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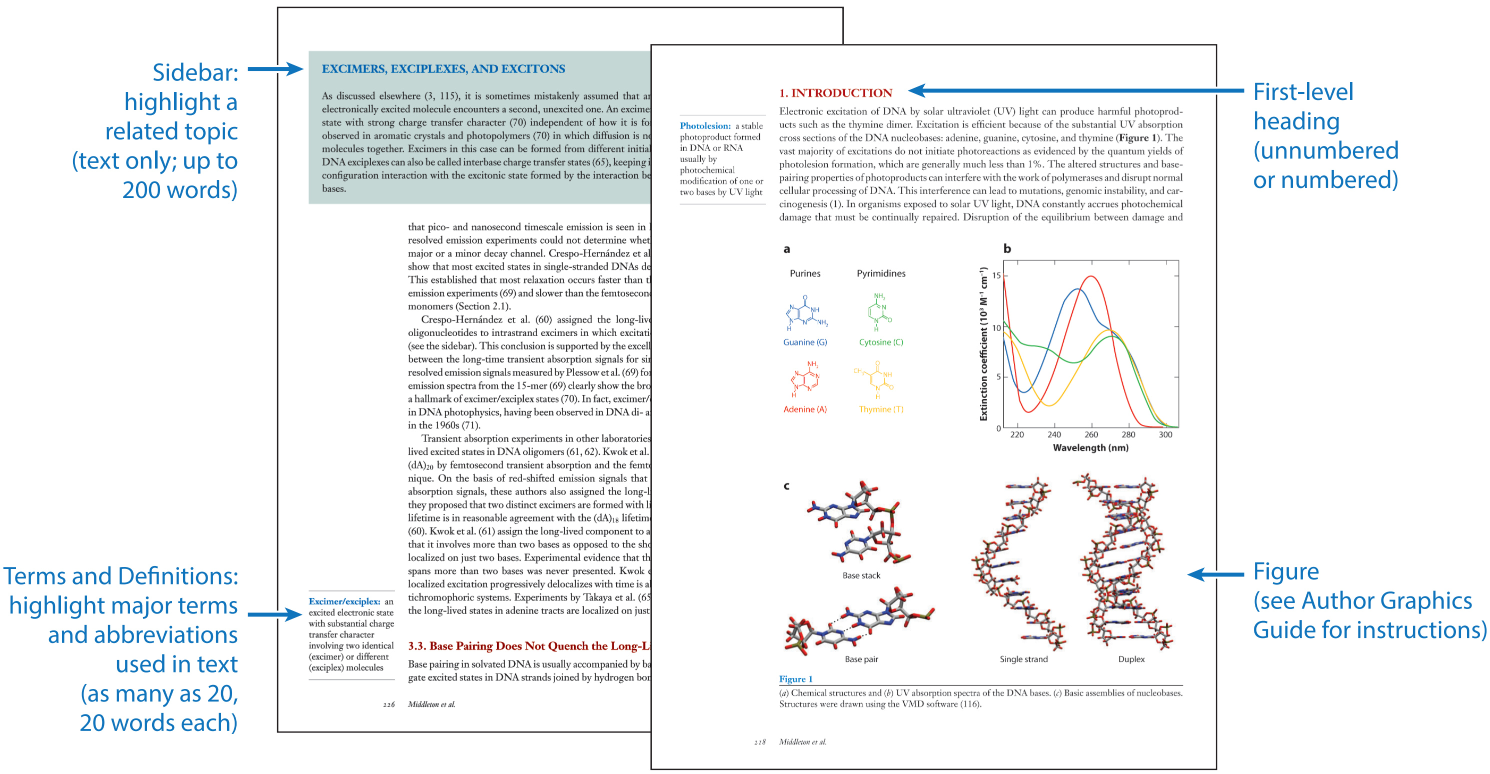

