entries with a semicolon (Brown 1982; Smith 1983). If more than two references are cited by the same first author (or single author), use “et al.” where appropriate plus the date, even if the subsequent authors are not the same in all the references (Brown et al. 1982, 1983). Note the use of commas between two consecutive years or nonconsecutive years and do NOT use dashes for ranges (Brown et al. 1982, 1983, 1986, 1987, 1988, 1989). If more than two references with the same year and author(s) are cited, use lowercase letters after the year (Brown 1982a, 1982b). Lowercase letters should be inserted in the same-year references in the reference list.

Footnotes

Text footnotes should be numbered consecutively throughout. These should be assembled on a separate page as endnotes.

Types of Articles

The APS Journals publish a variety of article types in addition to the regular research papers. For descriptions of the types of articles published in a particular journal, go to that journal’s page at the APS website (<http://www.the-aps.org>).

Figures

APS uses digital publishing methods throughout the journal production process. Your article will be published both in the print journal and online. We have several specific requirements for digital graphics formats to ensure the best possible reproduction in both media.

Computer screens, laser printers, and offset presses are significantly different devices. The ability to print your graphics well on a desktop laser printer does not mean the image is suitable for composition and production of your article in final form. A detailed set of guidelines is available from APS to help you prepare image files that will provide high-quality reproductions in the APS Journals, both in print and online.

Authors may be asked to prepare new figures if those submitted are not suitable for publication; this will most likely delay publication of the paper.

Always prepare original graphics at print publication-quality resolution. If your manuscript is accepted for publication, APS will require the high-resolution files for print output.

Use applications capable of creating high-resolution PDF files.

Figures should be generated at the size they are to appear in the journal (printed 1:1).

For complete guidelines, go to <http://www.the-aps.org/publications/authorinfo/figures/index.htm>. **These guidelines include important descriptions of inappropriate figure manipulation (and how to avoid these presentation errors), as well as what constitutes unethical manipulation of figures. Fabricating a report of research or suppressing or altering data to agree with one’s conclusions is considered fraud. This includes altering figures in such a way to obscure, move, remove, or introduce information or features.**

Use of Animals or People in Photographs

- Photographs of animals or people may be published when scientifically necessary to illustrate a setup or convey the findings of the paper. For a photograph of a person, a signed letter of consent is required from the person or their legal agent or guardian.
- When a diagram is preferable to illustrate a setup, if it is not possible to obtain a drawing, the author should describe the setup in the methods section of the paper.
- Photographs to convey findings may be published when the data are conveyed in the image as in developmental biology or genetic modifications where such photographs are standard practice.
- With respect to other areas, the decision whether to publish a

photograph will be based upon the editor's determination whether the photograph is scientifically necessary.

- The journals should avoid publishing photographs that might be perceived as raising animal welfare concerns. For example, it is preferable to show only the relevant portion of the animal, and photographs should not show blood or people handling the animals except close-ups where only gloved hands are seen.

Tables

Whenever possible, authors are encouraged to submit figures rather than tables. Statistical summary tables should be submitted when possible, rather than tables with many lines of individual values. Lengthy tables of data that cannot be presented in a suitable manner, according to APS standards for print publication, may be extracted and set as a supplement to the online article. These supplements remain an integral part of the article for the reader, as referring text to these tables will remain in the article, and links directly to the supplements will be embedded and prominently indicated at all points of entry to the online article (see *Data Supplements*, below).

Submitted tables should adhere to the following guidelines:

- Tables must not duplicate material in text or figures.
- Tables should be numbered consecutively with Arabic numerals and prepared with the size of the journal page in mind: 3.5 in. wide, single column; 7 in. wide, double column.
- Each table should have a brief title; explanatory notes should be in the legend, not in the title.
- Nonsignificant decimal places in tabular data should be omitted.
- Short or abbreviated column heads should be used and explained if necessary in the legend.
- Statistical measures of variations, SD, SE, etc., must be identified. (Example: "Values are means \pm SE.")
- Table footnotes should be listed in order of their appearance and identified by standard symbols: *, †, ‡, § for four or fewer; for five or more, consecutive superior lowercase letters should be used.

