Robert Koch & Tuberculosis

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Introduction

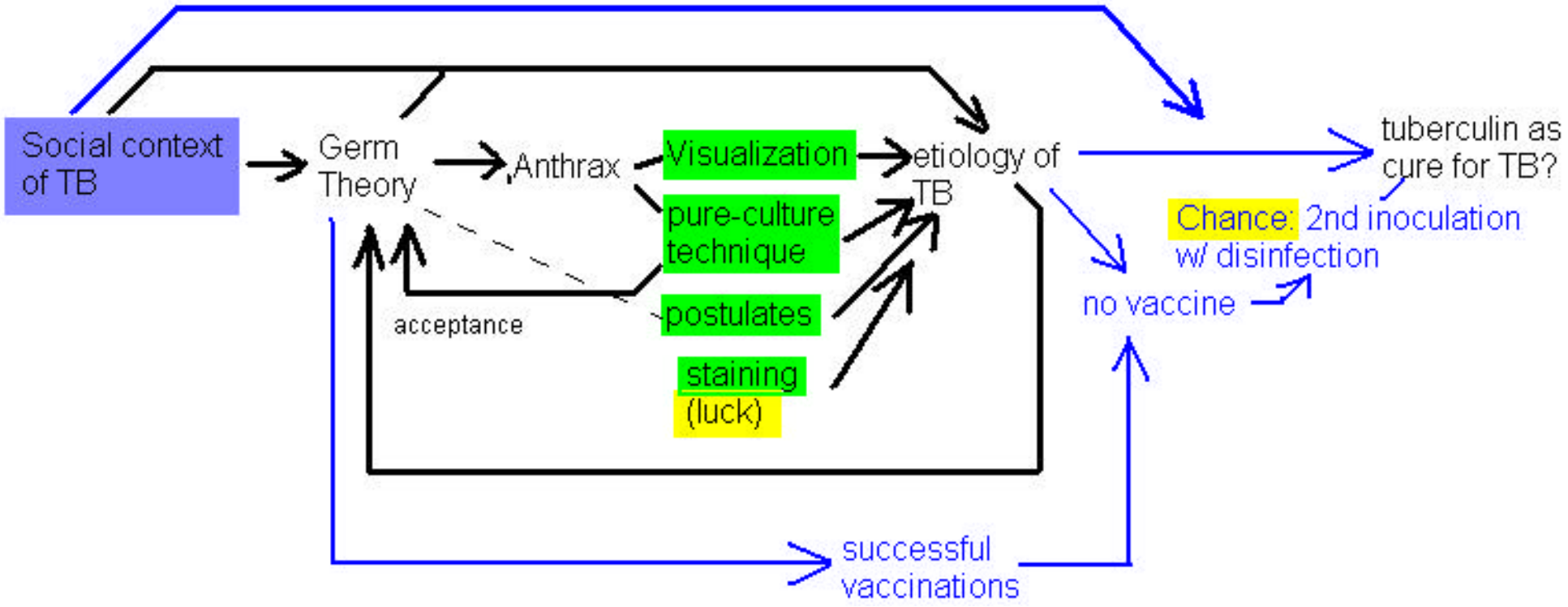
In today's world, it is taken for granted that bacteria often cause disease. This is why as children we are taught to wash our hands. Towards gaining a better understanding of how paradigms of science change, this module examines the origin of the idea of *germs as disease-causing agents*, focusing on Robert Koch's work on tuberculosis.

The module is set up as a discussion to engage a class. Students have an opportunity to see what factors contribute to paradigm change by thinking about how social factors, technical limits, access to resources, and even luck all shaped Koch's work on tuberculosis. The module highlights science as a problem-solving enterprise, rather than as a drab collection of data.

The techniques discussed and the reasoning behind their use are also featured in a parallel series of experimental exercises. The scenario presents a problem which can be solved through an inoculation, gram staining, and pure culture separation. As the narrative shapes the student's perception of science, this short experimental series should give a deeper understanding of *why* these techniques are used, not simply how.

The information is organized as:
I. a **Narrative**, in outline format
II. **Thematic Questions and Questions** for discussion, paralleling the narrative, and
III. a set of experimental **Exercsies**

See separate **Flowchart** of narrative.


Social context of TB
Germ Theory
Anthrax
Visualization
pure-culture technique
postulates
staining
(luck)
acceptance
etiology of TB
tuberculin as cure for TB?
Chance: 2nd inoculation w/ disinfection
no vaccine
successful vaccinations

Narrative

Social Context of Tuberculosis

1) Known as far back as 668-626 BCE
    a. Tablets showing symptoms on Assyrian tablet (TD 106)
2) Symptoms medically described by Hippocrates [470-375 BCE] (TD 106)
3) Mostly the poor were affected (TD 110-1)
    Jewish at times stigmatized with it (TD 111)
4) 1/7th of all deaths to 1/3rd of all adult deaths attributed to tuberculosis in 19th century (EK xv, EK 83, & BR 117)
5) Large cities tended to be worst affected
    a. 25% of New York and Boston's deaths in 1801 (TD 110-1)
6) Most morbid of all infectious diseases of the time (SO 151)
7) Different epidemiology than other diseases (SO 151)
    a. Most constant yearly death toll
    b. Highest death toll of all major diseases
8) Death of many famous people of the time
    a. Baruch Spinoza 1633-1677 (TD 108)
    b. Fyodor Dostoevsky 1821-1881 (TD 109)
    c. Sir Walter Scott 1771-1832 (TD 109)
    d. Edgar Alan Poe 1809-1849 (TD 109)
    e. Henry David Thoreau 1817-1862 (TD 109)

