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Except in reviews and invited editorials, the APS Journals will not accept submissions in which, other than in abstracts of less than 400 words, a significant portion of the data in the form of figures and/or tables has been published elsewhere. For the APS guidelines regarding duplicate and/or prior publication, see the *APS Ethical Policies and Procedures* at <http://www.the-aps.org/publications/journals/apsethic.htm>.

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If you realize that changes to authorship (e.g., altering the order of authorship or adding/removing a name) are needed, please follow these steps:

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- Have ALL authors sign it.
- Fax, mail, or e-mail the signed form to the APS Peer Review office (301-634-7243).

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If you have realized that an author's name was misspelled in such way as to affect finding the article in PubMed or through other searches, notify the Peer Review office so that the article can be fixed by amending the Articles in PresS edition. Please note: this is the ONLY case when the Articles in PresS edition will be corrected. Follow the steps above when submitting the correction. Other authorship corrections can still be made for the final print and online editions (see paragraph below).

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- Download the Change of Authorship Form (at http://www.the-aps.org/publications/journals/pub_author_form.pdf).
- Have ALL authors sign it.
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Any changes to authorship can only be made through a corrigendum to the print edition. The online version will have a permanent link to the corrigendum. Follow the steps in the previous section (*During Production of the Final Print and Online Editions*) when submitting the changes.

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“Submitted” and “Accepted” Dates

The “submitted” date for a manuscript is the date when the manuscript was submitted to *APS Central* online peer review system (<http://www.apscentral.org>). The “accepted” date is the date when the official letter of acceptance is sent out (usually via e-mail) from the Review Editor. For specific requirements, see details at <http://www.the-aps.org/publications/i4a/acceptance.htm>.

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The APS is required by US Postal regulations to affix the following note on the title page of all articles for which page charges are assessed: “The costs of publication of this article were defrayed in part by the payment of page charges. The article must therefore be hereby marked ‘advertisement’ in accordance with 18 U.S.C. Section 1734 solely to indicate this fact.”

Ethical Policies

See the inside back cover of this journal for the APS Ethical Policy (or go to http://www.the-aps.org/publications/i4a/prep_manuscript.htm#apsethic).

Use of Humans and/or Animals in Experiments

The research described in papers submitted to any of the APS publications that involve the use of human beings, including healthy volunteers, must adhere to the principles of the Declaration of Helsinki (see <http://www.wma.net/e/policy/b3.htm>), as well as in Title 45, US Code of Federal Regulations, Part 46, Protection of Human Subjects, Revised November 13, 2001, effective December 13, 2001 (see <http://www.hhs.gov/ohrp/humansubjects/guidance/45cfr46.htm>). Research involving animals must adhere to APS's *Guiding Principles in the Care and Use of Animals*. 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 were used, evidence must be provided that anesthesia of suitable grade and duration was employed. Manuscripts reporting the results of experiments on human subjects, including healthy volunteers, must include a statement that informed consent was obtained. 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.

Registering of clinical trials is a requirement for peer review and publication for any study that uses clinical trials. There must be a statement in the Methods section that states where the clinical trial was registered (for example, see the registration site sponsored by the United States National Library of Medicine, at <http://www.clinicaltrials.gov>).

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The American Physiological Society Publications require all papers submitted to any of the APS Journals and involving the use of human fetuses, fetal tissue, embryos, and embryonic cells to adhere to the US Public Law 103-41, effective August 1991. Please read the *APS Policy Regarding Publication of Research on Human Fetuses, Fetal Tissue, Embryos, and Embryonic Cells* (see http://www.the-aps.org/publications/journals/fetal_tissue_policy.htm) and the criteria that must be met by all researchers submitting their work to the APS Journals.

Conflict of Interest

Authors of research and other articles are required at the time of submission to disclose to the APS Publications Office any potential conflict of interest (e.g., consultancies, stock ownership, equity interests, patent-licensing arrangements, lack of access to data, or lack of control of the decision to publish). In such cases, the author(s) will be asked to fill out a Conflict of Interest Disclosure form. The information provided in the form, unless already disclosed in the submitted article, will be held in confidence while the paper is under review. If the article is accepted for publication, information on the potential conflict of interest—including a lack of control of the decision to publish—will be included in the Disclosures section, following the Acknowledgments section.