Mathematical Equations and Modeling

Mathematical aspects of articles normally should be addressed to the many readers of the Journal who are not mathematicians. The presentation should include the mathematical strategy, the assumptions on which the mathematics are based, and a summary of the meaning of the final mathematical statement and its limitations.

Equations

Mathematical equations should be simplified as much as possible and carefully checked.

Use the slant line (/) for simple fractions $(a + b)/(x + y)$ in the text rather than the built-up fraction

$$\frac{a + b}{x + y},$$

which should only be used if the equation is offset from the text as in this example.

Use subscripts or superscripts wherever feasible and appropriate, to simplify the equations.

Please use notation that is consistent with the standard nomenclature in applied mathematics. As an aid to the reader, please state the convention that you are following, especially if it is uncommon.

Symbols should be defined as they first appear in the text, and a Glossary may be included (and helpful) in articles with many different symbols, specifying the units (dimensions) as well as each definition. The

Glossary will usually precede the Methods section.

APS style allows punctuation in displayed equations.

Mathematical Models

Presentation of the model(s) must be sufficiently clear to allow physiologists with limited experience in modeling to follow the model development, limitations, and physiological relevance. Assumptions concerning the importance of physiological processes included in the model should be clearly stated.

If the model equation(s) require solution, the method of solution should be described in sufficient detail to permit readers to duplicate the solution in their own laboratories. Algorithms from commercial software libraries should be so identified. Details of the solution strategy may be summarized in an Appendix (for an example, see <http://jap.physiology.org/cgi/reprint/96/1/65.pdf>).

For simulations, sources or estimation methods for all parameter values should be presented and the numerical values given in the text or a table. A sensitivity analysis must be performed for important parameters (covering ranges of values relevant to the manuscript) to determine how the model predictions are affected by numerical parameter values.

If the model is used to estimate parameter values, measures of the uncertainties associated with the estimated parameter values should be presented.

For models intended for use in a predictive setting, validation of the model with a data set not used for model parameter estimation (i.e., cross-validation) is recommended. Sensitivity analysis or parameter uncertainty determination is an important component of modern modeling practice that allows assessment of the validity of a model.

Results obtained with the model(s) should be compared with appropriate physiological data, either from literature or from new experiments. Simulation results may be examined for prediction of changes or trends in physiological variables similar to those reported for in vitro or in vivo studies. The discussion should include information on the physiological significance of the model study, limitations of the model, and suggestions for new modeling and/or experimental studies.

Data Supplements

Video files, extensive tables of data, and other supplemental material that cannot be feasibly published in the printed journal may be submitted for inclusion in the online journal (without charge to the author). Such material must be submitted for peer review along with the finished manuscript and must meet the approval of the journal Editor.

Questions regarding data supplements may be directed to the Online Production Editor (mgentry@the-aps.org). For microarray data deposits, see above (*MIAME Standard for Microarray Data*).

Video

Authors are responsible for compiling their own digital video. Files should be in MPEG or Quicktime format and should be no more than 10 megs in size. Authors may be requested to resubmit their videos with shorter running time, smaller frame size, or lower resolution in order to conform to the recommended file size. Authors should include a written caption with each video file, explaining what is happening in the video.

Contact the Online Production Editor (mgentry@the-aps.org) for further assistance or questions.

Long Data Tables

Long data tables should be submitted in Microsoft Excel or in Microsoft Word table format. Each table should include a title explaining what the table shows. Tables published online may look different from how they were originally submitted due to the limits of the HTML format.

Ethical Policies and Procedures

Authorship. The Editors of the journals of the American Physiological Society (APS) expect each author to have made an important scientific contribution to the study and to be thoroughly familiar with the original data. The Editors also expect each author to have read the complete manuscript and to take responsibility for the content and completeness of the manuscript and to understand that if the paper, or part of the paper, is found to be faulty or fraudulent, that he/she shares responsibility with his/her coauthors. The Mandatory Submission Form should be signed by each author. In cases in

which obtaining a signature from each author would delay publication, the corresponding author's signature is sufficient provided that the corresponding author understands that he or she signs on behalf of the other authors who have not signed the form. An author's name can be removed only at his/her request, but all coauthors must sign a change of authorship agreement for any change in authorship (additions, removals, or change of order) to be made.