    Tuberculosis historical etiology
9) Hippocrates thought a cause of bad air [460-375 BCE] (TD 106)
10) Aristotle suggested a communicable contagion; "bad and heavy air" [384-322 BCE] (TD 106)
    a. Theory accepted by Romans: Galen [129-200 CE]
11) Franciscus Sylvius characterized the tubercles in 1650 (TD 107)
    a. To become diagnostic
12) Benjamin Martin hypothesized as a "breath contagion" in 1722 (TD 107)
13) Entry to the 19th century, pathology view predominated (TD 107)

    Conflicting Paradigms
14) Philosophical concept of organic entities of disease common in German schools (EK xi)
    a. Disease could live independently of diseased
15) Experimental pathology provided a researchable paradigm (EK xii)
    a. Drown out philosophical earlier view in academia
16) Focused on the changes in tissues that caused death (EK xii)
    a. Aspect that could be empirically studied
17) 1837 Jacob Henle proposes microorganisms could cause disease (EK x)

a. Muscardine disease in silkworms study of Agostino Bassi 1835-6 (EK x)

18) Pasteur's work on fermentation as caused by microorganisms (EK x)
    a. Fermentation seen as a similar process as the tissue decay in disease

19) Work on anthrax by Casmir Davaine and Friedrich August Brauell (EK x)
    a. Davaine identified microscopic rods as infectious in 1850
    b. Brauell used rod-free placental blood of infected animal as control inoculation

20) Pathologists, such as Rudolf Virchow, viewed germ theory as aged theory
    a. "Diseases have no independent or isolated existence…" –Virchow

21) Arguments against germ theory:
    a. One finds bacteria present as often as one does not when studying diseased (EK xii)
    b. Unusual and often contradictory epidemiologic predispositions (EK xii)
        i. Anthrax from:
            1. Weather?
            2. Soil?
            3. Bacteria blood?
            4. Non-bacteria blood?
    c. Bacteria only correlated with disease; no causality proved
        i. Disease could make tissue more habitable for bacteria

<u>Tuberculosis study in climate of conflict</u>

22) Tuberculosis was induced in rabbits from human tuberculosis victim inoculation (MI 434 & TD 112)
    a. Jean-Antoine Villemin announced to French Academy of Medicine (1865)

23) Poor reception from Academy, critique led by Hermann Pidoux (TD 112-3 & MI 434)
    a. Infection viewed as a "Historical relic"
    b. Tuberculosis viewed as a product of social vices/afflictions found mostly in poor
        i. Malnutrition
        ii. Gluttony
        iii. Overwork

24) Tuberculosis explained by pathologists, such as Virchow, as result of many non-specific factors (EK xvi)

<u>Koch's entry into the discussion</u>

25) Koch entered the discussion through work resolving anthrax etiology
    a. Studied lifecycle of Anthrax explaining the odd epidemiology (EK 1)

26) A student at University of Göttingen, Koch studied under Jacob Henle, Friedrich Wöhler, and Rudolf Hermann Lotze (BR 11)
    a. Henle early Germ Theorist
    b. Wöhler synthesized urea to counter vitalism theory
    c. Lotze historical opponent of vitalism

27) Koch showed strong interest in research: won monetary award for work (BR 11)
    a. "On the presence of Ganglion Cells on the nerves of the Uterus."
28) Koch researched for experimental physiologist Georg Meissner (BR 11-2)
    a. Exposed to animal experimentation
    b. Ate ½ a pound of butter per day for several days for one experiment
29) Koch became licensed to practice medicine in 1866 and married Emmy Fatz (BR 14-5)
    a. Required a family income
30) Unable to maintain good positions for much more than a year (BR 15-9)
    a. Settled into small practice in Rakwitz just before Franco-Prussian war of 1870
    b. Served short time in the war as a field surgeon
31) Following war service, in 1872 took position of District Medical Officer in Wollstein (BR 21)
32) Upon establishing practice, Koch researched health issues in open time (BR 27)
    a. Hygiene and public health of smelting & mining through father's work
    b. General natural history of environment (BR 24)
33) Anthrax a problem for local for local farmers in Bomst district (BR 31)
    a. Koch studied anthrax with his minimal lab equipment (began 1873)
        i. Small darkroom
        ii. Sink
        iii. High quality microscope
        iv. Incubator
        v. Work bench
    b. Animal inoculation studies
    c. Saw, but could not control, spores
34) Early in 1876 began using aqueous humor for culturing the bacilli (BR 32)
    a. Provided a standard media to study the bacilli
        i. Quickly characterized growth conditions
35) Use of a heated, covered microscope slide allowed direct lifecycle characterization (BR 34)
    a. Results were reproducible