Standards

MIAME Standard for Microarray Data

The American Physiological Society has adopted the microarray data standard developed by the Microarray Gene Expression Data society (MGED; <http://www.mged.org>) and requests that all authors using mi-

croarray data analysis in their research submit a complete data set to one of three databases prior to manuscripts submission: the National Center for Biotechnology Information (NCBI) Gene Expression Omnibus (GEO; <http://www.ncbi.nlm.nih.gov/projects/geo/>); the European Bioinformatics Institute (EMBL-EBI) ArrayExpress repository (<http://www.ebi.ac.uk/arrayexpress/>); or the Center for Information Biology Gene Expression (CIBEX) database (<http://cibex.nig.ac.jp/index.jsp>). Also, provide the set of login credentials (user name and password) that will let referees access the data set during review, if it is set up as a private resource.

HUGO Gene Nomenclature

In accordance with the HUGO Gene Nomenclature Committee (HGNC), the APS requests that authors obtain approval for new human and mouse gene symbols by contacting either Dr. Sue Povey for human genes (e-mail: nome@galton.ucl.ac.uk) or Lois Maltais for mouse genes (e-mail: nomen@informatics.jax.org). Additional information on gene nomenclature guidelines is available from the HGNC (<http://www.gene.ucl.ac.uk/nomenclature/>).

Technical Requirements

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Please submit a Microsoft Word (.doc) file or a Rich Text Format (.rtf) file to APS Central (<http://www.apscentral.org>). Separate files must be submitted for all discrete elements of the manuscript [e.g., separate files for each figure and table, a separate file for the complete text of the manuscript (including abstract, all main text, bibliography, figure legends and table legends, etc.)].

The APS Central system will concatenate the various files into a single document for review. If the paper is accepted, the separate files will be moved forward into the final print production process.

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The pages should be numbered in the upper right-hand corner (beginning with the first page of text).

Arrange as follows (all should begin on separate pages):

- title page
- abstract and keywords on the same page
- main text (introduction; Materials and/or Methods, or Experimental Procedures; Results; Discussion, with conclusions)
- text footnotes
- acknowledgments
- references
- figure legends
- tables

Be sure the text is clear and concise, conforming to accepted standards of American English style and usage. Avoid jargon, clichés, and laboratory slang. See *Manuscript Sections*, below, for further description.

Abbreviations, Symbols, and Terminology

All abbreviations must be explicitly defined at first usage. However, internationally accepted biochemical abbreviations such as ADP, NADH, and P_i do not need to be defined; other abbreviations need only be defined at first mention. Please consult the list of accepted abbreviations for our journals (<http://www.the-aps.org/publications/journals/abbrv.pdf>). Other abbreviations need only be defined at first mention. 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. 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 Symbol font or use the “Insert Symbol” function in Microsoft Word; do **not** use math font or

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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.

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Proprietary (trademarked) names should be capitalized, with the spelling carefully checked. The chemical or generic name should precede the trade name or abbreviation of a drug the first time it appears.

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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 mycoplasmal 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* (below) and *Ethical Policies and Standards* (above) for other requirements.

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DDBJ: Center for Information Biology and DNA Data
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Japan
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Fax: +81 559 81 6849
<http://www.ddbj.nig.ac.jp/>

EMBL: EMBL Nucleotide Sequence Submissions
European Bioinformatics Institute
Wellcome Trust Genome Campus
Hinxton, Cambridge CB10 1SD
UK
Tel: +44 1223 494444
Fax: +44 1223 494468
<http://www.ebi.ac.uk/support/>

GenBank: National Center for Biotechnology Information
National Library of Medicine
Bldg. 38A, Rm. 8N-803

Bethesda, MD 20894
Tel: 301-496-2475
Fax: 301-480-9241
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See also *MIAME Standard for Microarray Data* (above) and *Data Supplements* (below).

Manuscript Sections

Title Page

The title page must contain the 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; the name, e-mail address, and address for correspondence.

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.

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 55 characters including spaces between words.

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A full address for correspondence will be published and must be included, **with a current, valid e-mail address** for the corresponding author. This address will be published on the title page. Please note that a valid e-mail address is essential to participate in the APS electronic proofing service called “Rapid Proof.” 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 (www.the-aps.org) and choose the appropriate journal’s web page.

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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. Note that longer abstracts are usually cutoff at the end when displayed on Medline.

Keywords

Include three to five words or short phrases, relevant to the article, that do not appear in the title or running head. (**NOTE:** Authors submitting to the *Journal of Neurophysiology* are not required to provide keywords.)

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

(Sometimes called “Experimental Procedures”). Describe techniques, cell/animal models used, and lists of reagents, chemicals, and equipment, as well as the names of manufacturers and suppliers, 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 your research involved the use of microarrays, see *MIAME Standard for Microarray Data* (above), and insert in this section the URL pointing to your microarray 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 (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. Regarding the use of statistics, including reporting standard error (SE) and standard deviation (SD) values, an Editorial (“Guidelines for reporting statistics in journals published by the American Physiological Society”) was published in all August 2004 issues of the APS Journals. The Editorial is freely available (see, for example, <http://physiolgenomics.physiology.org/cgi/content/full/18/3/249>), and the 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

List the people indirectly involved with the research whom you may wish to thank. Also, 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. Dedications of articles are not permitted.