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Duplicate Publication, Plagiarism, Falsification. The journals of the APS accept only papers that are original work, no part of which has been submitted for publication elsewhere except as brief abstracts. When submitting a paper, the corresponding author should include copies of related manuscripts submitted or in press elsewhere. Taking material from another's work and submitting it as one's own is considered plagiarism. Taking material (including tables, figures, and data; or extended text passages) from the author's own prior publications is considered redundant publication or self-plagiarism and is not permitted.

The prohibition against duplicate publication includes data from control experiments. Repetition of control experiments is scientifically warranted when the methodology and/or conditions have changed, even to a minimal degree. However, when the methodology and conditions are identical, repetition of control experiments in animal subjects may violate U.S. Animal Welfare Act and Public Health Service Policy requirements as well as standards in other countries, for use of the minimum number of animals needed to accomplish the science. In this case only, reuse of control data will not be considered duplicate publication. Fabricating a report of research or suppressing or altering data to agree with one's conclusions is considered fraud; this includes altering figures in such a way as to obscure, move, remove, or introduce information or features. Examples of fraudulent/inappropriate alteration of figures include, but are not limited to, splicing and reassembling noncontiguous lanes of gels without separation by white space or lines and altering the background of blots such that information is lost.

Prior Publication. Material published by the author before submission in the following categories is considered prior publication: 1) articles published in any publication, even online-only, non-peer reviewed publications, such as *Nature Precedings* or the physics arXiv (see exception below for the *Journal of Neurophysiology*); 2) articles, book chapters, and long abstracts containing original data in figures and tables, especially in proceedings publications; as well as posters containing original data disseminated beyond meeting attendees, e.g., displayed in websites such as that maintained by F1000; 3) widely circulated, copyrighted, or archival reports, such as the technical reports of IBM, the preliminary reports of MIT, the institute reports of the US Army, or the internal reports of NASA.

Doctoral dissertations that are made available by UMI/Proquest or institutional repositories that are not considered prior publication. Data portions of submitted papers that have appeared on web site will be permitted, with the proviso that the author inform the Editor at the time of the submission that

such material exists so that the Editor can determine the suitability of such material for publication. Failure to do so will result in an automatic rejection of the manuscript. Examples of such work include, but are not limited to, immunofluorescence micrographs and/or animated gif/video files posted on a web site, or NIH-mandated posting of DNA microarray data. After the article is published in an APS journal, the data should be removed from the author's web site.

Authors with concerns about possible prior publication that does not fall clearly into one of these categories should contact the Director of Publications and forward the material for examination.

Authors submitting to the *Journal of Neurophysiology (JN)* may submit papers that have been previously posted to preprint servers and other non-peer-reviewed websites. Once you have submitted your manuscript to *JN*, we ask that you not subsequently post this manuscript, or a revised version of it, to a preprint server. However, if your manuscript receives a final reject decision at *JN* or if you withdraw it from editorial consideration at *JN*, this restriction is then lifted. Authors submitting manuscripts to preprint servers must be sure to retain the copyright to their work, which can then be transferred to the publisher when a later version of the work is accepted at a traditional peer-reviewed journal (this is standard at arXiv and Nature Precedings). Questions about whether a particular preprint server venue is allowed under this rule should be addressed to the *JN* Editor in Chief, David Linden at dlinden@jhmi.edu. Authors will be asked at submission to disclose whether their manuscript has been posted to a preprint server, to identify the preprint server, and to provide a file of the most recent version of the posting and the DOI or a working link to it. This is a trial exception to APS policy that applies to submissions to the *Journal of Neurophysiology* through **March, 2013** and subject to change thereafter.