    <u>Koch improvement of visualization</u>

36) Koch demonstrates work to Ferdinand Cohn, a renowned bacteriologist at Breslau (BR 45)
    a. Cohn a bacteriologist who directed the Institute of Plant Physiology (BR 40)
    b. Cohn had Koch publish his work in Cohn's prestigious journal (BR 49)
    c. Received dubious confirmation from A. Frisch (BR 53)
37) Began focusing on preparation of photomicrographs (BR 54)
    a. Important for communication and classification (BR 61, LC 46-8, EK xiv)
    b. 1877 paper on photomicrograph techniques and his procedures (BR 62)

i. Fixing bacteria (BR 63 & LC 45)
ii. Staining with aniline dyes (BR 63 & LC 45)
iii. Photographing bacteria preparations

38) Koch first to test run Ernst Abbe's oil emersion and condenser microscope in 1878 (BR 68)
    a. Powerful well lit microscope impressed upon Koch the superiority of stained samples for resolving bacteria (BR 69)
39) 1878 Koch applied his new techniques to better study the work done by Davaine and Kelbs on septicemia (BR 74)
    a. Applied the Cohn's idea of distinct bacteria which had not been applied before (BR 74 & LC 55)
    b. Detailed inoculation studies in small animals (BR 76-7)
        i. Applied microscopy to diseased tissue sections (BR 76)
    c. Confirmed in humans by Alexander Ogston (BR 80)

<u>Koch's work on culturing</u>

40) 1880 Koch was appointed to a paid research position as the director of the Laboratory of Hygiene in Berlin, an arm of the Imperial Health Office. (BR 86-9)
    a. First assistants Georg Gaffky and Freidrich Löeffler (BR 91)
    b. Was able to more easily interact with educated scientists (BR 92)
41) 1881 Koch publishes "Methods for the study of pathogenic organisms" (BR 97 & RK)
    a. Explains the benefits of solid media for pure culture isolation (LC 53-4)
    b. Used gelatin, requiring lower growth temperatures (RK)
42) Pure-culture methods allowed for new series of tests to be carried out (BR 101)
    a. Species isolation for characterization (EK xiv)
        i. Tropism: temperature, media, toxins
        ii. Pathogenic capacity (LC 55)
    b. Quantitative characterization of samples (BR 101)
        i. Able to now assess methods of sterilization (BR 105-13)

<u>Etiology of Tuberculosis</u>

Koch and his lab began studying tuberculosis in August 1881 (BR 117)

    c. Berlin Charité Hospital provided tuberculosis material (BR 118)
    d. Applied his repertoire of techniques to (BR 118)
        i. First show the presence of bacteria in diseased (EK 84)
        ii. Isolate pure cultures of the bacteria (EK 88)
        iii. Inoculate healthy organisms (EK 89)
43) Tuberculosis provided a couple of problems for the methods Koch had tailored for use on anthrax and in his septicemia studies (BR 118)

a. Major problems with staining (EK 83)
b. Problems with cultivation (EK 83)

44) Chance contaminant in methylene blue made tuberculosis bacteria retain dye after counterstain (BR 120)
    a. Identified the contaminant as ammonia (BR 120)

45) Koch was able to use coagulated blood to culture the bacteria (BR 123)
    a. Able to identify culture temperature limitations (BR 123 & EK 88 & 94)
    b. Also able to identify other media that would grow the bacteria (EK 88)
        i. Agar with meat-infusion and peptone

46) Infection studies were carried out on many different animals and performed autopsies on all inoculated animals (BR 123-5 & EK 90-3)
    a. Inoculated guinea pigs, mice, rats, hedge-hogs, hamsters, pigeons, frogs, rabbits, cats, and dogs in his experiments using cultured tuberculosis from a similar variety of sources (EK 90-3)

47) March 1882 presentation to Berlin Physiological Society of collected evidence (BR 126)
    a. His presentation included more than 200 microscope slides (BR 128)
    b. General immediate praise (BR 129-37 & EK xvi)

48) A few were critical, but eventually almost all critics accepted the bacteria nature of tuberculosis (BR 136-7)
    a. Virchow among them

<u>Germ-theory: a medical paradigm</u>

49) Within the two years that followed Koch's work on tuberculosis, he and his group had shown the practicality of their techniques (EK xvii)
    a. Löeffler identified the Glanders and diphtheria bacteria
    b. Gaffky identified the typhoid bacteria
    c. Koch identified the ophthalmia and cholera bacteria
    d. Techniques also put to use for public health sanitation improvement

50) Koch took a professorship in the newly formed Institute of Hygiene in Berlin in 1885 (BR 183)
    a. New duties included (BR 187)
        i. Three separate courses
        ii. Guide research of new assistants
        iii. Continue monitoring research of Imperial Health Office assistants

51) Louis Pasteur came into light again for his rabies treatment which was followed by the establishment of the Pasteur Institute in 1886 (BR 203-4)
    a. Previous work of Pasteur had generate successful vaccines for cholera and anthrax in livestock (ID 296, PK 4)
    b. Tuberculosis was not a candidate for making a vaccine
        i. No immunity had been seen for inoculated (ID 296)

52) By 1889, Koch spent most of his time on courses to which he had not adapted well to (BR 193 & MM 63)
    a. Koch had not been able to do laboratory work after his appointment (BR 195)
    b. He took a long vacation in 1889 (BR 194)
53) Koch returned and went back to research (BR 195 & ID 297)
    a. Testing many different chemicals ability to kill tuberculosis (ID 297)
        i. In January 1890, tested 100 in 4 weeks
    b. Infected guinea pigs re-inoculation stopped disease progression
        i. Koch isolated tuberculin agent as able to stop disease progression
        ii. Koch theorized it halted disease bacterial by inducing necrosis in the infected animal tissue (ID 297 & 299)
54) Koch kept the details of his cure secret in the beginning (ID 297, BR 201-5)
55) By late 1890's, tuberculin was seen to have no value (BR 209 & ID2 98)
    a. Koch was accused of fraud (MM 71)

Thematic Concepts and Questions

Each question follows specific points in the narrative outline. Some concepts are illustrated by multiple questions. The intention is for the teacher to select what will be most interesting to apply in class.