Grants

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Disclosures

Authors of research articles are required at the time of submission to disclose to the APS Publications Office any potential conflict of interest (e.g., consultancies, stock ownership, equity interests, patent-licensing arrangements, lack of access to data, or lack of control of the decision to publish). In such cases, the author(s) will be asked to fill out a Conflict of Interest Disclosure form. The information provided in the form, unless already disclosed in the submitted article, will be held in confidence while the paper is under review. If the article is accepted for publication, information on the potential conflict of interest—including a lack of control of the decision to publish—will be included in the Disclosures section, following the Acknowledgments section. The Disclosures section will also include acknowledgments of industry-sponsored grants that supported the research.

References

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.

References should be double-spaced, arranged alphabetically by author, and numbered serially. The reference number should be placed in parentheses at the appropriate place in the text.

Important Note: The reference list should not include citations of submitted papers still in preparation, in peer review, or of other unpublished materials. Such information may be provided in parentheses in the text as “unpublished observations” (e.g., “J. M. K. Smith, unpublished observations”).

The APS Journals discourage the use of “personal communications.” However, if they are used, the author(s) must have in their file a letter

granting permission from the communicant and send it to the APS Publications Office if requested.

For both unpublished observations and personal communications provide the cited person's last name and all initials.

Note for references in the Journal of Neurophysiology

References for the *Journal of Neurophysiology* should be double-spaced and arranged alphabetically by author. The 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, 1986–1988). Note the use of commas between two consecutive years or nonconsecutive years and dashes for ranges (Brown et al. 1982, 1983, 1986–1988). If more than two references with the same year and author(s) are cited, use lowercase letters after the year (Brown 1982a,b). Lowercase letters will be inserted in the same-year references in the reference list.

Although the *Journal of Neurophysiology* does not require that the reference list be numbered, the examples given below are shown with numbers because that is the style for most APS Journals. In all other respects, the reference style used in the example below is the same across all journals.

The style of citation should be as follows, with journal name abbreviated as in Medline, PubMed, and Index Medicus. APS offers a selection of output styles available for a variety of citation management software (<http://www.the-aps.org/publications/journals/styles.htm>).

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

Large textbooks require very specific citation information. For example, the APS Handbooks series contains a huge amount of information, and the inclusion in the citation of the section, volume, part, and chapter is essential to aid the reader in finding the information quickly (please note that the APS chooses not to list editors for the APS Handbooks).

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, chapt. 10, p. 381–447.

Articles Published on the Web

Many reports are being published primarily, if not exclusively, on the World Wide Web. Such articles should be cited in the "online" style as shown below.

Format:

Author/editor (if known). (Revision or copyright date, if available). Title of page [Publication medium]. Page publisher. URL (Protocol://Site/Path/File) [Access date].

1. **Dudoit S, Yang YH, Callow MJ, Speed TJ.** Statistical methods for identifying differentially expressed genes in replicated cDNA microarray experiments [Online]. Dept. of Statistics, Univ. of California at Berkeley. <http://www.stat.berkeley.edu/users/terry/zarray/Html/matt.html> [3 Sept. 2000].

Note that the date may be general or specific, to the day.

Some citations may have portions published in print and other relevant portions reposted online. However, if directions to the online portions are available in the printed work, this sort of citation should be avoided.

1. **Joachims T.** Making large-scale SVM learning practical. In: *Advances in Kernel Methods: Support Vector Learning*, edited by Schölkopf B, Burges C, and Smola A. MIT Press, 1999. [The software is available at http://www.-ai.cs.uni-dortmund.de/SOFTWARE/SVM_LIGHT/svm_light.eng.html]

2. **Spellman PT, Sherlock G, Zhang MQ, Iyer VR, Anders K, Eisen MB, Brown PO, Botstein D, Futcher B.** Comprehensive identification of cell cycle-regulated genes of the yeast *Saccharomyces cerevisiae* by microarray hybridization. *Mol Biol Cell* 9: 3273–3297, 1998. [The data are available at <http://cellcycle-www.stanford.edu>]

DOIs and Early Publication in Articles in PresS

Current technology allows publication of an article in several editions. For example, the final, citable draft of an accepted article may be posted to a web site, pending final copyediting and page layout/design. This initial post to the web qualifies as publication, but eventually the article will reach the readership in a final, polished form.

The APS publishes peer-reviewed articles upon acceptance, as 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; 10.1152/physiolgenomics.00075.2001.