Experiments Involving Animals or Humans. Authors using humans, animals, Authors using humans, animals, or fetal tissue in their experiments should refer to the APS policies on those subjects: Guiding Principles for Research Involving Animals and Human Beings; and the Policy on the Publication of Research on Human Fetuses, Fetal Tissue, Embryos, and Embryonic Cells.

Ethical Procedure. APS reviewers have a responsibility to report suspected duplicate publication, fraud, plagiarism, or concerns about animal or human experimentation to the Editor. A reviewer may recognize and report that he/she is refereeing, or has recently refereed, a similar or identical paper for another journal by the same author(s). Readers may report that they have seen the same article elsewhere, or authors may see their own published work being plagiarized. In all cases we address ethical concerns diligently following an issue-specific standard practice as summarized below. The first action of the journal Editor is to inform the Publications Committee Chair through the Director of Publications by supplying copies of 1) the relevant material and 2) a draft letter to the corresponding author asking for an explanation in a nonjudgmental manner. The Publications Committee Chair must approve any correspondence before it is sent to the author. If the author's explanation is unacceptable and it seems that serious unethical conduct has taken place, the matter is referred to the Publications Committee. After deliberation, a decision is made whether the case is sufficiently serious to warrant a ban on future submissions to, and on serving as a reviewer for, APS journals and/or if the offending author's institution should be informed. The decision has to be approved by the Executive Cabinet of the APS Council, and the author has the right to appeal a sanction, with the opportunity to present his/her position to the Publications Committee and the full APS Council.

If the infraction is less severe, the Editor, upon the advice of the Publications Chair, sends the author a letter of reprimand and reminds the author of APS publication policies; if the manuscript has been published, the Editor may require the author to publish an apology in the journal to correct the record. If, through the author's actions, APS has violated the copyright of another journal, the Publications Chair writes a letter of apology to the other journal.

In serious cases of fraud that result in retraction of the article, a retraction notice will be published in the journal and will be linked to the article in the online version. The online version will also be marked "retracted" with the retraction date.

Updated Spring 2011.

GUIDING PRINCIPLES FOR RESEARCH INVOLVING ANIMALS AND HUMAN BEINGS

The research described in papers submitted to any of the APS publications that involve the use of human beings must adhere to the principles of the Declaration of Helsinki and Title 45, U.S. Code of Federal Regulations, Part 46, Protection of Human Subjects, Revised November 13, 2001, effective December 13, 2001 (<http://www.hhs.gov/ohrp/humansubjects/guidance/45cfr46.htm>). Research involving animals must adhere to APS's Guiding Principles for the Care and Use of Vertebrate Animals in Research and Training. APS insists that all investigations involving humans or animals reported in its publications be conducted in conformity with these principles and that a statement of protocol approval from an IRB or IACUC or equivalent is included in the methods section of the paper. In describing surgical procedures, the type and dosage of the anesthetic agent should be specified. Curarizing agents are not anesthetics; if these are used, evidence must be provided that anesthesia of suitable grade and duration was employed. Editors/Associate Editors are expected to refuse papers in which evidence of the adherence to these principles is not apparent. They reserve the right to judge the appropriateness of the use of animals and humans in experiments published in the journals. Differences of opinion will be adjudicated by the Publications Committee.

WORLD MEDICAL ASSOCIATION DECLARATION OF HELSINKI Ethical Principles for Medical Research Involving Human Subjects¹

A. Introduction

1. The World Medical Association has developed the Declaration of Helsinki as a statement of ethical principles to provide guidance to physicians and other participants in medical research involving human subjects. Medical research involving human subjects includes research on identifiable human material or identifiable data.

2. It is the duty of the physician to promote and safeguard the health of the people. The physician's knowledge and conscience are dedicated to the fulfillment of this duty.

3. The Declaration of Geneva of the World Medical Association binds the physician with the words, "The health of my patient will be my first consideration," and the International Code of Medical Ethics declares that, "A physician shall act only in the patient's interest when providing medical care which might have the effect of weakening the physical and mental condition of the patient."

4. Medical progress is based on research which ultimately must rest in part on experimentation involving human subjects.

5. In medical research on human subjects, considerations related to the well-being of the human subject should take precedence over the interests of science and society.