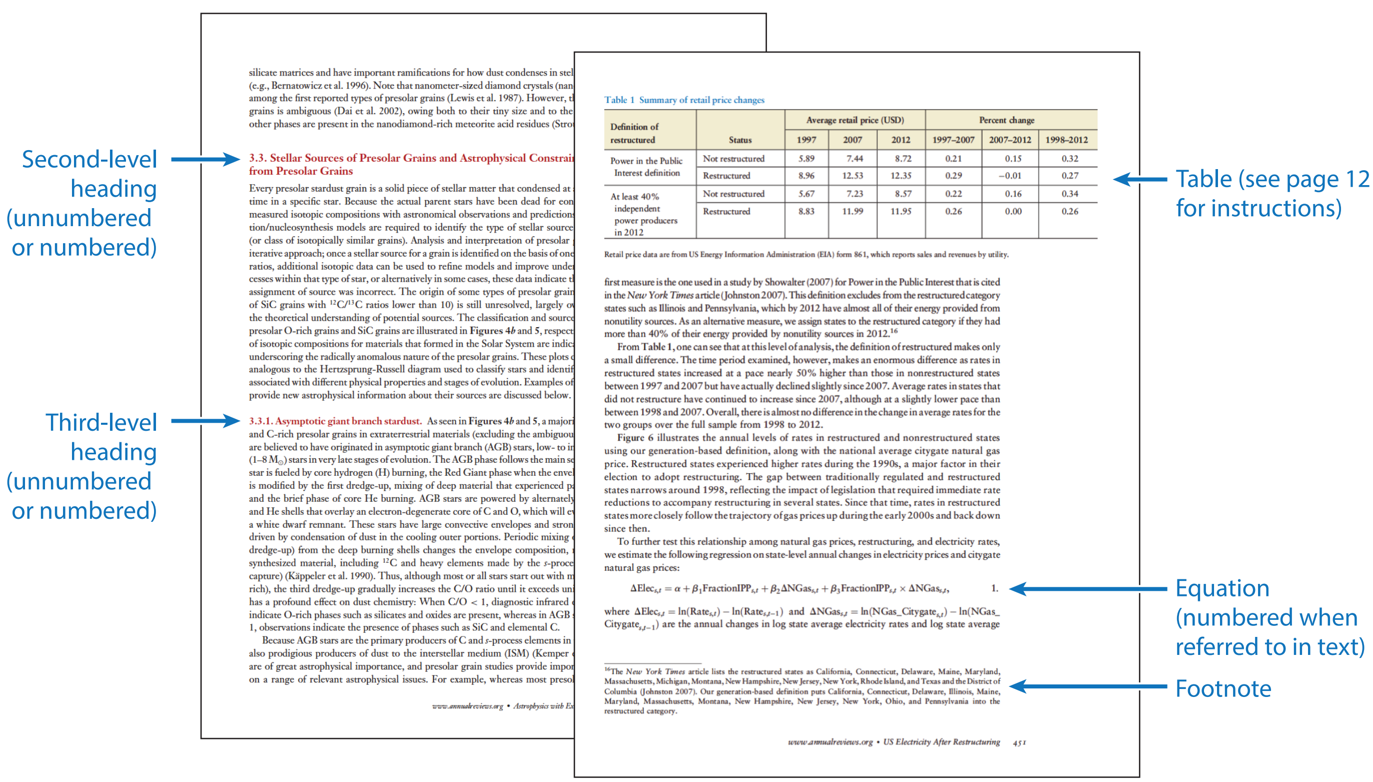

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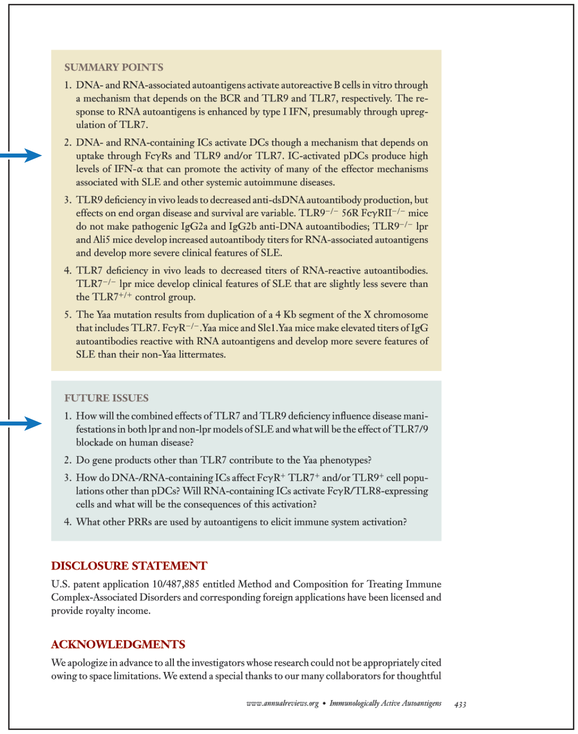

SUMMARY POINTS

1. DNA- and RNA-associated autoantigens activate autoreactive B cells in vitro through a mechanism that depends on the BCR and TLR9 and TLR7, respectively. The response to RNA autoantigens is enhanced by type I IFN, presumably through upregulation of TLR7.
2. DNA- and RNA-containing ICs activate DCs though a mechanism that depends on uptake through FcγRs and TLR9 and/or TLR7. IC-activated pDCs produce high levels of IFN-α that can promote the activity of many of the effector mechanisms associated with SLE and other systemic autoimmune diseases.
3. TLR9 deficiency in vivo leads to decreased anti-dsDNA autoantibody production, but effects on end organ disease and survival are variable. $TLR9^{-/-}$ 56R $Fc\gamma RII^{-/-}$ mice do not make pathogenic IgG2a and IgG2b anti-DNA autoantibodies; $TLR9^{-/-}$ lpr and Ali5 mice develop increased autoantibody titers for RNA-associated autoantigens and develop more severe clinical features of SLE.
4. TLR7 deficiency in vivo leads to decreased titers of RNA-reactive autoantibodies. $TLR7^{-/-}$ lpr mice develop clinical features of SLE that are slightly less severe than the $TLR7^{+/+}$ control group.
5. The Yaa mutation results from duplication of a 4 Kb segment of the X chromosome that includes TLR7. $Fc\gamma R^{-/-}$.Yaa mice and Sle1.Yaa mice make elevated titers of IgG autoantibodies reactive with RNA autoantigens and develop more severe features of SLE than their non-Yaa littermates.

FUTURE ISSUES

1. How will the combined effects of TLR7 and TLR9 deficiency influence disease manifestations in both lpr and non-lpr models of SLE and what will be the effect of TLR7/9 blockade on human disease?
2. Do gene products other than TLR7 contribute to the Yaa phenotypes?
3. How do DNA-/RNA-containing ICs affect $Fc\gamma R^{+}$ $TLR7^{+}$ and/or $TLR9^{+}$ cell populations other than pDCs? Will RNA-containing ICs activate FcγR/TLR8-expressing cells and what will be the consequences of this activation?
4. What other PRRs are used by autoantigens to elicit immune system activation?

DISCLOSURE STATEMENT

U.S. patent application 10/487,885 entitled Method and Composition for Treating Immune Complex-Associated Disorders and corresponding foreign applications have been licensed and provide royalty income.

ACKNOWLEDGMENTS

We apologize in advance to all the investigators whose research could not be appropriately cited owing to space limitations. We extend a special thanks to our many collaborators for thoughtful

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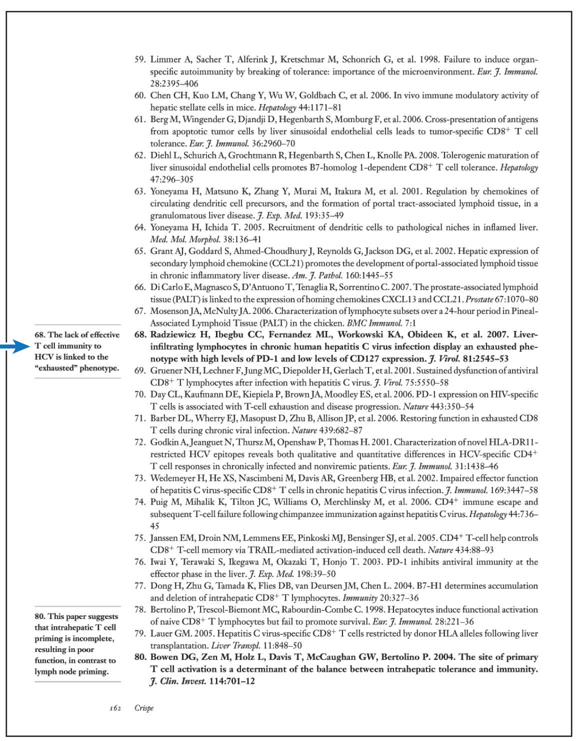