However, once this article has reached its final stage of publication, it will be cited with its new publication data, as follows:

1. **Scarafia LE, Winter A, Swinney DC.** Quantitative expression analysis of the cellular specificity of HECT-domain ubiquitin E3 ligases. *Physiol Genomics* 4: 147–153, 2001. First published April 26, 2001; 10.1152/physiolgenomics.00075.2001.

Technical Documents, Congress Proceedings, etc.

Technical documents, congress proceedings, and some other sorts of material may often be published by the specific institution that sponsored the research.

1. **Efron R, Tibshirani B, Goss V, Chu G.** *Microarrays and Their Use in a Comparative Experiment* (Technical Report). Palo Alto, CA: Department of Statistics, Stanford University, 2000.

Corrigenda/Errata

If an article required a correction, after first publication, this should be noted in the citation of the original article.

1. **Hallows KR, Packman CH, Knauf PA.** Acute cell volume changes in anisotonic media affect F-actin content of HL-60 cells. *Am J Physiol Cell Physiol* 261: C1154–C1161, 1991. (Corrigendum. *Am J Physiol Cell Physiol* 268: March 1995, following table of contents)

2. **Steenman M, Chen YW, Le Cunff M, Lamirault G, Varró A, Hoffman E, Léger JJ.** Transcriptomal analysis of failing and nonfailing human hearts. *Physiol Genomics* 12: 97–112, 2003. First published November 12, 2002; 10.1152/physiolgenomics.00148.2002. (Corrigendum. *Physiol Genomics* 18: 128, 2004)

Translations

1. **Gavrilov KA, Perel TS.** Earthworms and other invertebrates in the soil under...[in Russian]. *Pochovedenia* 8: 133–140, 1958.

2. **Gavrilov KA, Perel TS.** Earthworms and other invertebrates in the soil under...[in Russian, English summary]. *Pochovedenia* 8: 133–140, 1958.

3. **Fritsch G, Hitzig E.** Über die Elektrische. In: *Some Papers on the Cerebral Cortex*, translated and edited by von Bomin G. Springfield, IL: Thomas, 1960, p. 73–96.

4. **Vol'kenshtein MV.** *Molecules and Life: An Introduction to Molecular Biology*. New York: Plenum, 1970. [Transl. from the Russian.]

Many Authors

It is APS Publications policy to list all authors in a research group. That is, the use of only the first author's name, followed by "et al." is unacceptable.

However, if there is an inclusive name for the research group as a whole (for example, the "International Human Genome Sequencing Consortium," which comprises some 250 researchers), it should be used rather than listing hundreds of authors.

So, the following format is acceptable:

1. **International Human Genome Sequencing Consortium.** Initial sequencing and analysis of the human genome. *Nature* 409: 860–921, 2001.

Consult recent issues of the APS Journals for more examples.

Citing Personal Communications or Unpublished Observations

Do not include such citations in the Reference list (see Important Note, in References section above, for more information). Instead, place this sort of citation in parentheses in the body of the article where it logically belongs, following the format below. Make sure to include all initials and, for personal communications, obtain a signed letter of permission from the person(s) cited.

(A. B. C. Jones and Z. Smith, personal communication)

(J. Jones, unpublished observations)

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Footnotes

Text footnotes should be numbered consecutively throughout. They should be double-spaced and assembled on a separate page.

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>). A full listing of article types is also available on the Mandatory Submission Form at *APS Central*, during submission to the Journal of your interest.

If your research paper is submitted in response to a Call for Papers, please make sure to mark it as such during submission to *APS Central*.

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.

Important: 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 can be printed successfully, or at all, on an offset press. These guidelines are intended 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.

Each figure must have a legend.

For further help in preparing figures, see the Cadmus website guidelines (<http://cjs.cadmus.com/da/guidelines.html>), or contact the APS Art Department:

APS Art Department
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or e-mail questions to art@the-aps.org.

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Always prepare original graphics at print publication-quality resolution. From these high-resolution versions you will be able to create low-resolution versions for online submission. When your manuscript is accepted for publication, APS will require the high-resolution files for print output.

Acceptable File Formats

Use applications capable of creating high-resolution TIFF or EPS files. These file formats ensure the highest success rate for printing and are supported by both Mac and Windows platforms and applications.

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The Cadmus website (<http://cjs.cadmus.com/da/>) lists several graphics applications that support TIFF and EPS file formats for both Mac and Windows.

- Choose your platform (Mac/Win).
- Choose the application used to create original images.