6. The primary purpose of medical research involving human subjects is to improve prophylactic, diagnostic and therapeutic procedures and the understanding of the aetiology and pathogenesis of disease. Even the best proven prophylactic, diagnostic, and therapeutic methods must continuously be challenged through research for their effectiveness, efficiency, accessibility and quality.

7. In current medical practice and in medical research, most prophylactic, diagnostic and therapeutic procedures involve risks and burdens.

8. Medical research is subject to ethical standards that promote respect for all human beings and protect their health and rights. Some research populations are vulnerable and need special protection. The particular needs of the economically and medically disadvantaged must be recognized. Special attention is also required for those who cannot give or refuse consent for themselves, for those who may be subject to giving consent under duress, for those who will not benefit personally from the research and for those for whom the research is combined with care.

9. Research Investigators should be aware of the ethical, legal and regulatory requirements for research on human subjects in their own countries as well as applicable international requirements. No national ethical, legal or regulatory requirement should be allowed to reduce or eliminate any of the protections for human subjects set forth in this Declaration.

B. Basic Principles for All Medical Research

10. It is the duty of the physician in medical research to protect the life, health, privacy, and dignity of the human subject.

11. Medical research involving human subjects must conform to generally accepted scientific principles, be based on a thorough knowledge of the scientific literature, other relevant sources of information, and on adequate laboratory and, where appropriate, animal experimentation.

12. Appropriate caution must be exercised in the conduct of research which may affect the environment, and the welfare of animals used for research must be respected.

13. The design and performance of each experimental procedure involving human subjects should be clearly formulated in an experimental protocol. This protocol should be submitted for consideration, comment, guidance, and where appropriate, approval to a specially appointed ethical review committee, which must be independent of the investigator, the sponsor or any other kind of undue influence. This independent committee should be in conformity with the laws and regulations of the country in which the research experiment is performed. The committee has the right to monitor ongoing trials. The researcher has the obligation to provide monitoring information to the committee, especially any serious adverse events. The researcher should also submit to the committee, for review, information regarding funding, sponsors, institutional affiliations, other potential conflicts of interest and incentives for subjects.

14. The research protocol should always contain a statement of the ethical considerations involved and should indicate that there is compliance with the principles enunciated in this Declaration.

15. Medical research involving human subjects should be conducted only by scientifically qualified persons and under the supervision of a clinically competent medical person. The responsibility for the human subject must always rest with a medically qualified person and never rest on the subject of the research, even though the subject has given consent.

16. Every medical research project involving human subjects should be preceded by careful assessment of predictable risks and burdens in compar-

¹ The Declaration of Helsinki (Document 17.C) is an official policy document of the World Medical Association (WMA), the global representative body for physicians. It was first adopted by the 18th WMA General Assembly, Helsinki, Finland, June 1964, and amended by the 29th WMA General Assembly, Tokyo, Japan, October 1975; 35th WMA General Assembly, Venice, Italy, October 1983; 41st WMA General Assembly, Hong Kong, September 1989; 48th WMA General Assembly, Somerset West, Republic of South Africa, October 1996; and the 52nd WMA General Assembly, Edinburgh, Scotland, October 2000. Note of Clarification on Paragraph 29 added by the WMA General Assembly, Washington 2002. Note of Clarification on Paragraph 30 added by the WMA General Assembly, Tokyo 2004.

ison with foreseeable benefits to the subject or to others. This does not preclude the participation of healthy volunteers in medical research. The design of all studies should be publicly available.

17. Physicians should abstain from engaging in research projects involving human subjects unless they are confident that the risks involved have been adequately assessed and can be satisfactorily managed. Physicians should cease any investigation if the risks are found to outweigh the potential benefits or if there is conclusive proof of positive and beneficial results.

18. Medical research involving human subjects should only be conducted if the importance of the objective outweighs the inherent risks and burdens to the subject. This is especially important when the human subjects are healthy volunteers.

19. Medical research is only justified if there is a reasonable likelihood that the populations in which the research is carried out stand to benefit from the results of the research.