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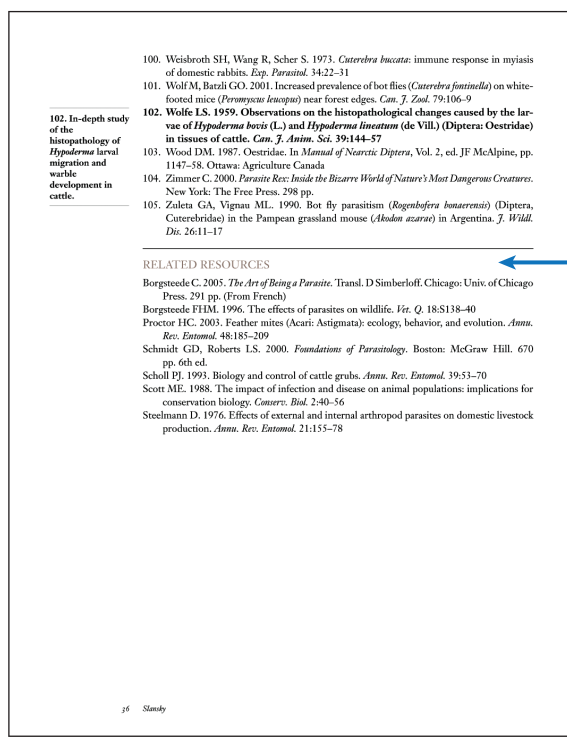

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Table 1 Values of muscle-fiber length and muscle physiological cross-section area reported in the literature

	Muscle-fiber length (cm)				Muscle PCSA[c] (cm^2)			
Muscle	**Wickiewicz[a]**	**Friederich[a]**	**Ward[a]**	**Tate[b]**	**Wickiewicz[a]**	**Friederich[a]**	**Ward[a]**	**Tate[d]**
Gluteus maximus (superior)	NA[e]	10.8	NA	NA	NA	17.4	NA	NA
Gluteus maximus (middle)	NA	13.0	NA	NA	NA	14.6	NA	NA
Gluteus maximus (inferior)	NA	13.9	NA	NA	NA	14.1	NA	NA
Gluteus medius (anterior)	NA	4.7	NA	NA	NA	19.0	NA	NA
Gluteus medius (middle)	NA	6.8	NA	NA	NA	13.3	NA	NA
Gluteus medius (posterior)	NA	6.0	NA	NA	NA	15.4	NA	NA
Vastus medialis	7.0	7.8	9.7	NA	21.1	41.2	20.6	46.1
Vastus intermedius	6.8	7.6	9.9	NA	22.3	49.6	16.7	54.3
Vastus lateralis	6.6	8.0	9.9	NA	30.6	40.4	35.1	69.9
Soleus	2.0	3.0	4.4	NA	58.0	122.2	51.8	NA
Gastrocnemius (lateral)	5.1	6.1	5.9	NA	NA	11.5	9.7	23.9
Gastrocnemius (medial)	3.5	3.9	5.1	NA	32.4	33.8	21.1	43.7

[a]Data reported by Wickiewicz (51), Friederich (49), and Ward (50) were obtained by dissection of cadaver specimens.
[b]Data reported by Tate (59) were obtained from magnetic resonance imaging performed on living subjects. Muscle-fiber lengths were not measured by Tate (59).
[c]Abbreviation: PCSA, physiological cross-sectional area.
[d]Muscle PCSA was calculated using muscle-fiber lengths reported by Ward (50).
[e]Abbreviation: NA, not applicable.

Include additional information in footnotes keyed to the title, heading, or entry of the table as appropriate, a, b, c, etc.

Abbreviate longer headings to conserve space and explain the abbreviations in a footnote.

GRAPHIC COMPONENTS

Annual Reviews strongly encourages the effective use of figures and tables. Article page allotments include space used for figures and tables. Thus, information presented graphically should be referenced, but not repeated, in the text. Figures and tables you submit with your article will appear in both typeset and HTML versions of your article.

The digital methods for creating and sending your figures are treated in the Annual Reviews Author Graphics Guide.

TABLES

Only material requiring several columns and several entries should be submitted in tabular form (incorporate other material into the text). Tables should fit within an Annual Reviews page width (6.33 in; approximately 15 cm). Submit editable electronic files for all tables.

All tables will be formatted according to house style. Please adhere to the following guidelines when preparing your tables.

BODY OF TABLE Align entries under the appropriate heading or subheading. Make sure your table clearly indicates the vertical alignment of headings and data. Type longer entries in block style, leaving extra space between entries. Align numbers on the decimal; if numerical data are mixed, center entries in the column. Write out repeated entries or merge cells; do not use ditto marks. Use ND (no data or not determined), NA (not applicable or not available), and NT (not tested) as needed; do not use a dash or leave a cell blank.

FOOTNOTES Footnotes should be at the bottom of the table; label each with a lowercase superscript letter (a, b, c, etc.) keyed to the title, heading, or entry on the table. Begin the lettering anew for each table. If a footnote applies to more than one table, key it to the title of subsequent tables. Include references in the body of the table rather than as footnotes.

ACCEPTABLE FILE TYPES Table files must be compatible with Microsoft Word [.doc(x) or .rtf] or Excel (.xls). Mathematically complex tables may be submitted in LaTeX.

The illustration on the previous page is a guide for laying out the title, columns, rows, and footnotes for a table.

FIGURES

Please refer to the Author Graphics Guide for details on the preparation of illustrations.

Figures should be well-designed drawings or well-chosen photographs that illustrate key points in your article or that present relevant data in an economical way. Annual Reviews Illustration Editors will work with you to enhance your figures' legibility, color, style, and consistency. Modified figures will be sent to you for approval before publication.

To maximize their usability, all figures must be submitted in editable digital form. Export your figures to PDF format (sometimes available under the "print" menu) directly from your graphics creation program. If such files are not available, please contact your Production Editor. Regarding scanning originals, please see the Author Graphics Guide for scan resolution. Other acceptable file formats and additional details are discussed in the Author Graphics Guide.