- Follow step-by-step instructions for saving or exporting files as TIFF or EPS.
- If you do not see the application used to create your original figures, you may be able to create high-resolution PDF files using Adobe Acrobat Distiller. From these files, you can create TIFF or EPS files using Adobe Photoshop or Illustrator.

Applications use software “drivers” to convert their native-format files into the TIFF or EPS formats that we require. Each application uses its own driver to make these conversions. So, the quality and usability of the TIFF and EPS files depends on the quality of the driver used to create them. A graphic that looks and prints fine on your computer may not be usable by our graphic software such as Adobe Photoshop, Adobe Illustrator, Corel Draw, or Corel PhotoPaint. **Please Note:** If you are not using one of these major graphics authoring programs, your TIFF and EPS files may require extra processing or even be unusable.

Figure Style Guidelines

Size

Figures should be generated at the size they are to appear in the journal (printed 1:1). Figures may be printed in one of three formats:

- single column (3.5 in., or 21 picas)
- double column w/ side legend (4–5 in., or 25–30 picas)
- full page width (7 in., or 43 picas)

The maximum depth allowable is 9 in. (54 picas). If it is necessary to submit figures that require reduction, the indicated size characteristics must be achievable after resizing. Multi-paneled figures should be assembled in a layout that leaves the least amount of blank space and does not exceed 7×9 in.

Type

For serif fonts, use Times Roman or Times New Roman. For sans-serif, use Helvetica or Arial. Fonts should be used consistently throughout all figure(s). Freehand, typewritten, and dot-matrix lettering are not acceptable.

Font Sizes:

- Primary (axis labels): 8–10 points
- Secondary (key information): 7–8 points
- Tertiary (numeric values): 5–7 points
- Panel Labels (i.e., A, B, C): 12–14 points

All lettering and key information should be within the framework of the illustration, unless the figure is so filled that symbols need to be explained in the legend.

Resolution

- Line drawings: 600–1200 dpi
- Halftones: no text, 300 dpi; with text, 600 dpi
- Color graphics: 600 dpi

Line Drawings

Line art uses only black and white to convey its information. These images are typically produced in a vector-based drawing program. Save or export graphics as EPS or TIFF files at 600–1200 dpi in resolution. If figures require reduction to fit into a particular column width, all lettering, line weights, and symbols must be of a size and weight that will meet the guidelines for final size.

Halftones

Many graphics include shades of gray. These grays may be simple fills (screened dot patterns to simulate grays) or they may be subtle and complex tones in digitized photographs or intricate drawings. Save or export halftone graphics that **do not contain text** as EPS or TIFF files at 300 dpi in resolution. Halftone graphics **that contain text and symbols** should be saved or exported as EPS or TIFF files at 600 dpi in resolution.

When necessary, include an internal scale marker to account for any needed reduction. Special features on photomicrographs should be designated by letters, numerals, arrows, and other symbols that contrast with the background.

Photographs of equipment should be used sparingly; good line drawings are usually more informative.

Photographs of animals or humans are acceptable if they are the only way to show results and only with the approval of the Editor.

For a photograph of a human, you will need to provide a signed permission from the photographed subject, agreeing to the publication of his or her image.

Color Graphics

APS encourages the use of scientifically necessary color images in its publications. For an explanation of what is considered “scientifically necessary” color see http://www.the-aps.org/publications/i4a/scientifically_necessary.htm. To ensure that your files are prepared appropriately for offset printing, please follow these guidelines:

- **NEW: Authors should create and submit all color images for print in RGB separation format** (http://www.the-aps.org/publications/i4a/cmyk_vs_rgb.htm). APS will now be following an RGB workflow for all scientifically necessary images. Online journal publication allows for the use of original RGB color images as they were captured and seen in author’s laboratories and presentations. RGB images will be preserved throughout the online publication process and displayed as the author intended. The RGB workflow allows for the preservation of fluorescent blues, greens, and reds.
 - **Note:** All color images will still have to be converted to CMYK for publication in the printed journals. The print quality should not suffer and in many cases will look much better, because the conversion will be done by our printer with much more sophisticated software than is being used in-house to do the conversions.
- **Use an illustration or graphics software program such as Adobe Photoshop or Illustrator** for creating or scanning images.
- **APS will accept PowerPoint figures/presentations.** Please be sure that all imported scanned material is scanned at the appropriate resolution: 1200 dpi for line art, 600 dpi for grayscale, and 300 dpi for color.
- **Save each image in EPS or TIFF format.** See the list of applications at the Cadmus web site (<http://cpc.cadmus.com/da/applications.asp>) that support saving or exporting graphics as EPS or TIFF files.
- **Submit Acrobat PDF files in lieu of TIFF or EPS.** If the program that you are using to generate your image does not offer an EPS or TIFF format for saving or exporting, you can create high resolution PDF (portable document format) with the full version of Adobe Acrobat/Acrobat Distiller (http://www.the-aps.org/publications/i4a/pdf_hires.htm).