20. The subjects must be volunteers and informed participants in the research project.

21. The right of research subjects to safeguard their integrity must always be respected. Every precaution should be taken to respect the privacy of the subject, the confidentiality of the patient's information and to minimize the impact of the study on the subject's physical and mental integrity and on the personality of the subject.

22. In any research on human beings, each potential subject must be adequately informed of the aims, methods, sources of funding, any possible conflicts of interest, institutional affiliations of the researcher, the anticipated benefits and potential risks of the study and the discomfort it may entail. The subject should be informed of the right to abstain from participation in the study or to withdraw consent to participate at any time without reprisal. After ensuring that the subject has understood the information, the physician should then obtain the subject's freely-given informed consent, preferably in writing. If the consent cannot be obtained in writing, the non-written consent must be formally documented and witnessed.

23. When obtaining informed consent for the research project the physician should be particularly cautious if the subject is in a dependent relationship with the physician or may consent under duress. In that case the informed consent should be obtained by a well-informed physician who is not engaged in the investigation and who is completely independent of this relationship.

24. For a research subject who is legally incompetent, physically or mentally incapable of giving consent or is a legally incompetent minor, the investigator must obtain informed consent from the legally authorized representative in accordance with applicable law. These groups should not be included in research unless the research is necessary to promote the health of the population represented and this research cannot instead be performed on legally competent persons.

25. When a subject deemed legally incompetent, such as a minor child, is able to give assent to decisions about participation in research, the investigator must obtain that assent in addition to the consent of the legally authorized representative.

26. Research on individuals from whom it is not possible to obtain consent, including proxy or advance consent, should be done only if the physical/mental condition that prevents obtaining informed consent is a necessary characteristic of the research population. The specific reasons for involving research subjects with a condition that renders them unable to give informed consent should be stated in the experimental protocol for consideration and approval of the review committee. The protocol should state that consent to remain in the research should be obtained as soon as possible from the individual or a legally authorized surrogate.

27. Both authors and publishers have ethical obligations. In publication of the results of research, the investigators are obliged to preserve the accuracy of the results. Negative as well as positive results should be published or otherwise publicly available. Sources of funding, institutional affiliations and any possible conflicts of interest should be declared in the publication. Reports of experimentation not in accordance with the principles laid down in this Declaration should not be accepted for publication.

C. Additional Principles for Medical Research Combined with Medical Care

28. The physician may combine medical research with medical care, only to the extent that the research is justified by its potential prophylactic, diagnostic or therapeutic value. When medical research is combined with medical care, additional standards apply to protect the patients who are research subjects.

29. The benefits, risks, burdens and effectiveness of a new method should be tested against those of the best current prophylactic, diagnostic, and therapeutic methods. This does not exclude the use of placebo, or no treatment, in studies where no proven prophylactic, diagnostic or therapeutic method exists. *Note of clarification on paragraph 29 of the WMA Declaration of Helsinki:* The WMA hereby reaffirms its position that extreme care must be taken in making use of a placebo-controlled trial and that in general

this methodology should only be used in the absence of existing proven therapy. However, a placebo-controlled trial may be ethically acceptable, even if proven therapy is available, under the following circumstances: Where for compelling and scientifically sound methodological reasons its use is necessary to determine the efficacy or safety of a prophylactic, diagnostic or therapeutic method; or Where a prophylactic, diagnostic or therapeutic method is being investigated for a minor condition and the patients who receive placebo will not be subject to any additional risk of serious or irreversible harm. All other provisions of the Declaration of Helsinki must be adhered to, especially the need for appropriate ethical and scientific review.

30. At the conclusion of the study, every patient entered into the study should be assured of access to the best proven prophylactic, diagnostic and therapeutic methods identified by the study. *Note of clarification on paragraph 30 of the WMA Declaration of Helsinki:* The WMA hereby reaffirms its position that it is necessary during the study planning process to identify post-trial access by study participants to prophylactic, diagnostic and therapeutic procedures identified as beneficial in the study or access to other appropriate care. Post-trial access arrangements or other care must be described in the study protocol so the ethical review committee may consider such arrangements during its review.