Overall, the questions are meant to guide thinking. Answers should primarily rely on the view of those who are questioned. "What would you think in this position, given the information discussed thus far?"

Social Context of Tuberculosis

This first section serves to set the social scene at the time of this case. Tuberculosis had been a long-standing problem for society and was likely the worst disease up to this point in history. The better this concept is retained by the students the easier it will be for them to see how the social context of the time influenced the science.

In this section it may also be convenient to introduce the experimental scenario. The better the students can connect this scenario to the narrative the better then will understand them both, so describe the glowing solution as an analogy of tuberculosis in people.

4) The severity of tuberculosis was well known by the public. How might this have influenced what medical researchers studied?

The objective of this question is to get people started thinking about the ***social context*** *that will play into the* ***paradigm change*** *of this module.*

5) Do you think a negative impression of the 'city life' may have resulted from such high rates of tuberculosis in cities? How might a negative impression of city life have influenced how people viewed tuberculosis?

These questions are meant to start getting students to think in the **social context** *of the time.*

7) a & b. If diseases where diagnosed by symptoms common to many diseases (ie. coughing), how might the constant nature of tuberculosis have appeared to a clinician who made such diagnosis? Could the high rate have been explained by tuberculosis a general diagnosis of many distinct diseases?

These questions are an attempt to convey how doctors of the time would have looked at a disease like tuberculosis. The deeper idea is how ***techniques limit paradigms****.*

8) How do you think the being the cause of many famous people's deaths impacted how people might have viewed tuberculosis? Do you think it might have increased the attention paid to it in general?

These questions are, again, meant to get the students to actively understand the ***social context*** *of tuberculosis in the 19th century. The second question is to get students thinking*

about how the social context may influence science.

Tuberculosis historical etiology

Thinking about the historical etiology of tuberculosis prior to the time of the case study allows the students to take baby steps into thinking about paradigm change and how techniques factor into that. The second and third questions of this section are slightly more probing into the narrative and being able to fluidly think about how the techniques shaped their respective paradigms will ultimately determine the success of this module.

9 & 10) What might account for the difference between Hippocrates and Aristotle in their views on the contagious nature of tuberculosis, then called phthisis? Might the fact that the Roman view of tuberculosis was similar to that of Aristotle help explain this?

*These two questions are an attempt to start thinking about **paradigm change** and why it happens. Answers that favor environmental explanations (eg. Larger cities) should be encouraged over ideas that explain it as 'progress' towards common understanding.*

11) How might this have changed the academic view of tuberculosis? Knowing that tubercles could only be seen upon surgery, how might this have affected how useful this observation was as a diagnostic tool?

*The first question is presented to discuss how **techniques limit paradigms**. The second question is along these lines; the diagnostic ability of the germ theory paradigm is one of the reasons why it enjoyed success. So the second question also illustrates how new techniques expand the limits of paradigms, contributing to **paradigm change**.*

13) Why do you think the pathologists view of tuberculosis was the most accepted in the early 19th century? Does it matter that their field of study was held the most definitive process for diagnosis (tubercle presence) at the time?

*These questions attempt to get students to think about how paradigms with the most accepted technical abilities are the most accepted paradigms. This suggests how **paradigms change**, while also showing how **techniques limit** newer **paradigms** from being accepted.*

Conflicting paradigms

The start of contrasting the paradigms of germ theory and pathology begins in this section. Optimally, one would want the students to continue contrasting these ideas throughout the rest of the module as it will help them think about the limits of Koch's work in refuting the contrasting paradigm. This point is especially true for the arguments against germ theory. A better ability to contextually contrast these paradigms as they engage the narrative should make the students start to question whether paradigm change can be thought of as progress towards truth.

It would serve well to enter the first exercise of the experimental scenario here. The best strategy will likely be to begin the exercise before discussing Casmir Davaine's work on anthrax

(point 19). If the exercise can reasonably be paused, the second round of hypothesizing for 'what causes the glow' can be done after discussion of Casmir Davaine's work. This should hopefully have focused the students attention to a 'grow, no-grow' categorization. Since the reason for making this a discussion module is to get the students to come up with the answers themselves, this scenario is preferable to one in which they are given the categories.

14 & 15) If this 'philosophical concept' is closer to the modern view of tuberculosis, then why would medical academia have opposed it? What does this tell us about how science makes progress?

> *These questions are intended to get students to think about the nature of "progress;" **paradigm change** should not be considered as becoming more correct.*

16) a. If there was an equal amount of evidence at the time for both views on the cause of tuberculosis, why would the view that could be studied empirically be the most favored? What does this tell us about the importance of techniques in science?

