Teaching Guide

Overview

This teaching guide will cover ways to include Sinclair Lewis' Pulitzer Prize winning novel on phage and biomedical research *Arrowsmith. Arrowsmith* traces the career arc of physician-scientist Dr. Martin Arrowsmith as he moves from small town doctor to a leading researcher at a large biomedical research institute. Through select chapter readings, the reader (students!) follow along as Dr. Arrowsmith discovers bacteriophages, then uses them in a phage therapy trial during a plague outbreak on the fictitious island of St. Hubert's. Even though the novel was written around 100 years ago, students will find much in the novel familiar to their journey through Bacteriophage Discovery and Genomics. However, there are also some striking differences and limitations that make for interesting discussion topics. The central tension of the book involves the phage therapy study design and whether to use a control group during an outbreak of plague. This provides many opportunities to relate the events of the book with current issues in the COVID-19 pandemic and other recent disease outbreaks. There also are oppotunities to discuss the impacts of gender discrimination on scientific research and medical colonialism. As an extra activity, students may read an actual research article published close to the time the novel was written to allow additional topics of discussion and comparison.

Background information

Sinclair Lewis, who was born in 1885, rose to prominence with the publication of *Main Street* in 1920. His experience growing up in Sauk Centre, Minnesota enabled him to portray in this novel the unpleasant side of small towns instead of idealizing life in such places, as had been the tendency in American fiction. Lewis then produced four other highly-regarded, best-selling novels during the 1920s: *Babbitt* in 1922, a satire on the American small businessman; *Arrowsmith* in 1925; *Elmer Gantry* in 1927, an exposé of charlatan preachers; and *Dodsworth* in 1929, a story about the failure of a marriage. The decade was crowned in 1930 by the Nobel Prize for Literature, making Lewis the first American writer ever to win this award. Although he published several novels before *Main Stree*t and many after 1930, the 1920s were the time of his greatest critical success.

Lewis got the idea for *Arrowsmith* during summer 1922 after finishing Babbitt. Hoping to write a novel about labor, he went to Chicago to visit Eugene Debs, the famous American union organizer and socialist. While in the city, Lewis paid a visit to Dr. Morris Fishbein, an editor of the *Journal of the American Medical Association*, which kept files on patent medicines and quackery. Conversation led to the idea of a novel on the American medical world. Fishbein even had an acquaintance at hand, Paul de Kruif, who could serve as a resource. De Kruif had a PhD in bacteriology from the University of Michigan and had done research at the Rockefeller Institute. Once the idea arose, Lewis could see how to write a novel on medicine more readily than one on labor. He already had more of a connection to doctors than workers. His father in

Sauk Centre, MN was a general practitioner, and his older brother Claude was a surgeon in St. Cloud, MN.

De Kruif, who wanted to be a writer of popular science and who went on to publish the best-selling non-fiction book *Microbe Hunters* in 1926, was more than willing to accompany the successful novelist on a fact-finding trip and along the way fill in what Lewis did not know about medical research. They took ship for the Caribbean, where they visited several islands, then headed to England. When Lewis had a draft of the novel completed, de Kruif read it and provided detailed advice about what to cut or emphasize.

The impact of *Arrowsmith* since then has mainly been in serving as a focal point for discussion about problems in the world of medicine. These problems, very clear in the 1925 book, have resisted resolution. They include the way temptations of wealth and prestige can corrupt health care, the way society resists good medical advice (for the sake of convenience or economic interest or simply because of ignorance), and the way the demands of clinical practice may conflict with the demands of scientific research. The novel could give focus to these issues for decades after 1925 because it was such a hit. It won the Pulitzer Prize, which Lewis turned down, and it was made into a movie in 1931 with Hollywood stars Ronald Colman and Helen Hayes. In 1944, a poll of contributors to the Saturday Review of Literature chose *Arrowsmith* as the best novel of the previous twenty years—better than books by Hemingway, Faulkner, or Willa Cather. It was so prominent that, together with de Kruif's *Microbe Hunters*, it inspired many young people to pursue careers in medical research. It has been heralded as the first novel in America to feature a medical researcher as a protagonist, not just a doctor but a scientist, and it compellingly dramatizes in its climax the scientific and ethical problems associated with finding a cure for an epidemic in progress. Since about 1970, the book has not had the same prominence. However, readers notice its continuing relevance, especially during epidemics such as the present one with Covid-19. Dr. Arrowsmith's struggle with plague on the island of St. Hubert in the novel still seems sadly similar to the struggles of public health officials in real life.

Reading of this classic work of fiction is combined with a scientific research article describing phage discovery at a similar time. The bacterial host in the article is Bacillus anthracis, an organism also encountered in Arrowsmith during mentor Max Gottlieb's bacteriology course, for which Martin Arrowsmith serves as a teaching assistant.