31. The physician should fully inform the patient which aspects of the care are related to the research. The refusal of a patient to participate in a study must never interfere with the patient-physician relationship.

32. In the treatment of a patient, where proven prophylactic, diagnostic and therapeutic methods do not exist or have been ineffective, the physician, with informed consent from the patient, must be free to use unproven or new prophylactic, diagnostic and therapeutic measures, if in the physician's judgement it offers hope of saving life, re-establishing health or alleviating suffering. Where possible, these measures should be made the object of research, designed to evaluate their safety and efficacy. In all cases, new information should be recorded and, where appropriate, published. The other relevant guidelines of this Declaration should be followed.

APS GUIDING PRINCIPLES FOR THE CARE AND USE OF VERTEBRATE ANIMALS IN RESEARCH AND TRAINING²

As noted in the U.S. Government Principles for the Utilization and Care of Vertebrate Animals Used in Testing, Research, and Training,³ "Procedures involving animals should be designed and performed with due consideration of their relevance to human or animal health, the advancement of knowledge, or the good of society." The use of animals is also justified to provide scientific, veterinary, and medical training that is not possible through other mechanisms.

Investigators should consider the appropriateness of the experimental procedures, the species of animals used, and number of animals required. Prospective approval of procedures on animal subjects should be obtained from an institutional animal care and use committee (IACUC) or similar oversight body as required under the relevant regulatory authorities. This review should also consider whether the use of animals in a given protocol could be replaced by other experimental approaches such as *in vitro* studies or computer modeling.

Only animals that are lawfully acquired shall be used in research and teaching. The procurement, transport, maintenance, and use of animals must in all cases comply with federal, state and local laws and regulations. In the United States, animal research may be subject to the Animal Welfare Act, the Public Health Service Policy on Humane Care and Use of Laboratory Animals, or other guidelines established by funding agencies. The PHS Policy requires institutions to use the *Guide for the Care and Use of Laboratory Animals*⁴ to develop and implement an institutional animal care and use program.

Analgesics and other techniques should be used to minimize discomfort and pain except when the intervention would compromise experimental goals. Appropriate anesthetics must be used to eliminate sensibility to pain

² The Guiding Principles for the Care and Use of Animals in Research and Teaching were adopted by the American Physiological Society in 1953. They are based upon humane care principles formulated by Walter B. Cannon in 1909. The revision was approved by the APS Council on July 16, 2010.

³ URL: <http://grants.nih.gov/grants/olaw/references/pspol.htm#USGovPrinciples>

⁴ Institute for Laboratory Animal Research (ILAR). *Guide for the Care and Use of Laboratory Animals*. Washington, D.C.: National Academy Press, 1996. URL: http://www.nap.edu/catalog.php?record_id=5140. A prepublication version of the 8th edition of the *Guide* was released June 2, 2010, but NIH's Office of Laboratory Animal Welfare has announced that the 1996 edition will remain in effect for the PHS Policy on Humane Care and Use of Laboratory Animals until the new edition of the *Guide* is published in its final form.

during all surgical procedures. Drugs that produce muscle paralysis are not anesthetics. They must never be used alone for surgical restraint, only when animals are under anesthesia.

If the study requires the death of an animal, humane endpoints should be identified, and an approved method of euthanasia stipulated in the American Veterinary Medical Association's *Guidelines on Euthanasia*⁵ should be used. Death is acceptable as the endpoint of a study only where

euthanasia would compromise scientific outcomes and an IACUC or similar oversight body has approved the exception.

Animals used in research and education must be housed, fed, and maintained in a manner appropriate for their species and their condition. They should also be given appropriate veterinary care.

Personnel who care for or perform procedures on animals must receive training for these tasks. When students or trainees use animals in educational activities or for the advancement of science, such work shall be conducted under the direct supervision of an experienced teacher, investigator, or veterinarian.

⁵ URL: http://www.avma.org/issues/animal_welfare/euthanasia.pdf.

INTEGRATING THE LIFE SCIENCES



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