> *In a similar manner to questions for 13), these questions are meant to get students to think about how **techniques limit paradigms** by seeing how the paradigm lacking in techniques is less accepted.*

17 & 19) The evidence which pointed to microorganisms causes for disease was hard to come by and difficult to repeat (EK xiii). In this light how might the pathologists, favoring experiment-based science, have interpreted the theories that came from such work? Do you think this disconnect, between how each group values empirical reasoning, is likely to be present when new paradigms interact with established paradigms?

> *Thinking about how **paradigms change**, the first question above is an attempt to get students thinking about how competing paradigms justify one against the other while both describing the same data. The second question probes deeper into this concept and asks the students to think about if this scenario would be common to most episodes of **paradigm change**.*

20) How wrong was Virchow? Think about a cough. What is a cough without lungs to cough? What does this say about what Virchow thought was important in understanding the etiology of disease? How do you think his profession affected his view?

> *The answer to what Virchow focused on should be that he cared about how tissue damage caused disease, not what caused tissue damage. This should not limit discussion of the question, though it should be conveyed at some point. These questions are meant to get the students into the mindset of the pathologist's paradigm; with the evidence available at the time, it should be viewed as very well reasoned. The discussion should help improve the understanding of **paradigm change** and how it cannot be thought of as "progress." Also important for the final question is how Virchow's techniques limited what he cared about, again illustrating how **techniques limit paradigms**.*

21) Knowing that germ theory is an accepted view of disease today, what do you think that this means for these arguments against it? Were they resolved?

> *This question is to plant the ideas for what eventually will be resolved later in the narrative. This is to illustrate the interesting aspects of how **paradigms change** and that*

it is more about what can be studied with the paradigm than if the paradigm proved the others wrong.

Tuberculosis study in climate of conflict

This section offers a more focused view of the paradigm conflict of the previous section by showing how it played out for tuberculosis. The objectives are similar for this section as they were for the previous section. Only because this section follows the section that introduced the ideas of paradigm conflict, this section should push the students understanding to a more in-depth level. This is partly the reason this section contains the ***historical perspective*** *question.*

Since this section is similar in nature to the previous section, it is also reasonable to begin exercise 1 here as well (results can be discussed independently of the narrative). Similarly to the previous section, if one discusses the work of Villemin before the second round of hypothesis, it may help the students to come up with the 'grow, no-grow' categories.

22) Is it likely that Villemin randomly perform these experiments? What might have caused Villemin to perform such studies?

These questions should discuss ***paradigms roles*** *in directing research. Villemin likely thought that tuberculosis was infectious before he decided to test whether it was infectious. This should show that without the germ theory paradigm, Villemin would likely not have thought of such an experiment.*

23) Assuming Pidoux was a pathologist along the lines of Virchow, yet in France, what does this tell us about why he disagreed with Villemin's interpretation of his inoculation? Many current historical summaries of this situation make light of only one of Pidoux's argument against Villemin, that it would hurt public health programs (MI 434). This is not an argument that discusses the validity of Villemin's results, why do you think it is the only one portrayed in such summaries?

The first question serves to remind the students of how ***techniques limit paradigms****. In this case, Pidoux's study of pathology set his paradigm. The second question is one to get students to think about the* ***historical perspective*** *which favors one paradigm over the other and whether that perspective is accurate. Optimally, this should gauge how well students are viewing this episode from the context in which it occurred.*

Koch's entry into the discussion

Koch is specifically dealt with for the first time in this section. The goal for this section is to paint a picture of Koch that can be used in the following sections of the narrative. This should not limit the more thematic points of this section, of which there are many.

Establishing Koch's general attitude towards research is important here as it plays out in the last section of the module. Also without this context, it may be more difficult for the students to reason out the importance of resources in Koch's eventual study of microbes.

25) Which of the arguments against germ theory did this work of Koch address? His work had only applied to anthrax, what might this mean for how it addressed the arguments against germ

theory?

*These questions are along the line of 17 & 19) where the students are challenged to think about how two competing paradigms can look at the same data and see different things. The ultimate goal is to better understand the complexities involved in how **paradigms change**.*

30) Koch was not required to serve in the military because of his poor eyesight, what might have motivated him to join the military?

*The answer to this question should be something dealing with a sense of nationalism. This question serves as an **aspect of the narrative** to help prepare the students for how Koch interacts with Pasteur. Eventually, this will result in a drive for Koch to find a treatment for tuberculosis.*

32) If Koch's primary occupation was to practice medicine, how would you characterize the research he did? What does this suggest to you about how Koch approached research in general?

*This question serves as an **aspect of the narrative** establishing Koch's approach towards research. His approach was a sense of enjoyment similar to that of a hobby. This becomes important when students see how certain research paths were limited for him in the following question.*

29 & 32) Koch required a position that would support his family, how does this appear to have affected his ability to do research?

*This question should to get students to think about the factors outside of theory and technique that affect science; in this case **monetary resources**.*

33) Considering Koch's generic interest in research, what role do you think the outbreaks of anthrax in local livestock played in focusing Koch on bacteriology?