Outcomes

After completing the related activities and assignments, students should be able to:

- Recognize the timelessness and power of basic microbiology techniques
- Understand the limitations of microbiology field at the time of original phage discovery
- Evaluate the ethical considerations when conducting medical trials, particularly the use of control groups during an epidemic
- Evaluate the potential of prophylactic phage therapy

Timeline

It should be noted that students do not need to read the entire book to meet the outcomes of the unit. In fact, readings of around 30 and 60 pages are the minimum needed. Students may be encouraged to read the entire novel, but it is not necessary. There are certainly additional relevant chapters to read and you may choose to read the entire book throughout the semester. Further areas to explore are Dr. Arrowsmith's motivations for pursuing research over a career of private practice, the role of research in society, and the importance of collaboration in research. You may consider having students write regular reflections on the novel that connect back to class.

Completion of all activities provided in this module requires 4-6 weeks in total time, but only 2-3 dedicated one hour class sessions. It is certainly possible to perform only some of the provided activities. An example timeline is provided below:

Week	**Activity**
1	Introduce novel to class, provide *Arrowsmith* Assignment #1
2	Discuss *Arrowsmith* Assignment 1 in class, provide 1931 *Bacillus anthracis* phage discovery paper and question set
3	Discuss 1931 Bacillus anthracis phage discovery paper, provide Arrowsmith Assignment #2
4	Students read assigned chapters for Assignment #2
5	Discuss Assignment #2 in class

These activities can be appropriately incorporated into either Bacteriophage Discovery or Bacteriophage Genomics. The advantage of including this unit during Bacteriophage Discovery is the close alignment of experimental activities in class with those in the novel. The advantage of including this unit during Bacteriophage Genomics is it gives a nice break from the computer work and provides a unique way to appreciate the vast improvement in the pace of scientific discovery in the past century.

Overview of assignments and slides and how to use them

There are three distinct activities and related assignments in this unit. The assignments are flexible and may be altered to meet the needs of the instructor. The included assignments are:

-***Arrowsmith* Assignment #1** (questions and discussion related to Dr. Arrowsmith's phage discovery)

-***Arrowsmith* Assignment #2** (questions and discussion related to ethics and biology of Dr. Arrowsmith's phage therapy trial)

-**1931 *Bacillus anthracis* phage discovery article assignment** (questions and discussion comparing events in research article and *Arrowsmith; serves as a companion to Arrowsmith Assignment #1)*

Each assignment has an associated slide deck. Most slides have additional instructor notes that add context and supplementary information that helps facilitate classroom presentation and discussion. Below you will find the *Arrowsmith* assignment questions and the Journal Club question set along with some possible responses and citations for further discussion in red.

***Arrowsmith* Assignment #1**

Note: These questions help initiate discussion regarding the similarities and accuracy of the microbiology displayed in Arrowsmith. They can serve as a springboard to the 1931 *Bacillus anthracis* phage discovery article assignment

1) Identify and describe 3 aspects or findings of Dr. Arrowsmith's work that are accurate or familiar today.

See slides for additional details. Students may identify some of the following

- media preparation (details found in chapters not found in assigned chapters, but presented in the slides)
- importance of lab notebook maintenance (details not found in assigned chapters, but presented in slides)
- very similar techniques in isolation, propagation and characteristics of bacteriophages
- Struggles and joys of lab work

2) How were the microbiology practices portrayed in the book different from modern procedures?

See slides for additional details. Students may identify some of the following:

- No regard for personal protective equipment
- Smoking?!
- All glass and metal materials (no plastic)
- Lack of female representation in research

3) What limitations did microbiologists have at this time? How was their progress held back? In other words, what did they not know?

See slides for additional details. Students may identify some of the following:

- Could not visualize the phage
- No sequencing or other molecular biology techniques. Written before DNA was identified as hereditary material

4) Find one unique finding, study, or biographical attribute of Felix d'Herelle.

Felix d'Herelle, one of the real-life discoverers of bacteriophages, is mentioned in the book. In response to this question, students may comment on:

- His lack of professional training
- Involvement of family in some of his research
- His association with early centers of phage therapy in Tiblisi, Georgia
- Important legacy in setting the stage for the molecular biology revolution

- Views on phage playing role in human immune system (oversold this idea, but has been vindicated somewhat with recent developments)

***Arrowsmith* Assignment #2**

1) Describe Dr. Arrowsmith's phage therapy trial. Do you think this is an ethical way to conduct a medical trial? Why or why not?

See slides for additional details. Students may identify some of the following:

- It appears that Dr. Arrowsmith will administer his phage prophylactically, more like a vaccine
- There will be two experimental groups, the study group which receives the phage and a control group which does not receive the phage

2) Why was Dr. Arrowsmith reluctant to change his study design?

Students may identify some of the following:

- After the death of a member of the medical team, Dr. Arrowsmith eliminates the control group and instead provides the phage injections to everyone
- Eliminating the control group will invalidate the study results

3) What are modern medical professional/bioethicist opinions on the use of controls drug/vaccine trials in human populations?