FIGURE SIZING On an Annual Reviews page the maximum space available for figures is 6.33 in wide × 7.66 in high (approximately 15 cm × 19.5 cm). Annual Reviews' in-house Illustration Editors will determine the appropriate final figure size unless you give specific directions. (Note that photographs should not be enlarged beyond the size at which they retain 300-dpi resolution.)

LETTERING AND SYMBOLS Lettering in figures must be of professional quality and large enough to be legible. Specify type at 7, 8, or 9 pt. Use a standard sans-serif font such as Helvetica, Arial, or Myriad Pro. If you plan to submit scaled images that contain type, be certain that type is still legible (no smaller than 6 pt) and consistent in size for all the figures in your review. Ensure that text remains editable (not converted to shapes or outlines or flattened into images) to allow us to make house style or sizing changes.

GRAPHS Graphs should be in editable vector format. Using Photoshop or other raster-based programs to create graphs is strongly discouraged. For plot points in graphs, use symbols that are readily available (Zapf Dingbats or another computer-generated symbol font), and choose symbols that can be seen as separate entities along a line. In final form, the plot symbols should be large enough to be legible (8 pt). For plots with multiple lines/symbols, use color to distinguish elements.

CHEMICAL STRUCTURES Complex equations and chemical structures that cannot be typeset in one or two lines are considered art (see p. 21). If possible, such equations should be submitted in math-friendly software applications such as LaTeX or MathType. Submit complex chemical structures as editable vector graphics.

FIGURE CAPTIONS Every figure must have an accompanying descriptive caption. Bundle figure captions together in a text file (or place them at the bottom of the article's text file). Please do not attach captions to figure files.

COLOR FIGURES Color figures are integrated into the article's page layout and printed at no cost to you.

We strongly encourage the use of color in all illustrations. You can make use of color to differentiate and to group elements in complex illustrations, while also applying a consistent color scheme across multiple illustrations. Our Illustration Editors are here to help. Contact your Production Editor with questions.

See the Author Graphics Guide for details on submitting figures.

NUMBERING AND NAMING FIGURES Number your figures consecutively as you wish them to appear in your review and as they are referenced in the text. When preparing your text files, spell out the word "Figure" in captions and text. If a figure has multiple panels, refer to parts of the figure as (*a*), (*b*), (*c*), etc. in the caption and as, e.g., Figure 1*a* in the text. If further distinction is needed, subparts can be described as (*left*), (*right*), (*top*), (*middle*), and (*bottom*). If a sequence of steps is shown, numbers may be used to label each step. The caption should then refer to Step 1, Step 2, etc.

ENHANCED FIGURES Annual Reviews Illustration Editors work closely with editors and authors to identify figures that can be enhanced with links, pop-up text, other interactive elements, and videos. These enhancements appear online only. Please ask your Production Editor for samples if you are interested in enhancing the online version of your figures.

PERMISSIONS You must obtain permission to reuse and modify figures prior to submitting your manuscript. Please contact publishers of the source publication directly for permission to reuse figures. Include only figures for which you have obtained such permission. The source of the material should be credited at the end of the figure caption. The copyright holder may specify the exact language to be used. If a figure has a Creative Commons (CC) copyright or is in the public domain, you may not need permission to use it, but generally attribution of the source is still required.

☑ You are responsible for obtaining permission to use any copyrighted material. If you need assistance in paying any incidental fees, please contact your Production Editor.

SUPPLEMENTAL MATERIAL

Article-relevant material that is costly, difficult, or impossible to include in the typeset PDF may be posted on our website. These materials are fully linked to the PDF and HTML versions of your article.

Candidates for inclusion in this online repository are figures that will not reproduce well in print, lengthy tables, data sets, and multimedia objects (e.g., sound, video, animations, 3D objects, etc.).

☑ It is the author's responsibility to put Supplemental Material in a final, copyedited form before submission. We do not have the personnel to check, revise, or maintain these materials upon submission or thereafter.

Authors who wish to publish Supplemental Material should notify their Production Editor early in the production process. Ideally, such materials will be submitted on the manuscript due date along with the rest of the article.

Authors should also review our Supplemental Material Policy (online at http://www.annualreviews.org/page/authors/author-instructions/preparing/supmat). This policy provides detailed guidelines for the submission of Supplemental Material, including

- Preparation guidelines
- Submission guidelines
- Supported file types
- Size limitations on Supplemental Material
- Maintenance guidelines
- How to call out your Supplemental Material in the printed version of your article.

LITERATURE CITED

Here, you will find general guidelines for citing sources in your Annual Reviews article. In Appendix A of this handbook, numerous examples illustrate how to list various types of sources (books, articles, websites, conference papers, etc.) in your Literature Cited section.

☑ Each reference in the Literature Cited section must be mentioned in text, figure captions, or tables.

HARVARD-STYLE REFERENCES

The following Annual Reviews use the unnumbered, name and year (Harvard) bibliographic style: *Anthropology*; *Astronomy and Astrophysics*; *Cancer Biology*; *Cell and Developmental Biology*; *Clinical Psychology*; *Criminology*; *Developmental Psychology*; *Earth and Planetary Sciences*; *Ecology, Evolution, and Systematics*; *Economics*; *Financial Economics; Fluid Mechanics*; *Food Science and Technology; Law and Social Science*; *Linguistics*; *Marine Science*; *Neuroscience*; *Organizational Psychology and Organizational Behavior*; *Political Science*; *Psychology*; *Resource Economics; Sociology*; *Statistics and Its Application;* and *Vision Science*.

NUMBERED REFERENCES: Some Annual Reviews use numbered citations: *Analytical Chemistry; Animal Biosciences; Biochemistry; Biophysics; Biomedical Engineering; Biomedical Data Science; Chemical and Biomolecular Engineering; Condensed Matter Physics; Control, Robotics, and Autonomous Systems; Entomology; Environment and Resources; Genetics; Genomics and Human Genetics; Immunology; Materials Research; Medicine; Microbiology; Nuclear and Particle Science; Nutrition; Pathology: Mechanisms of Disease; Pharmacology and Toxicology; Physical Chemistry; Physiology; Phytopathology; Plant Biology; Public Health;* and *Virology*.