The information contained within a submitted color graphic file is the responsibility of the author. APS will not alter (i.e., color correct) the information contained in a submitted file. Extensive author corrections and changes at proof stage will incur additional charges.

Color figures are subsidized by APS at a cost to authors of only \$400 per figure, assuming that color is scientifically warranted and page charges are paid. **Unnecessary color figures are not permitted in the Journals**, and in such cases authors will be required to provide a black and white version suitable for print publication. Color figures that are scientifically necessary are free of charge if the first or last author is an APS member in good standing when the paper is accepted. For more information, see *Cost of Publication* (near the top of this document).

Use of Animals in Photographs

- Photographs of animals may be published when scientifically necessary to illustrate a setup or convey the findings of the paper.
- 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, photographs should not show blood or people handling the animals except close-ups where only gloved hands are seen.

Graphs

Electrocardiograms, kymograms, and oscillograms should be prepared so that the crosshatched background is eliminated. To avoid problems in

processing, use non-photo blue-ruled instead of black-ruled recording paper for the originals.

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, on the Editor’s recommendation and with the approval of the author, will be deposited by the APS Publications (see *Data Supplements*, below).

Submitted tables should adhere to the following guidelines:

- Each table should appear on a separate page of the manuscript.
- 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 be double-spaced.
- Each table should have a brief title; explanatory notes should be in the legend, not in the title.
- Horizontal and vertical rules should be omitted.
- 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.

Use subscripts or superscripts wherever feasible and appropriate, because they often simplify the equations by eliminating the need for extraneous operations: R_A/R_D instead of RA/RD or $(RA)/(RD)$.

Use circles for pools in compartmental or flow-type models and whole arrows for interconnections or flows (not arrows with half-heads, as in reversible chemical equations).

Do not use nonstandard mathematical notations; e.g., do not use computer symbols in equations (* for multiplication or ** for exponentiation).

Use lowercase letters for time-varying symbols in compartmental model equations, preferably $q(t)$ for masses, $c(t)$ for concentrations, with subscripts as needed.

Our convention for numerical subscripts for rate constants (k_{21}) is the same as that used in most life sciences but opposite to that currently used in pharmacokinetics; i.e., our k_{ij} is the fractional rate of transfer from compartment j to compartment i (or to compartment i from compartment j , if you prefer). Our notation is consistent with standard nomenclature in applied mathematics for matrices and matrix manipulation algorithms in commercial software packages for scientific/mathematical computations involving matrices. However, the author(s) may use a different convention if it is clearly defined in the manuscript.

Symbols should be defined as they first appear in the text, and a Glossary should also be included 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 Web Copy 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 should include a written caption with each video file, explaining what is happening in the video.

There are many different factors that can affect the file size of a video. Authors are advised to keep the following general guidelines in mind:

- Length of videos should be no more than 30 seconds.
- Frame size should be no more than 320×240 pixels.
- Do not include sound unless scientifically necessary. Do not use voice-over narration to explain what is happening in the video; this information should be written in the caption, which will be displayed on the web page that contains the video.

Contact the Web Copy 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 than how they were originally submitted due to the limits of the HTML format.

Microfiche

At the author's request, supplemental material may be submitted for deposition at:

National Auxiliary Publications Service (NAPS)
c/o Microfiche Publications
P. O. Box 3513, Grand Central Station
New York, NY 10017

A footnote will be inserted noting the availability of the material on microfiche and giving the NAPS Document Number.

Abbreviations

Listed below are abbreviations and their definitions. These may be used without definition in the APS Journals. See Information for Authors (www.the-aps.org/publications/journals/pub_quick.htm) for other abbreviations, symbols, and terminology.

