A Primary (Sourced) Education

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I remember the first class where a professor said, while reviewing his syllabus, 'My primary goal for this class is for you to be able to read a scientific article.' Sitting in the classroom that day, I thought to myself, this is the dividing point. *Aha! I've just been learning well-worn biochemical pathways and never getting into any new material, but from now on, things are going to be different*! But things weren't different, because we still learned from the book and whenever I tried reading the literature, it was hopeless. I had several more classes that boldly stated the same goal only to result in the same outcome: disappointment and hopelessness.

Nevertheless, reading primary scientific journal articles is *the critical divide* when students become scientists; however, even when stated as a goal for a course, it is seldom explicitly taught.

This article provides a comprehensive review of one approach aimed at teaching undergraduate biotechnology students to effectively read primary articles. It further identifies common challenges faced by instructors and their students in obtaining and reading articles, including locating relevant articles, understanding technical terminology, comprehending complex methods, and navigating dense writing styles. Here, we outline an instructional strategy, which incorporates explicit instruction, modeling, and scaffolded support. We discuss potential pitfalls and evaluate the overall effectiveness of the approach. And finally, we present a curated list of articles used in the most recent iteration of our 'Topics in Biotechnology' class, serving as a resource for instructors interested in implementing a journal club class as part of an undergraduate program.

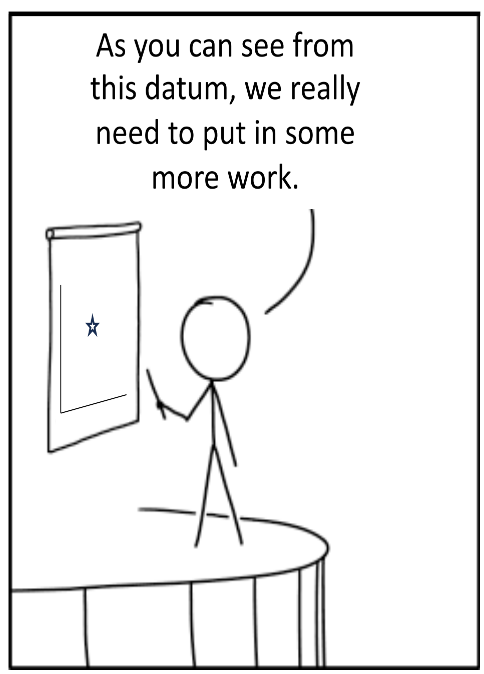
Scientific research plays a crucial role in advancing knowledge across all fields. Many journals still have titles referring to their origins, such as FEBS *Letters,* which evokes a time when scientists around the globe updated one another on their work by literally writing letters to one another.

Today, journal articles are fundamental to the research process, enabling scientists to stay informed about the latest discoveries, methodologies, and theories in their respective fields. Unfortunately, the explicit teaching of this skill is often non-existent in scientific training programs. This knowledge gap can pose challenges for young scientists, hindering their ability to keep up with advanced studies, stay updated on the latest research, and remain informed about developments in their field. It also leaves students ignorant of the rigor required to present their own work.

This article presents a review of one approach to teaching novice scientists to effectively read journal articles. It is worth noting that even experienced scientists, such as the instructors who teach these courses, had to learn this skill at one point in their careers. It is useful to adopt the beginner's mind in determining how to teach this skill.

One central challenge encountered by all scientists, students, and educators outside of the world's largest institutions, is *access*. Access to the full text of articles, including figures is essential to understanding and being able to reproduce data. In the absence of full text, following the development of ideas and locating important references is nearly impossible. The significance of searchable databases like the National Library of Medicine's PubMed notwithstanding, only full text can contextualize references fully. Fortunately, at least for research funded publicly by the US government, new rules are opening up access to articles.[1–3]

Once a major stumbling block, the availability of online search engines and reference tools has relegated the



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terminology barrier to a mere speed bump. Nevertheless, the complexity of novel methodologies and the density of scientific writing pose ongoing difficulties for budding scientists encountering these terms and concepts for the first time. This is precisely why journal clubs play an indispensable role in overcoming the steep learning curve and fostering lifelong learning environments. The need for hands-on, instructor engagement cannot be overstated.