For journals with numbered references, please download, or obtain from your Production Editor, the appropriate Author Instruction Handbook.

CITATIONS IN TEXT

- Use the name-and-year system.
- Use ampersand to indicate authorship for two authors. For three or more authors, use "et al.," "and coworkers," or "and associates" in text. Use no comma before ampersand.

```
White & Gray (2004) experimented...
Smith et al. (1999) tested the theory.
```

- Distinguish between references with the same author(s) and year by indicating 1987a, 1987b, etc.

```
Byron et al. (1986; 1987a,b)
determined...
```

- In multiple citations, references should appear in either chronological or alphabetical sequence throughout. If inconsistent, alpha order will be applied in copyediting.
- Use semicolons to separate unlike elements within the parentheses.

```
...(Moorehouse 2006; J.S. Smith,
unpublished information).
```

- Do not use author's initials for published references in text unless necessary to distinguish two authors of the same surname.
- Italicize titles of books and journals.
- References to unpublished observations, personal communications, papers in preparation, etc., should be enclosed in parentheses in text `(R.S. Jones, unpublished observations)`. List all authors up to six (for seven or more authors, list five followed by et al.) and include all their initials (as well as your own) in these citations. Except for *Physical Chemistry*, do NOT list these citations as references in the Literature Cited section. *Entomology* does not permit the citation of unpublished works.

CITATIONS IN BIBLIOGRAPHY

- Do not list references as footnotes to the text.
- Do not use Microsoft Word's Footnotes or Endnotes functions for citing/listing references.
- Set line spacing to 2 throughout the Literature Cited section.
- Do not indent the first line of each entry.
- For each author, use last name first, then initials, no periods.

☑ Responsibility for the accuracy of the bibliographic references rests entirely with the author.

- List references in alphabetical order by last name of author, then by initials, by last name of coauthors, and finally by year. Alphabetize compound surnames by the first word, e.g., list under "de," "van," "von," etc.

```
Zeiger E. 1990. Article title.
Zeiger E, Armond P, Melis A. 1981.
     Article title.
Zeiger E, Bloom AJ, Hepler PK. 1990.
     Article title.
Zeiger E, Field C, de Vitry C. 1988.
     Article title.
Zeiger E, Field C, Mooney HA. 1981.
     Article title.
Zeiger E, Hepler PK. 1991. Article
     title.
Zeiger E, Hepler PK. 1993. Article
     title.
```

- Include titles of articles or chapters for all Annual Reviews **EXCEPT** *Astronomy and Astrophysics, Condensed Matter Physics*, and *Nuclear and Particle Science.*

- Use italics for the book or journal title (see Appendix A for examples). Do not abbreviate book titles. Abbreviate titles of journals, proceedings, symposia, and serial compendia according to the *ISSN List of Title Word Abbreviations* (*LTWA*), published by the International Organization for Standardization. (Go to http://www.issn.org/services/online-services/access-to-the-ltwa/ for general information on using the guide, and scroll down to the "View the LTWA" section for the online guide.) Do not abbreviate one-word journal titles.

BIBLIOGRAPHIC STYLE

Most cited sources can be formatted using the general guidelines below. For exceptions or special cases (websites, conference papers, errata, abstracts, etc.), see Appendix A at the end of this handbook.

List numbered references in the Literature Cited with numerals and period, without parentheses. Include the following information (in this order):

1. Name(s) of author(s), last name first, followed by initials without periods. Include both (or all) initials for each author whenever they were included in the original article or book. Do not leave space between initials. Do not use a comma between surnames and initials—use commas only to separate different authors' names. If a given reference has seven or more authors, list the first five, then type "et al." in the bibliography. (But in text, use et al. for three or more authors.) If a reference has six or fewer authors, list them all. (**EXCEPTION**: For the *Annual Review of Astronomy and Astrophysics*, if a given reference has six or more authors, list the first three, then type "et al." in the bibliography. If a reference has five or fewer authors, list them all.)

2. Year of publication of the article or book, followed by a period, with no parentheses. If the article has recently been accepted for publication and is actually in press, list it in the Literature Cited section. Provide journal title and expected year of publication, plus volume and pages when known.

3. Title of article or chapter (except *Astronomy and Astrophysics*, *Condensed Matter Physics*, and *Nuclear and Particle Science*).

4. Title of journal (abbreviated unless only one word) or book (not abbreviated unless part of a periodical series), e.g., *J. Psychol.*

5. For a book reference, name(s) of editor(s).

6. Volume number, then a colon and inclusive page numbers; if there is no volume number, inclusive page numbers preceded by a comma and "pp." Do not repeat hundreds digit unless needed, e.g., 3–10, 71–77, 100–9, 331–35, 1002–3, 1198–202, 1536–38. The issue number can be included in parentheses immediately following the volume if necessary.

For example: 10(4):123–30

7. For a book reference, place of publication, name of publisher, and edition, if necessary. For example: New York: Sage (do not put a period at the end of the reference).

CITATION MANAGEMENT SOFTWARE

If you are using Thomson Reuters' EndNote®, you may download the journal's EndNote style file from the AR website at http://www.annualreviews.org/page/authors/author-instructions/preparing/endnotes.

If you are using another reference management program, it may include the style for the Annual Reviews journal for which you are writing. If not, you may be able to use the style for another Annual Reviews journal (contact your Production Editor), or you can edit the citation manager's style module to accord with the Annual Reviews journal style, namely:

- Author names are given last name first, followed by initials—with NO punctuation except for commas between authors and a period at the end.

Sample: `Brown J, Smith R, Jones CE.`

- The year comes after the names, followed by a period.
- Journal article titles are lowercase except for the first word, proper nouns, and acronyms.
- Journal titles are italic. Abbreviations are followed by periods.

If you have any difficulty setting up your EndNote system, please go to http://www.endnote.com/support.

WEBSITE CITATIONS

GENERAL GUIDELINES When you cite a specific source that is housed online, you should include it in the Literature Cited section. Entries in the Literature Cited section should contain as many items from the following list as are relevant and available.