ACh	acetylcholine	IRMS	isotope ratio mass spectrometry
ACTH	adrenocorticotropic hormone	JAK	Janus-activated kinase
ADP (CDP, GDP, IDP, UDP, XDP, TDP)	adenosine 5'-diphosphate (and similarly for cytidine, guanosine, inosine, uridine, xanthosine, thymidine)	JNK	c-Jun NH ₂ -terminal kinase
AM	acetoxymethyl ester	JNKK	JNK kinase
AMP, etc.	adenosine 5'-monophosphate, etc.	kb	kilobase(s)
ANG I, etc.	angiotensin I, etc.	K_m	equilibrium constant related to Michaelis-Menten kinetics (similarly, K_d , K_a , K_{eq} , K_s)
ANOVA	analysis of variance	LDL	low-density lipoprotein
ATP, etc.	adenosine 5'-triphosphate, etc.	LH	luteinizing hormone
ATPase, etc.	adenosine 5'-triphosphatase, etc.	LH-RH	luteinizing hormone-releasing hormone
AVP	arginine vasopressin	LPS	lipopolysaccharide
BAPTA	1,2-bis(2-aminophenoxy)ethane- <i>N,N,N',N'</i> -tetraacetic acid	MAb	monoclonal antibody
BCECF	2',7'-bis(2-carboxyethyl)-5(6)-carboxyfluorescein	MAPK	mitogen-activated protein kinase
bp	base pair(s)	MAPKK	MAP kinase kinase (also known as MEK or MKK)
BSA	bovine serum albumin	MAPKAPK	MAP kinase activated protein kinase
CaM	calmodulin	MEM	Eagle's minimum essential medium
CaMK	Ca ²⁺ /calmodulin-dependent kinase	MES	2-(<i>N</i> -morpholino)ethanesulfonic acid
CaMKK	CaMK kinase	MKP	MAP kinase phosphatase
cAMP, etc.	adenosine 3',5'-cyclic monophosphate, etc.	MOPS	3-(<i>N</i> -morpholino)propanesulfonic acid
CCCP	carbonyl cyanide <i>m</i> -chlorophenylhydrazone	MPO	myeloperoxidase
CCK	cholecystokinin	M_r	relative molecular mass (unitless)
cDNA	complementary DNA	MRI	magnetic resonance imaging
CFTR	cystic fibrosis transmembrane conductance regulator	MSH	melanocyte-stimulating hormone
CGRP	calcitonin gene-related peptide	NAD	nicotinamide adenine dinucleotide
CoA	coenzyme A (also, acyl-CoA)	NADH	reduced nicotinamide adenine dinucleotide
CRF	corticotropin-releasing factor	NADP	nicotinamide adenine dinucleotide phosphate
DDAVP	desmopressin	NF- κ B	nuclear factor- κ B
DEAE	diethylaminoethyl	NGF	nerve growth factor
DIDS	4,4'-diisothiocyanostilbene-2,2'-disulfonic acid	NMR	nuclear magnetic resonance
DMEM	Dulbecco's modified Eagle's medium	NSAID	nonsteroidal anti-inflammatory drug
DMSO	dimethyl sulfoxide	nt	nucleotide(s)
DNA	deoxyribonucleic acid	PAGE	polyacrylamide gel electrophoresis
DNase	deoxyribonuclease	PAH	<i>p</i> -aminohippuric acid
DOC	deoxycorticosterone	PBS	phosphate-buffered saline
DOCA	deoxycorticosterone acetate	PCNA	proliferating cell nuclear antigen
dpm	disintegrations per minute	PCR	polymerase chain reaction
DTNB	5,5'-dithiobis(2-nitrobenzoic acid)	PDGF	platelet-derived growth factor
DTT	dithiothreitol	PET	positron emission tomography
EC ₅₀	concentration giving half-maximal response	PG	prostaglandin (PGE ₁ , PGE ₂ , PGF ₂)
ECG	electrocardiogram	P _i	inorganic phosphate
ECM	extracellular matrix	PIPES	piperazine- <i>N,N'</i> -bis(2-ethanesulfonic acid)
EDTA	ethylenediaminetetraacetic acid	PKA	cAMP-dependent protein kinase
EEG	electroencephalogram	PKB, PKC	protein kinase B and C
EGF	epidermal growth factor	PLC	phospholipase C (similarly, PLA)
EGTA	ethylene glycol-bis(β -aminoethyl ether)- <i>N,N,N',N'</i> -tetraacetic acid	PMA	phorbol 12-myristate 13-acetate
EIPA	ethylisopropyl amiloride	PMSF	phenylmethylsulfonyl fluoride
ELISA	enzyme-linked immunosorbent assay	Po ₂	partial O ₂ pressure or O ₂ tension (similarly, PCO ₂)
EMSA	electrophoretic mobility shift assay	POPOP	1,4-bis[2-(5-phenyloxazolyl)]benzene
ERK	extracellular signal-regulated kinase	PPO	2,5-diphenyloxazole
FAD	flavin adenine dinucleotide	psi	pounds per square inch
FADH ₂	reduced flavin adenine dinucleotide	PTK	protein tyrosine kinase
FBS, FCS	fetal bovine/calf serum	RIA	radioimmunoassay
FCCP	carbonyl cyanide <i>p</i> -trifluoromethoxyphenylhydrazone	RNA	ribonucleic acid (also, mRNA, rRNA, tRNA)
FGF	fibroblast growth factor	RNase	ribonuclease
FITC	fluorescein isothiocyanate	rpm	revolutions per minute
FSH	follicle-stimulating hormone	RT	reverse transcriptase
GABA	γ -aminobutyric acid (also, "GABAergic")	SAPK	stress-activated protein kinase
GAP	growth-associated protein	SAPKK	stress-activated protein kinase kinase (also known as SKK)
GAPDH	glyceraldehyde-3-phosphate dehydrogenase	SDS	sodium dodecyl sulfate
GC-MS	gas chromatography-mass spectrometry	SITS	4-acetamido-4'-isothiocyanostilbene-2,2'-disulfonic acid
GDP β S	guanosine 5'- <i>O</i> -(2-thiodiphosphate)	SSC	standard sodium citrate
GSH, GSSG	reduced and oxidized glutathione	SOD	superoxide dismutase
GTP γ S	guanosine 5'- <i>O</i> -(3-thiotriphosphate)	STAT	signal transducer and activator of transcription
GSK	glycogen synthetase kinase	TAME	<i>N</i> α - <i>p</i> -tosyl-L-arginine methyl ester
Hb	hemoglobin	TCA	trichloroacetic acid
HBSS	Hanks' balanced salt solution	TEAE	triethylaminoethyl
Hct	hematocrit	TES	<i>N</i> -tris(hydroxymethyl)methyl-2-aminoethanesulfonic acid
HDL	high-density lipoprotein	TLC	thin-layer chromatography
HEPES	<i>N</i> -2-hydroxyethylpiperazine- <i>N'</i> -2-ethanesulfonic acid	TNF	tumor necrosis factor
HETE	hydroxyeicosatetraenoic acid	TPA	12- <i>O</i> -tetradecanoylphorbol 13-acetate
HPLC	high-performance liquid chromatography	TPCK	<i>N</i> -tosyl-L-phenylalanine chloromethyl ketone
5-HT	5-hydroxytryptamine (serotonin)	TRH	thyrotropin releasing hormone
IBMX	3-isobutyl-1-methylxanthine	Tris	tris(hydroxymethyl)aminomethane
IC ₅₀	concentration giving half-maximal inhibition	TSH	thyroid-stimulating hormone
ICAM	intercellular adhesion molecule	TTX	tetrodotoxin
IFN	interferon	UV	ultraviolet
IGF-I, -II	insulin-like growth factor I and II	VCAM	vascular cell adhesion molecule
IgG, etc.	immunoglobulin G, etc.	VEGF	vascular endothelial growth factor
IKK	I κ B kinase	VIP	vasoactive intestinal peptide
IL-1	interleukin-1 (IL-2, etc.)	VLDL	very low-density lipoprotein
		V_{max}	maximum velocity or maximum rate of change or transition