See slides for additional details. Students may identify some of the following:

- Control group should still receive the "standard of care."
- Concept of "clinical equipoise:" is there genuine uncertainty whether or not experimental drug or vaccine will work?
- See:
  - **BMJ 2017;359:j5787 and Science 17 Oct 2014: Vol. 346, Issue 6207, pp. 289-290**
  - **Science 17 Oct 2014: Vol. 346, Issue 6207, pp. 289-290**

4) How are vaccine trials being conducted in the COVID-19 outbreak? Are/should control groups offered the vaccine immediately once a vaccine has proven efficacy?

Students may identify some of the following:

- Double blind, placebo controlled
- Control group often delayed in receiving the vaccine to follow longer term outcomes
- See:
  - N Engl J Med 2020; 383:2603-2615 December 31, 2020 DOI: 10.1056/NEJMoa2034577

5) How were vaccine trials conducted in the 2014 Ebola epidemic?

- Modified control groups
- Ring vaccination/delayed vaccination study design
- See:
  - Lancet Volume 389, No. 10068, p505–518, 4 February 2017
  - Lancet Volume 389, No. 10069, p621–628, 11 February 2017

- WHO 21 May 2018 News Release: WHO supports Ebola vaccination of high risk populations in the Democratic Republic of the Congo

6) Would the prophylactic (preventative) use of phage work to prevent bacterial infections? Use literature to support your stance.

See slides for additional details and references below:

- Front Microbiol. 2016; 7: 1253
- Nature Communications volume 8, Article number: 14187 (2017)
- BMC Microbiol. 2009; 9: 169.
- Can J Infect Dis Med Microbiol. 2007 Jan; 18(1): 19-26
- Intralytix.com

7) Were Dr. Arrowsmith's data from his phage therapy trial published in an ethical way? Why or why not? Was his trial still valuable? What would be a more forthcoming way of presenting his results?

Students may identify some of the following:

- Pressure to publish despite compromised trial design
- Not forthcoming with trial limitations

8) How are female characters portrayed in the novel? What is the current landscape of the intersection of gender and biomedical research compared to that portrayed in Arrowsmith?

Students may identify some of the following:

- There are few female characters of consequence in the book, especially in biomedical research
- Leora receives the most attention and is portrayed relatively sympathetically, but are largely kept out of active research
- Though significant obstacles remain in many STEM fields, PhDs are now awarded to more females than males in biomedical field

9) How are the residents of St. Hubert's portrayed in the novel? Are they true partners in the phage therapy trial? Do you think this is an example of medical colonialism?

Students may identify some of the following:

- Although the most competent physician/scientist in the portrayed in the book is of African descent, there are echoes of colonial medicine in portrayal of outbreak response
- The reader learns little about what the recipients of the phage therapy think about the trial
- See:
  - The Lancet VOLUME 394, ISSUE 10203, P996, SEPTEMBER 21, 2019 Transcending the guilt of global health

Journal Club Question Set

A bacteriophage for *B. anthracis*
Philip B. Cowles
J Bacteriology
1931, p 161-166

1. Can you derive the 'lytic principle' of a bacteriophage? What does 'lytic principle' mean?
    - This is to connect an older vocabulary to students understanding.

2. You know how to find a phage by enrichment culture and direct plating. Read the methods in the article carefully and draw a flow-chart/picture of their phage hunting methods. (Hint: It starts with sewage, it ends with plaques. What's in the middle?) Bring your drawing to class and we will compare/contrast to our methods.
    - Students should understand their own phage discovery process and relate their methods to the article's older methods.
    - Instructor might remove the hint if your students have done this themselves.
    - Chamberland candle is mentioned in the paper, and students will need to look this up
    - Students will need to understand cc is ml

3. Lab math: Page 164 describes "Duplicate dilutions of organisms were made by adding 0.5cc of an eighteen-hour broth culture of *B. anthracis* to 4.5 cc of broth and making 0.5 cc. transfers through ten tubes. One-tenth cubic centimeter of potent bacteriophage was then added to each tube of one series, while the other series served as a control."
    a) What does this mean, what process is the author describing here?
        - Students should recognize serial dilution, in a different vocabulary compared to what they are used to hearing and reading.

    b) Can you draw it?
        - Drawing indicates level of understanding, and supports understanding of an experiment in the article.

Relating this article to the novel Arrowsmith, written by Sinclair Lewis

4. This article was written in 1931, and Sinclair Lewis published Arrowsmith in 1924.

    a) What was the status of microbiology/virology and phage therapy around this time?
        - Re-connect phage discovery and therapy from a work of fiction to historical context (support from slide 3) and the methods of a research article.
    b) Martin Arrowsmith's research mentor Max Gottlieb teaches a microbiology course where students work with *B. anthracis* spores and he infects a guinea pig during class to illustrate a fatality result. *B. anthracis* is now categorized as a Biosafety level 2/3 organism requiring containment. Were any microbiology practices portrayed well from the perspective of safety?
        - Relates the host bacteria from the research article to Arrowsmith (and to

question 2 of Arrowsmith Assignment #1).