- Name of the author, editor, compiler, or translator of the web-based item (if available and relevant), followed by any appropriate abbreviations, such as ed.
- Title of article or other short work within a scholarly project, database, or periodical
- Title of an online book or periodical, in italics
- Name of the editor, compiler, or translator of a book (if applicable and if not already listed), preceded by any appropriate abbreviation, such as ed.
- Publication information for any print or PDF version
- Title of the scholarly project, database, periodical, or professional or personal site (in italics) or, for a professional or personal site with no title, a description such as home page (in italics)
- Version number (if not part of the title) or, for a journal, the volume, issue, or other identifying number
- Date of electronic publication or posting or latest update, whichever is most recent (if the resource is still being updated)
- Name of any institution or organization sponsoring or associated with the website
- URL

For example:

US Food Drug Admin. 2004. *Innovation or Stagnation: Challenge and Opportunity on the Critical Path to New Medical Products.* Washington, DC: US Food Drug Admin. http://www.fda.gov/oc/initiatives/criticalpath/whitepaper.html

Clinical Data Interchange Standards Consortium (CDISC). 2007. *CDISC and industry collaborative group lead FDA critical path initiative opportunity for data collection standards*. CDISC PR#33, May 15. http://www.cdisc.org/news/PR33cdisccdashprojectfinal.pdf

SPECIFIC VERSUS GENERAL SOURCES ON WEBSITES If you wish to cite a specific source that is housed on a website or that is a pamphlet or report that is downloadable only, these sources should be cited in the Literature Cited section according to the instructions described above. For example:

`Kennedy E, Dodd C, Clinton HR. 2005.` *`Letter to US Dep. Labor`*`, Apr. 12. http://www.nationalpartnership.org/site/DocServer/FMLASenateLettertoDOL.pdf?docID=963`

In contrast, to reference a general website that might be a good source of information for your reader, include it in text only, not in the Literature Cited section. For example:

```
A valuable clearinghouse of
information on the passage of
the Family and Medical Leave
Act is the online library at
the National Partnership
for Women & Family website
(http://www.nationalpartnership.org).
```

Unless instructed otherwise, we will attempt to make links and email addresses live in the online version of your review. However, we cannot maintain such external-to-Annual Reviews links, which will generate errors for your readers if the webpage is eventually [re]moved. We thus encourage you to refer only to URLs that you expect to be stable and accessible to readers of your article for many years to come.

You may wish to host material on unstable websites as Supplemental Material (see p. 15). Also, URLs can be included in the Related Resources section of your review (see p. 9).

NOMENCLATURE

GENERAL NOMENCLATURE

The primary nomenclature manual for Annual Reviews is *Scientific Style and Format: The CSE Manual for Authors, Editors, and Publishers* (8th edition). Other authoritative references are listed below.

BACTERIOLOGICAL NAMES Use the *List of Bacterial Names with Standing in Nomenclature* (http://www.bacterio.cict.fr) and the *Approved Lists of Bacterial Names* as guides for validly published scientific names of bacteria and archaea. Use *Bergey's Manual of Determinative Bacteriology* and *Index Bergeyana* as guides for names of unknown bacteria.

INORGANIC, ORGANIC, AND BIOCHEMICAL NOMENCLATURE We accept all abbreviations, symbols, and trivial names in the rules of the IUPAC-IUB.

DRUGS Use nonproprietary (generic) names for drugs. When the name is relatively unfamiliar, follow its first use with the trade name. *Entomology*, *Medicine*, *Nutrition*, *Pathology: Mechanisms of Disease*, and *Pharmacology and Toxicology* require the use of ® as a superscript on first use of a trade name.

EXCEPTION: In *Psychology*, the terms adrenaline and noradrenaline (not capitalized) are permissible in place of epinephrine and norepinephrine.

GENETICS The 8th edition of *Scientific Style and Format* covers all organisms for which they have been able to obtain rules and guidelines (http://www.councilscienceeditors.org/publications/resources.cfm). Also see the section on italics in this handbook.

GENUS-SPECIES SCIENTIFIC NAMES Spell out the full generic and specific names on first use: e.g., *Escherichia coli*. Thereafter, the genus name should be abbreviated to the first letter (*E. coli*). If the name appears frequently and may be confused with another genus whose first letter is the same, spell both names out every four or five pages.

INSECTS Use common and scientific names approved by the Entomological Society of America (http://www.entsoc.org/common-names) whenever possible. Authors from non–North American countries may use common names current in their countries. In general, do not capitalize the first letter of a common name unless a proper name is included.

ABBREVIATIONS AND SYMBOLS

Use abbreviations and symbols sparingly and only if terms are repeated frequently. Define all but the obvious standard symbols and abbreviations when they first appear in text (a list of standard abbreviations and units is provided in Appendix B on p. 26). Avoid using nonstandard abbreviations in titles and headings.

Chemical and graphic formulas may be used (see next section) and are set in roman type. Use U^{3+} rather than U^{+++}. Atomic weights of isotopes are to be indicated by superscripts preceding the element symbol: ^{14}C, [^{14}C]urea.

Use abbreviations of units of measure only when preceded by a numeral: 38 mm (but, a few millimeters).

Use the same abbreviations for units of measure when singular and plural, without periods or apostrophes except in special cases noted in Appendix B. Verbs must agree in number with the quantity: 1 mm is, 3 mm are.... Use a space between the numeral and the unit of measure, except with degree, percent, and Svedberg (5°C, 10%, 6S).

Spell out genus names upon first usage: The name may be abbreviated to its first letter afterward when used in combination with the species name. Never abbreviate generic names when used alone; also, do not abbreviate the species name when a subspecies is designated. For example, use *B. thuringiensis israelensis*, not *B. t. israelensis*.

EQUATIONS AND FORMULAS

SOFTWARE

If preparing your manuscript in Microsoft Word, please use MathType rather than Equation Tools to create your equations.

LAYOUT

Equations and formulas should be in complete sentence form; include punctuation after displayed equations/formulas.

Set out long equations/formulas on a separate line(s).

Number displayed equations/formulas if referred to later in the text. Use a single sequence of Arabic numerals, placed to the right of the equation/formula.

Complicated chemical formulas that cannot be typeset on one or two lines must be submitted as graphics (see section on figures); assemble these at the end of the text, preferably grouped together on one page.