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 in the Care and Use of Animals. 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 IN THE CARE AND USE OF ANIMALS²

Animal experiments are to be undertaken only with the purpose of advancing knowledge. Consideration should be given to the appropriateness of experimental procedures, species of animals used, and number of animals required.

Only animals that are lawfully acquired shall be used in the laboratory, and their retention and use shall be in every case in compliance with federal, state and local laws and regulations, and in accordance with the Institute for Laboratory Animal Research (ILAR) *Guide for Care and Use of Laboratory Animals*.³

Animals used in research and education must receive every consideration for their comfort; they must be properly housed, fed, and their surroundings kept in a sanitary condition.

The use of animals must be in accordance with the ILAR *Guide for Care and Use of Laboratory Animals*. Appropriate anesthetics must be used to eliminate sensibility to pain during all surgical procedures. Drugs that produce muscle paralysis are not anesthetics, and they must not be used alone for surgical restraint, but may be used in conjunction with drugs known to produce adequate anesthesia. The care and use of animals shall be such as to minimize discomfort and pain. All measures to minimize pain and distress that would not compromise experimental results may be employed.

If the study requires the death of an animal, the most humane euthanasia method consistent with the study must be used.

When animals are used by students for their education or the advancement of science, such work shall be under the direct supervision of an experienced teacher or investigator.

² Based on principles formulated in 1909 by Walter B. Cannon. APS Council first adopted the Guiding Principles in 1953. Latest revision approved July 2000.

³ Institute for Laboratory Animal Research. National Research Council. *Guide for the Care and Use of Laboratory Animals*. Washington, DC: National Academy Press, 1996.

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 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, which is published in the journals, 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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When an Editor in Chief submits a paper to his or her journal, the paper is automatically assigned to a Guest Editor, a Consulting Editor, or an Associate Editor, who will handle all aspects of the peer review of the paper. The reviews are handled outside the web-based peer review system, so that the Editor in Chief will not have access to them.

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