*This question attempts to get students to think about the degree to which Koch was limited to studying only what was around him. This question falls generally into probing the importance of **resources**.*

33) a. Koch had clearly enjoyed research, how do you think the limited recourses affected what he ended up focusing on? How do you think the limited resources affected what Koch learned about working with bacteria? (Economical approach, and hands on)

*This continues the previous line of questioning discussing the importance of **resources** in shaping what Koch studied. The second question should emphasize how his limited resources might have helped Koch be better at technique, so though resources limited what he got to study, they forced him into the path that made him successful.*

34) a. How did being able to control the growth of the anthrax bacteria change how Koch could study it?

*The main thing Koch could do now was control the growth of the bacteria, but discussion should not be limited to this. This question should illustrate how **techniques limit paradigms** by discussing the newfound studies Koch could do with this little advancement in technique.*

34) b. Koch had been working on this bacteria for more than two years before he found a good media that allowed him to effectively study the bacteria. What does this tell us about the research process?

*In line with the previous question, this one should also give an idea of how **techniques limit paradigms**, and upon finding new techniques, they can act as a catalyst for research.*

35) Anthrax epidemiology had been a problem for germ theorists up till this work of Koch. How did his observations of the Bacillus anthracis lifecycle affect this problem?

*This question should show that Koch didn't really prove anything about the epidemiology of Bacillus anthracis, he only showed it could explain the anthrax epidemiology. So this question is along the lines of question 21) about how **paradigms change**; often there is little done to prove the previous ideas wrong.*

<u>Koch improvement of visualization</u>

This section hinges on the application of exercise 2 to understand the techniques, where the narrative focuses on where the ideas came from and what they resulted in. In terms of the overall them, this section predominantly focuses on how important Koch's institutional connection were in his visualization work. It is rare for a student of science to appreciate that science is predominantly an exercise in troubleshooting. Explaining this during one of the discussions of Koch's institutional connections may make the discussion more fruitful and amiable towards viewing connections as important.

As mentioned above, this section is the best to begin exercise 2. Planning it so that the narrative for this section ends after the exercise has been completed may help stimulate discussion for question 39). Beyond this, it may also help with continuity of the lesson to talk about point 37) around the same time the gram stain technique is introduced to the students.

36) a. What do you think Koch's newfound prestige did for him? How might connections to the Plant Physiology institute have helped him in his research?

*This starts a new line of questioning focused on how resources affected Koch's work. The specific resources to be discussed fall under the **institutional connections** category. The resources should also be seen as a catalyst for Koch's research as they make it easier for him to 'trouble-shoot.'*

36) c. In a world where microscopic observations where drawn, how might Koch have explained Frisch's 'incorrect' confirmation?

*This question serves as an **aspect of the narrative** giving the students an idea why Koch began studying photomicrography.*

37) a. When he visited Cohn in Breslau, Koch had to take a good portion of his lab with him. Might photography have helped this situation? Would this also have contributed to standardizing pictures of bacteria (improvement on drawings)?

This question should help the students think about the importance Koch placed on reproducibility. Reproducibility has also played a role in previous discussions where

*germ theory data was hard to reproduce. One should view reproducibility as part of how **techniques limit paradigms**.*

37) b. ii) A member of the Plant Physiology institute led Koch on to the use of aniline dyes. What does this suggest about the importance of his connections at the Institute?

*This question should lead the discussion into how **institutional connections** are an important piece in Koch's work.*

37) b. iii) The photographs Koch made for publication are similar in quality to those used today. Do you think this is a testament to Koch's foresight, or does it just say we use similar techniques today?

*This question should provide another gauge into the student's emersion into the narrative's context. It should illustrate again how favoring a paradigm can bias our **historical perspective**.*

38) Abbe was interested in making a name for his company. What role do you think that Koch's 1877 paper played Koch gaining access to Abbe's prototype?

*In somewhat of an indirect way, this question attempts to get students to think about the importance of **institutional connections** as they emerge here as an aspect of Koch's new reputation.*

39) In your opinion, was Koch doing new work? What does this tell us about the nature of techniques in science and about 'new' science in general?

*This question should help illustrate that **paradigms roles** are often to old scientific data. This should help students better see that the paradigm one ascribes to affects how we view data.*

<u>Koch's work on culturing</u>

Like the previous section, the usefulness of these techniques will be best illustrated by carrying out exercise 3 in conjunction with the discussion. Though there are fewer discussion questions in this section, it is an important section for illustrating the importance of techniques in changing paradigms. It will likely prove best to do exercise 3 before discussing past point 40 on Koch's new position. The discussion should be focused on point 42) a. which the students should have a good understanding of after going through exercise 3.

40) b. Thinking of the advances allowed from Koch's more limited interactions, what might this new level of connection do for Koch?

*This question should get the students to think about how **institutional connections** were important in Koch's work.*

41) a. Where did the idea of solid media come from? Do you think it came out Koch's diligent technical abilities?

*These questions again bring up the idea of the **historical perspective**. It is important to point out here that the idea came from one of Cohn's associates in Breslau, Joseph Schroeter who worked with bacteria that grew on potato slices (BR 96).*

42) Nageli published a book attacking Cohn's idea that bacteria could be classified into distinct species groups with defined characteristics (BR 73). How does Koch's ability to separate individual bacteria play into this scenario?

*This question should help illustrate how **techniques limit paradigms**. In this case Koch was able to refute Nageli by making pure cultures of bacteria and seeing that they do not change.*

Etiology of Tuberculosis

This section is essentially the climax of the narrative; almost all of the ideas of science covered in the previous sections resurface here. Since all of the previous sections of the narrative have been to provide context for this section, this section should receive the most time.

