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(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.

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(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.

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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://celcycle-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). doi: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; doi: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; doi:10.1152/physiolgenomics.00148.2002. (Corrigendum. *Physiol Genomics* 18: 128, 2004)

Translations

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

Consult recent issues of the APS Journals for more examples.

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
9650 Rockville Pike
Bethesda, MD 20814-3991

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

Preparing Original Graphics

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.

Supported Applications

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/scientificallly_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 $RA \cdot RD$ 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)
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New York, NY 10017

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

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. Reviewed and approved 2006.

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

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Ethical Procedure

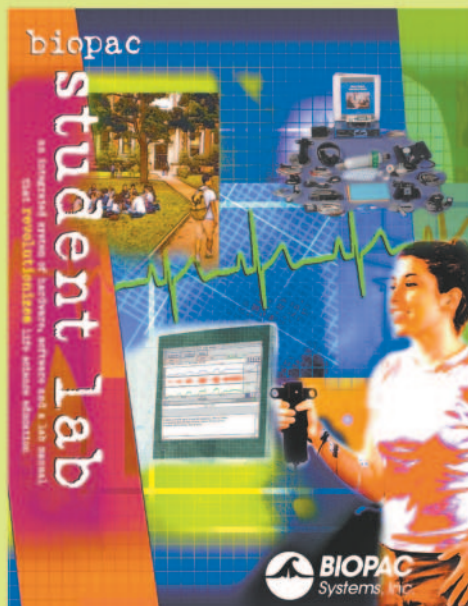
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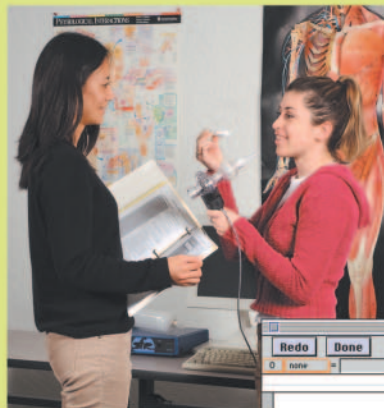
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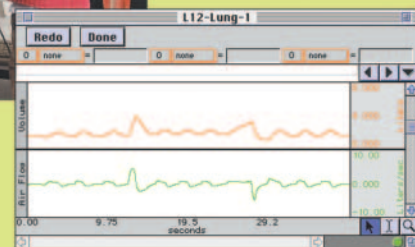
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