Challenges in Identifying and Obtaining Articles

Scientists face numerous challenges when reading scientific articles. But before beginning, it is necessary to address two initial challenges, the first being students identifying and locating articles and the second, particularly important to smaller institutions wishing to implement this course, is full access to the articles themselves.

Identifying and locating articles is typically done using PubMed (**Figure 1**), a free, publicly maintained search engine available to anyone with an internet connection.

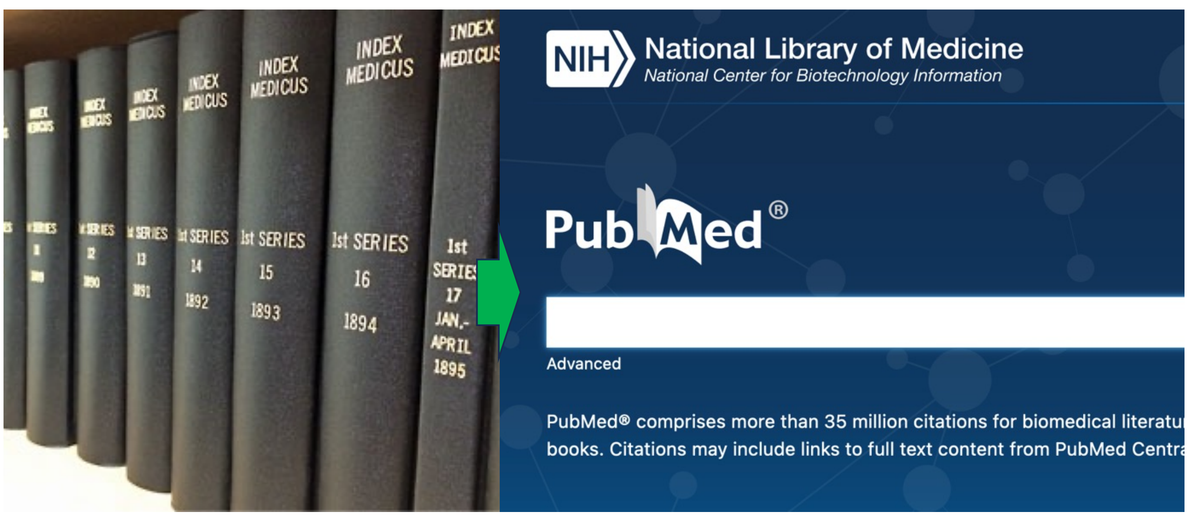

Figure 1 | From Index Medicus to Pubmed. http://pubmed.ncbi.nlm.nih.gov

Beginning in 1879, The National Library of Medicine has published the Index Medicus as a monthly guide to medical articles in thousands of journals. This was initially only available *in print* as an array of tomes housed in subscribing libraries (also **Figure 1**). This eventually became digitally organized as the Medical Literature Analysis and Retrieval System (MEDLARS).[4] MEDLARS became publicly available in 1964, however in the absence of the internet, it was housed in the National Library of Medicine and only locally accessible. In 1971, the system first supported off-site access at medical libraries and was given the name 'MEDLARS Online' or 'MEDLINE' and could only be accessed indirectly through librarians using pre-programmed searches in order to not overwhelm the system, which was capable of supporting up to 25 simultaneous users.[5] In 1996, as home computers were becoming capable of interacting with the internet via web browsers, the system was publicly launched online as PubMed, which contains the entire Indicus Medicus, as well as referencing additional databases. The search engine of PubMed only addresses the 'identification' problem but does not provide access to the articles beyond abstract viewing. The papers themselves often lie behind paywalls making regular access virtually impossible to any but large, research institutions. In August of 2022, the United States White House Office of Science and Technology Policy updated a 2013 memorandum that increased free access to publications of research resulting from the expenditure of public funds. The 2008 public policy had allowed for a 12-month embargo from public access, while the 2022 action moved "[t]o promote equity and advance the work of restoring the public's trust in Government science, and to advance American scientific leadership[by] amend[ing] federal policy to deliver immediate public access to federally funded research."[1,6,7] The goal for full, free access to all publicly-funded research immediately following publication is expected to be fully realized by 2025.[2]