It is advisable to finish exercise 4 by during this section so that by the final section, only one exercise remains.

43) a. Do you think Koch might have done research on another bacteria had he not had access to tuberculosis from the hospital? Why do you think he went after tuberculosis first?

*These questions should get the students to think about two independent concepts: how **resources** might have effected what Koch studied, and how the **social context** of tuberculosis likely focused his direction.*

44) Loeffler describes Koch as being convinced by "the same clinical and pathological-anatomical picture" that tuberculosis was the result of a living organism. Considering that pathologists, such as Virchow and Pidoux, could see the same pathology, how was it that Koch could see such a fundamentally different process?

*This question should get the students to think about two aspects of paradigms: how **paradigms change**, and **paradigm roles**. The role of the paradigm in this scenario is to guide Koch's interpretation of data, bringing up the idea that two opposing paradigms can look at the same data and see different things. This again makes us think about how this affects how paradigms change.*

45) a. It would not have been likely that Koch would have thought to add such an ingredient to the dye to improve its staining ability. Where might Koch have been without this extremely effective method of staining? If one were to assume that this technique alone allowed him his success, how might your impression of his being awarded the Nobel Prize, for the identification of tuberculosis, change?

*These questions seek to illustrate the importance of blind **luck** in science. Also the idea of **historical perspective** is again raised by the second question.*

46) Why do you think Koch tested coagulated blood serum as a media?

*This question serves as an **aspect of the narrative**. Koch likely reasoned that tuberculosis grew in blood, so it should grow on blood.*

46) a. Without having a media known to grow the bacteria, how would Koch be able to discern whether 'no growth' was the result of incorrect media or incorrect temperature?

*This should clearly illustrate the how **techniques limit paradigms** by illustrating how*

techniques limited Koch's study.

46) b. Why was Koch not able to identify the semi-synthetic media first?

*This question continues along the previous questions line by illustrating how **techniques limit paradigms**.*

47) a. Why such extensive infection studies? If it was know at the time that guinea pigs never naturally developed tuberculosis [BR 124-5], why would it have been advantageous for Koch to inoculate guinea pigs?

*The first question should be in the context of how **techniques limit paradigms**, specifically thinking about reproducibility. Koch was demonstrating that his work was reproducible from many angles. The second question is within the same topic, but simply asks the students to think more specifically about controls.*

48) Koch presented to a non-medial society (BR 126). Why might this have been the case in light of the gravity of his findings for the medical community?

*This question tries to get at the conflict between the pathology paradigm and the germ theory paradigm to help think about **paradigm change**.*

48) a. What do you think would have been more convincing to the scientists of the time: Koch's large amount of data collected, or the simple nature by which it could be reproduced?

*Both of the scenarios presented in this question get at the importance of reproducibility, yet from different angles. This question is working to get students to how **techniques limit paradigms**.*

48) b. & 49) What role do you think the social perception of tuberculosis play on the scientific acceptance of Koch's proposed etiology?

*This question is asking the students to think about how the **social context** of tuberculosis affected how Koch's work was received. Students should try to draw on what was covered in the very beginning of the narrative, but beyond that it should be open ended.*

49) a. Did Koch's work satisfy the problems the pathologists had laid out against germ theory? If not, why was it then so widely accepted?

*These questions should reconnect back to question 21). If the students look back, the third argument against germ theory was never resolved. This should stimulate a discussion on why Virchow accepted the new germ theory along the lines of how **paradigms chage**.*

<u>Germ-theory: a medical paradigm</u>

This section is meant to provide a sense of closure to the narrative and very clearly show the weaknesses of paradigms. Prior to this, the discussion has mainly focused about what factors into how paradigms change and how paradigms are used in science. This final discussion should unify the entire module by completing science as a process. The beginning of the module discussed how the pathology paradigm was mostly replaced by germ theory, and by the end of the module we see how Koch's germ theory began to require a new paradigm to explain where it

went wrong.

It would be best to finish exercise 5 sometime before discussing the final question, and optimal to finish it before starting the final section. If it helps illustrate the final points of the narrative discussion and time is available, an additional exercise looking at similar morphology yet non-glowing bacteria can be done. This may provide a logical analogy to Koch not seeing asymptomatic patients which had tuberculosis.

50) What do you think the rapid output of disease etiologies by Koch's lab do for the science of germ theory?

*This question should illustrate the catalytic power of techniques, in the topic of how **techniques limit paradigms**. The students should also get the idea that the germ theory paradigm was quickly becoming accepted.*

51) How would the etiological characterization of cholera, another infamous disease, have contributed to the professorship position opening?

*This question should get the students to think about how Koch's reputation improved his **institutional connections**.*

51) a. How do you think the new responsibilities affected Koch's research?

*This question serves as an **aspect of the narrative** to get students to contextualize how Koch might have viewed his position. Students should try to recall Koch's enjoyment of research illustrated in past sections.*

52) Koch never viewed Pasteur's work 'good technical science' [MM 63, PK 16, LC 57]. What do you think his personal reaction was to the successes of Pasteur?