Avoid the vertical placing of side chains. Use the following format, indented from the left margin:

$CH–C(:CH_2)–CH_2–CH(CH_3)CH_2–CH:CH–COOH$

SPECIAL CHARACTERS

Use the multiplication ex (×) in numerical and vector products only. In all other cases, use the multiplication (centered) dot.

Use the slash to mean “per”; write km/s, not km s^{-1}. In arrays, use brackets to indicate a determinant and vertical lines for a matrix.

Observe the following order for brackets: {[()]}; do not use parentheses within parentheses.

Use boldface roman rather than arrows for vectors. Use italics for variables, but subscript labels that are not themselves variables should be in roman. Numerals, symbols for chemical elements, and functions such as ln, exp, and cos should not be italicized.

Define uncommon symbols on first use for the nonspecialist.

Distinguish superscripts to superscripts and subscripts to subscripts from double superscripts and double subscripts (e.g., e^{a^2} versus e^{a2}, n_{H_3} versus n_{H3}).

Align subscripts with superscripts when appropriate to do so.

SUBMITTING YOUR MANUSCRIPT FILES

ONLINE SUBMISSION INSTRUCTIONS

We encourage invited authors to submit their manuscripts online. Your Production Editor will send you the URL in advance of your manuscript due date.

HELPFUL NOTES FOR ONLINE SUBMISSION

- If possible, please compress each file using, for example, WinZip, StuffIt, or GZip software. Then upload.
- Whenever uploading more than five files, compress all contents into a single folder and then upload.
- Always include a PDF file of your final manuscript, including figures and tables, in addition to separate, editable files.
- If uploading revisions, please again include a PDF file of revised text, figures, and/or tables.

EMAIL AND FTP SUBMISSION OPTIONS

- Files may be attached to an email message and sent directly to your Production Editor.
- Manuscript files must be compatible with Microsoft Word’s “.doc(x)” or “.rtf” format. Mathematically complex articles may be submitted in LaTeX.
- A PDF of the final submitted version, including all figures and tables, must accompany all submissions (but does not take the place of editable text and figure files).
- An FTP upload is also an option. Please contact your Production Editor for more information.

APPENDIX A: LITERATURE CITED EXAMPLES

References appear as follows (note patterns of abbreviation, capitalization, spacing, and punctuation):

ABSTRACT

Josen LA, Tollis TM, Anthony A. 1993. Finding solutions to sequences. *Fed. Proc.* 32(3):855 (Abstr.)

ARTICLE IN A JOURNAL WITH TITLE OF ARTICLE

Roberts DF. 2001. A demographic study of a Dinka village. *Hum. Biol.* 28:323-49

Wilmington SR, Matouschek A. 2016. An inducible system for rapid degradation of specific cellular proteins using proteasome adaptors. *PLOS ONE* 11:e0152679

ARTICLE IN A JOURNAL WITHOUT TITLE OF ARTICLE

Berson SA, Balow RS. 1999. *Am. J. Med.* 50:623-29

[use only for *Astronomy and Astrophysics*, *Condensed Matter Physics*, and *Nuclear and Particle Science*]

ARTICLE IN A JOURNAL IN PRESS

Park IJK, Wang L, Williams DR, Alegría M. 2017. Coping with racism: moderators of the discrimination–adjustment link among Mexican-origin adolescents. *Child Dev*. In press. **https://doi.org/10.1111/cdev.12856**

Brown MS, Radhakrishnan A, Goldstein JL. 2018. Retrospective on cholesterol homeostasis: the central role of Scap. *Annu. Rev. Biochem*. 87:In press. **https://doi.org/10.1146/annurev-biochem-062917-011852**

ARTICLE IN A JOURNAL WITH AN ERRATUM

Wilson P. 2001. Title of article. *J. Mol. Biol.* 229:1175–83. Erratum. 2001. *J. Mol. Biol.* 238:639

BOOK REFERENCE: WHOLE BOOK CITED

Seaver W. 1995. *Luck's Lady: The Theory of Probability*. Garden City, NY: Doubleday

Bronson D, Gerber RA, eds. 2003. *Handbook of Biochemistry*, Vols. 1, 2. San Francisco: Freeman. 2nd ed.

Lerner RM, ed. 2003. *Handbook of Child Psychology*, Vol. 1: *Theoretical Models of Human Development*. New York: Wiley

BOOK REFERENCE: INDIVIDUAL CHAPTER CITED

Bornstein L. 2002. Recombination in bacteria. In *Human Genetics*, Vol. 1, ed. R Johnston, E Smith, pp. 65-73. London/New York: Macmillan

New MI, Schram P. 2000. Congenital adrenal hyperplasia. In *Current Diagnosis*, ed. RB Conn, WZ Borer, JW Snyder, pp. 50–75. Philadelphia: Saunders

BULLETIN

Price GK, Lin W, Falck-Zepeda J. 2003. *Distribution of market benefits from adopting biotech crops*. Tech. Bull. 1906, US Dep. Agric., Washington, DC

DATABASE

Natl. Cancer Inst. 2012. *Adult primary liver cancer treatment*. PDQ: NCI's Comprehensive Cancer Database, Bethesda, MD, updated Feb. 23. **http://cancer.gov/cancertopics/pdq/treatment/adult-primary-liver/HealthProfessional**

World Bank. 2012. *Little Green Data Book*. Washington, DC: World Bank. **https://openknowledge.worldbank.org/handle/10986/12266**

MAGAZINE/NEWSPAPER/RADIO ARTICLE

Jones A. 2004. Title of article. *New York Times*, Jan. 15, p. A6

Ledge J. 1999. Spanish Signs. Atlanta, GA, *WABE Radio Broadcast*, March 15

[do not repeat year if year is the same]

NO AUTHOR ASCERTAINABLE

Begin reference with name of editor, compiler, or sponsoring body, if known. Otherwise begin with title of article, chapter, journal, or book, followed by year. Do not use "anonymous."