In the meantime, older publications are increasingly becoming available through Google Scholar or are often obtained via legally questionable sources such as ResearchGate. In the absence of any other means, another method is to directly contact the corresponding author and simply ask for a copy of the article.

Explicit Instruction & Modeling

Our 'Selected Topics in Biotechnology,' encourages collaboration between first-and second-year students (Juniors and Seniors, respectively). The experience of second-year students, combined with instructor-led sessions, guides first-year students through the reading process. These sessions involve detailed explanations of figures, experimental procedures, and results. Reading and comprehending articles prior to working with students can aid instructors in effectively guiding discussions. However, it is also useful to not thoroughly digest every detail prior to group meetings in order to model information processing in front of the group. This approach allows students to witness and take part in, the collective effort required to understand scientific concepts, explore references, critically analyze experiments, and question potentially ambiguous results or misleading interpretations.

While the instructor initially plays a significant role in interpreting the paper, it is important for undergraduate students to navigate the article independently to build their own understanding. As part of this process, student groups are encouraged to explore and explain new techniques within the context of their presentations to the class.

A method of scaffolded assistance is employed to prevent students from simply relying on the professor to do the intellectual work for them. This involves providing students with temporary support aimed at transferring responsibility to students as they as they gain proficiency.[8] This can involve providing students with a cartoon summary of the system, asking students to fill in the elements they understand, sketching cell-cell interactions with relevant receptors engaged, outlining the logical series of experiments performed, forming a list of key terms, and asking students to connect the main ideas in the article. With each interaction with students, scaffolding should be reduced as students take on more of these tasks themselves.

Explicit instruction is an instructional approach that is characterized by clear and direct teaching methods, including the use of modeling, coaching and guided practice. This can involve modeling how to read the abstract, introduction, methods, results, and discussion sections of scientific articles for students by verbally walking through the process with a small group. Although there are numerous ways to approach a primary research publication, the method employed in our course is very hands-on.

The course is structured in a way that establishes groups of students (preferably randomly or semi-randomly) that include one or more first-year students and one or more second year students (the program spans the junior and senior year of students' undergraduate term). Because we require students to take this course twice, second-year students have experience from their previous year and help guide first-years through the process. Each year, I as the instructor, present the first article as one-part presentation instruction and one-part model presentation. Students are provided with a template for a presentation and encouraged to use it, while I present both the content of the article and commentary on why I'm presenting the way that I am. It's important to keep this article short and simple because I also go over the syllabus and course requirements during the same one-hour class time.

In preparation for subsequent presentations, each group is required to schedule at least one meeting of about two hours with the instructor prior to presenting to the class. Although initially established as Q&A sessions to clarify any issues with complicated figures or interpretations, over the years, these quickly transformed into a figure-by-figure explanations of how each experiment was done and what the results revealed. If extra time is needed, these meetings are repeated until the entire paper is covered.

This models an approach to reading the articles by explaining the structure of a scientific article, identifying key concepts, and highlighting the use of technical terminology. Breaking down an article with students presents examples of effective reading strategies through involving them with the instructor's thinking. It is helpful to read through and understand an article before approaching it with students, but I often do not examine the details prior to my meeting so I can organically process the information in front of the group. Benefits to this may include, allowing students to see that everyone must work to understand the science, to demonstrate how to follow references while working out the problem, to openly inquire about the purpose of each experiment within a paper, and to question results that may be ambiguous or interpretations that are misleading.

Although the instructor does much of the initial work of interpreting the paper, at the undergraduate level, it is entirely appropriate as students will need to re-navigate the paper in building their presentation in a way that they can later explain to the rest of the class. As part of the process, groups are additionally asked to investigate new techniques when they occur and explain them to the class within the context of their presentations.

Even with this level of modeling and explicit instruction, students invariably find the workload to be heavy and intellectually rigorous.

Conclusion

With this course, I too boldly state that the objective of the course is to equip students with the skills to read journal articles. Hopefully, this course comes closer to meeting that goal than the legion of courses I heard that goal announced in.

Out of all the classes I teach, none has received as much positive feedback from students as my 'Topics' class. Many students have returned with comments such as, "This was the class that transformed me into a scientist" or "This was the first class that actually helped me comprehend the process of scientific inquiry." While it is important to remember that anecdotes do not constitute solid evidence, these are the responses that motivate me to continue teaching this course year after year, firmly believing that it genuinely makes a meaningful impact.

Reading List – Immune Evasion

Pages 13 and 14 contain the list of articles used in the most recent iteration of our course. This is the same course that established the background knowledge students had prior to selecting recent articles on immune evasion to base their review articles from the preceding section of this journal. The bold articles were assigned for presentation, while other articles were optional, supportive readings. When more than one paper within a topic is presented, "(class #)" is used to distinguish which paper was presented in each class. These were presented by different groups of students.

Future volumes of this journal will include the reading lists for this class (without an accompanying article). I encourage other educators to take and use these lists, in whole, or in part, in your own courses.

References

The comic at the beginning of this article was adapted from xkcd (https://xkcd.com/2797) under an CC BY-NC 2.5 license. Text and data table were altered.

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Selected Topics

Immune Evasion by Microbial Pathogens Reading List

1. <u>Review of Immune Evasion/MHC Presentation</u>
    a. **Ahn, K. et al. Human cytomegalovirus inhibits antigen presentation by a sequential multistep process. Proceedings of the National Academy of Sciences 93, 10990–10995 (1996).**
    b. Finlay, B. B. & McFadden, G. Anti-Immunology: Evasion of the Host Immune System by Bacterial and Viral Pathogens. Cell 124, 767–782 (2006).
    c. Ploegh, H. L. Viral Strategies of Immune Evasion. Science 280, 248–253 (1998).

2. <u>Antimicrobial peptides: Innate immunity effectors</u>
    a. **Legarda, D., Klein-Patel, M. E., Yim, S., Yuk, M. H., and Diamond, G. "Suppression of NF-kappa B-mediated Beta-defensin Gene Expression in the Mammalian Airway by the Bordetella Type III Secretion System." Cellular Microbiology 7 (2005): 489-497.**

3. <u>Toll Like Receptors</u>
    a. **Li, K. et al. Immune evasion by hepatitis C virus NS3/4A protease-mediated cleavage of the Toll-like receptor 3 adaptor protein TRIF. Proceedings of the National Academy of Sciences 102, 2992–2997 (2005). (class 1)**
    b. **Meylan, E., Curran, J., Hofmann, K. et al. Cardif is an adaptor protein in the RIG-I antiviral pathway and is targeted by hepatitis C virus. Nature 437, 1167–1172 (2005). https://doi.org/10.1038/nature 04193. (class 2)**
    c. Tan, Y., Zanoni, I., Cullen, T. W., Goodman, A. L. & Kagan, J. C. Mechanisms of Toll-like Receptor 4 Endocytosis Reveal a Common Immune-Evasion Strategy Used by Pathogenic and Commensal Bacteria. Immunity 43, 909–922 (2015).

4. <u>TAP</u>
    a. **Tan, Y., Zanoni, I., Cullen, T. W., Goodman, A. L. & Kagan, J. C. Mechanisms of Toll-like Receptor 4 Endocytosis Reveal a Common Immune-Evasion Strategy Used by Pathogenic and Commensal Bacteria. Immunity 43, 909–922 (2015).**
    b. van de Weijer, M. L., Luteijn, R. D. & Wiertz, E. J. H. J. Viral immune evasion: Lessons in MHC class I antigen presentation. Seminars in Immunology 27, 125–137 (2015).