PAGE SPAN WITH LETTERS

11:W50–55

11:125S–28S

PAPER PRESENTED AT A MEETING OR CONFERENCE

Andrade RG. 1990. *Culture shared and unique*. Paper presented at the 69th Annual Meeting of the American Anthropological Association, San Diego

PATENT

Crane P, Lackmeyer G, Longyear J, Melconian A, Steward D. 2006. *Electronically scanning direction finding antenna system*. US Patent 6,987,489

PREPRINT AND WORKING PAPER

Chiang E, Laughlin G. 2012. The minimum-mass extrasolar nebula. arXiv:1211.1673 [astro-ph.EP]

Pasaniuc B, Price AL. 2016. Dissecting the genetics of complex traits using summary association statistics. bioRxiv 072934. https://doi.org/10.1101/072934

Chase-Dunn C. 2016. *Social movements and collective behavior in premodern polities*. Work. Pap. 110, Inst. Res. World Syst., Univ. Calif., Riverside. **http://irows.ucr.edu/papers/irows110/irows110.htm**

PROCEEDINGS

Diftler MA, Mehling JS, Abdallah ME, Radford NA, Bridgwater LB, et al. 2011. Robonaut 2—the first humanoid robot in space. In *2011 IEEE International Conference on Robotics and Automation*, pp. 2178–83. New York: IEEE

Holder J. 2009. Galactic binary systems. *Proceedings of the 2009 Fermi Symposium, Washington, DC, Nov. 2–5*, eConf C091122. **http://www.slac.stanford.edu/econf/C0911022**

REPORT

New RL, Oldur S. 2001. *Propulsion jet streams*. NASA Tech. Rep. 32-1529, Jet Propuls. Lab., Pasadena, CA

SUPPLEMENT

If suppl. is part of journal title:

Martin RN, Barrett AH. 2001. *Ap. J. Suppl.* 36:1-51

If suppl. is not part of journal title:

Taylor CA. 1995. *J. Microbiol.* 11(Suppl. 2):5–10

THESIS OR DISSERTATION

Cafiso DS. 1997. *Electrical and ion selective properties of photoreceptor membranes.* PhD Thesis, Univ. Calif., Berkeley

[include thesis or dissertation title in journals that do not ask for article titles]

TRANSLATION

Aachen BL. 1937. *Basis of Society.* Transl. R Jones, 1958, in *Am. J. Sociol.* 23:18-57 (From German)

UNPUBLISHED INFORMATION

Refer to such data in the text as personal communication, submitted, unpublished data, etc., listing all researchers by initials and surname (e.g., W.C. Houser, U.M. Bandlier & C.F. Kim, unpublished data). Except for *Economics*, *Financial Economics*, *Physical Chemistry*, and *Resource Economics*, do NOT list these references in the Literature Cited section. Citations of unpublished works are not permitted in *Entomology*.

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REPEATED REFERENCES

If different sections of the same book, symposium, etc. are cited in separate references, give full information once, with the reference listed under the editor's name. Include title of chapter in each reference.

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Do not use "Ibid." Instead, repeat the name of the author each time.

APPENDIX B: STANDARD ABBREVIATIONS AND UNITS

Symbols and abbreviations on this list, as well as all SI base and derived units and prefixes, may be used in your manuscript without explanation.

acceleration of gravity	g
acquired immune deficiency syndrome	AIDS
alternating current	ac
angstrom	Å
ante meridiem	AM
approximately	~
approximately equal	≈
aqueous	aq
arbitrary unit	a.u.
astronomical unit	AU
atmosphere	atm
atomic mass unit	amu
atomic unit	au
atomic weight	at wt
bar	spell out
barn	b
British thermal unit	Btu
calorie (heat calorie)	cal
centimeter-gram-second	cgs
compare	cf.
cosecant	csc
cosine	cos
cotangent	cot
counts per minute	cpm
curie	Ci
curl	spell out
cycles per second	Hz
daltons	Da
day	spell out
decibel	B
degree	°
degrees Celsius	°C
degrees Fahrenheit	°F
deuteron	d
dextro	D
diffusion coefficient	D
direct current	dc
dyne	dyn
electromagnetic unit	emu
electromotive force	emf
electron	e
electron spin resonance	ESR
electron volt	eV
electrostatic units	esu
enthalpy change	ΔH
entropy change	ΔS
entropy unit	eu

equilibrium constant	K
equivalent	eq
erg	spell out
et alii (and others)	et al.
et cetera	etc.
exempli gratia (for example)	e.g.
exponential	exp.
figure	spell out
foot	ft
foot candle	fc
gauss	G
Gibbs energy change	ΔG (not ΔF)
giga-	G-
gram calories	gcal
gravitational constant	G
gravity, centrifugal	g
hour	h
human immunodeficiency virus	HIV
hydrogen ion (concentration)	pH
id est (that is)	i.e.
inch	spell out
infective dose	ID_{50}
infrared	IR
international unit	IU
kilo-	k-
kilobase, kilobase pair	kb
kilocycle	kc
kilowatt-hour	kWh
lethal dose	LD_{50}
levo	L
liter	L
logarithm	log
logarithm, natural	ln
magnitude	mag
maximum	max
mega-	M-
metric ton (tonne)	t
Michaelis constant	K_m
micro	µ-
microgram	µg (not λ)
micrometer (not micron)	µm
millibar	mbar
milliequivalent	meq
milliliter	mL
millimeters of mercury	mm Hg
million years ago, mega annum	Mya, Ma

minute	min
minutes of arc	arcmin
molar (concentration)	M (not μmol/mL)
mole	mol (not M)
molecular weight	M_r or mol wt
month	spell out
neutron	n
normal (concentration)	N
oersted	Oe
page, pages	p., pp.
parsec	pc
parts per million	ppm
percent	%
post meridiem	PM
potential difference	PD
probable error	pe
proton	p
radiation, ionizing, absorbed dose	rad
radiofrequency	RF
retardation factor	R_F
revolutions per minute	rpm
roentgen	r
root mean square	rms
second	s
seconds of arc	arcsec
sedimentation coefficient	*s*
solar mass	$M_\odot$
species	sp., spp.
Specific rotation	α
square centimeter	cm^2
Svedberg (10^{-13} s)	S
standard deviation	SD
standard error	SE
tangent	tan
tera-	T-
tesla	T
three-dimensional	3D
ton	spell out
tonne (metric ton)	t
torr	torr (not Torr)
two-dimensional	2D
ultrahigh frequency	UHF
ultraviolet	UV
universal gravitational constant	*G*
universal time	UT
variant	r.
versus	spell out
weight concentration	g/mL (not mg%)
weight percent	wt%
week	spell out
year	spell out