5. <u>MHC Class I Antigen Presentation</u>
    a. **Wiertz, E., Jones, T. R., Sun, L., Bogyo, M., Geuze, H. J., and Ploegh, H. L. "The Human Cytomegalovirus US11 Gene Product Dislocates MHC Class I Heavy Chains from the Endoplasmic Reticulum to the Cytosol." Cell 84 (1996): 769-779. (class 1)**
    b. Ye, Y. H., Shibata, Y., Yun, C., Ron, D., and Rapoport, T. A. "A Membrane Protein Complex Mediates Retro-translocation from the ER Lumen into the Cytosol." Nature 429 (2004): 841-847.
    c. **Neumann, L., Kraas, W., Uebel, S., Jung, G., and Tampe, R. "The Active Domain of the Herpes Simplex Virus Protein ICP47: A Potent Inhibitor of the Transporter Associated with Antigen Processing (TAP)." Journal of Molecular Biology 272 (1997): 484-492. (class 2)**

6. MHC Class II antigen presentation

a. **Pancio, H. A., Vander Heyden, N., Kosuri, K., Cresswell, P., and Ratner, L. “Interaction of Human Immunodeficiency Virus Type 2 Vpx and Invariant Chain.” Journal of Virology 74 (2000): 6168-6172. (class 1)**

b. Zuo J, Rowe M. Herpesviruses placating the unwilling host: manipulation of the MHC class II antigen presentation pathway. Viruses. 2012 Aug;4(8):1335-53. doi: 10.3390/v4081335. Epub 2012Aug 22. PMID: 23012630; PMCID: PMC3446767

c. **Stumptner-Cuvelette P, Morchoisne S, Dugast M, Le Gall S, Raposo G, Schwartz O, Benaroch P. HIV- 1 Nef impairs MHC class II antigen presentation and surface expression. Proc Natl Acad Sci U S A. 2001 Oct 9;98(21):12144-9. (class 2)**

7. The Proteasome and ubiquitin

a. Zhou, H. L., Monack, U. M., Kayagaki, N., Wertz, I., Yin, J. P., Wolf, B., and Dixit, V. M. “Yersinia Virulence Factor YopJ acts as a Deubiquitinase to Inhibit NF-kappa B Activation.” Journal of Experimental Medicine 202 (2005): 1327-1332.

8. Programmed cell death

a. **Everett, H., Barry, M., Lee, S. F., Sun, X. J., Graham, K., Stone, J., Bleackley, R. C., and McFadden, G.“M11L: A Novel Mitochondria-localized Protein of Myxoma Virus that Blocks Apoptosis of Infected Leukocytes.” Journal of Experimental Medicine 191 (2000): 1487-1498. (class 1)**

b. **Henderson, S., Rowe, M., Gregory, C., Croomcarter, D., Wang, F., Longnecker, R., Kieff, E., and Rickinson, A. " Induction of Bcl-2 Expression by Epstein-Barr-Virus Latent Membrane Protein-1 Protects Infected B-cells from Programmed Cell-death." Cell 65 (1991): 1107-1115. (class 2)**

9. Molecular Mimicry

a. **Reyburn, H. T., Mandelboim, O., ValesGomez, M., Davis, D. M., Pazmany, L., and Strominger, J. L. “The Class I MHC Homologue of Human Cytomegalovirus inhibits attack by Natural Killer Cells.” Nature 386 (1997): 514-517.**

10. Cytokines

a. **Kledal, T. N., Rosenkilde, M. M., Coulin, F., Simmons, G., Johnsen, A. H., Alouani, S., Power, C. A., Luttichau, H. R., Gerstoft, J., Clapham, P. R., ClarkLewis, I., Wells, T. N. C., and Schwartz, T. W. “A Broad-spectrum Chemokine Antagonist Encoded by Kaposi’s Sarcoma-associated Herpesvirus.” Science 277 (1997): 1656-1659.**