*This question serves as an **aspect of the narrative** to get student to reason out why Koch began work on tuberculosis treatments. Students should recall previous questions about Koch's nationalistic sentiments along with this question.*

52) b. Do you think Koch would have been aware of the inability of M. tuberculosis to have a vaccine made from it?

*This question serves as an **aspect of the narrative** to get student to reason out why Koch began work on tuberculosis treatments and not vaccines.*

54) a. Where might his 'internal disinfection' ideas have come from? He had preciously worked to characterize the causes of disease, why might Koch have changed course?

*The first question challenges the students to recall an obscure aspect of the narrative where Koch used solid plate techniques to study sterilization procedures. The second question should call in the **social context** of tuberculosis, and the context of competition between Koch and Pasteur.*

54) b. What reason might Koch have had for re-infecting tubercular guinea pigs?

This question is simply to get the students thinking from Koch's point of view. A likely explanation for this is Koch was experimenting with the concept of a vaccine.

55) Due to the widespread nature of tuberculosis, why do you think Koch kept his remedy's

contents a secret?

The typical answer to this question is that Koch wanted patent money. Asking the students to think about why Koch kept tuberculin a secret should get the students to think from Koch's perspective about this action. Optimally, they will reason that he would have more money for research.

56) The paradigmatic view of disease being a 'bacterial invasion' was how Koch viewed his previous work on bacterial infections. Why might this have misled his perception of the mechanism of tuberculin? Do you think that if Koch were exposed to asymptomatic patients who had a tuberculosis infection that this would have changed his view? Why would his research paradigm likely never encounter this situation?

This is the ultimate question of the narrative that should hopefully illustrate how paradigms should not be viewed as progress towards truth. Students should think about the disconnects discussed between the pathology paradigm and germ theory paradigm. The pathology paradigm focused on a different aspect of disease (how tissue damage caused death) than germ theory did (what caused tissue damage). The pathology paradigm had weaknesses that germ theory fixed. In the same way, Koch's paradigm of infection as 'bacterial invasion' had weaknesses which he could not see while witnessing the successes his paradigm afforded. As an end to this discussion explain that Koch never stopped studying and trying to improve his tuberculin remedy and that Koch's paradigm had to be explained by a new paradigm of immunology.

Exercises:

Robert Koch's contribution to science was to improve our ability to very simply control microorganisms. Being able to make pure-cultures and easily identify them under a microscope are fundamental tools of basic microbiology. This series of laboratory experiments walks through a simple situation, finding what causes 'the glow,' applying Koch's techniques in a similar way to how he used them to identify *M. tuberculosis*.

Scenario: a couple of liquid solutions are presented to the class which, when compared to similar looking solutions, glow. The objective of the project is to determine what about this glowing solution causes 'the glow.'

> *Solutions – Optimally is a mixed culture of bacteria containing lots of microscopic debris to look through. Glowing bacteria strains can be ordered from cell banks. The fluids should all contain multiple, microscopically distinguishable (assuming gram stained), bacterial strains. Mixed cultures may be difficult to set up for one media, so it may be necessary to grow each type of bacteria independently and then mix them before viewing.*

Exercise 1: Expose the class to the scenario. Brainstorm some simple answers – hypothesis – to what may be causing the solutions to glow. Using the microscope should allow the students to look through the solutions in more detail to hypothesize what may be causing the glow. Explain how to use a microscope and make wet mounts of the glowing solutions for microscopic examination. Again discuss – hypothesize – what may be causing the glow, only this time focus the results into two big categories: things that grow or inert chemicals in the solution.

Discuss an experiment that will test these hypotheses. If someone does not present the idea, suggest (after sufficient discussion) transferring a small amount of the glowing solution to a new, non-glowing, media to test the ability of the glow to increase in the media. Perform this test and incubate until the next class meeting.

> *Incubation condition will need to be determined before setting up this class project and will be dependant on the bacteria present in the solution. It is possible to only culture the glowing bacteria as it would likely be difficult to culture all the bacteria in the same solution. 'Spiking' the solution with extra bacteria following incubation is a viable option to maintain the mixed 'culture'.*

Exercise 2: Discuss the results [the glowing should have grown] of the 'grow' experiment (this can be done independently of exercise 2), and prepare new wet mounts of these cultures for microscopic examination. Typically, visualization of bacteria in wet mounts is very difficult so very few students should find anything. Discuss how this is a limitation in allowing the class to find what the cause is.

Introduce the fixing and staining to the class. Using a simple gram stain, have the class prepare slides for the cultured, glowing samples. Discuss how the gram stain works, and then again discuss which of these bacteria may be causing the glow. Use color and shape to define the different strains and then make new hypothesis as to which one causes the glow.

This exercise is improved by having many diverse bacteria present in the cultures. It may not be possible to culture all the bacteria together, and in this case it would be beneficial to 'spike' the cultures with extra bacteria, after culturing preceding staining. It would be suggested to use three additional strains to make the final 'culture.' The following would suffice: the glowing bacteria, gram$^+$ cocci, gram$^-$ cocci, gram$^+$ bacilli, and gram$^-$ bacilli.

Exercise 3: Discuss how one would show which bacteria causes the glow, and how separation is the limiting factor. After discussing how one might separate individual types of bacteria, introduce the streak-plate technique. Prepare streak plates from the mixed culture, and incubate them.

Previously identifying the solid media type to use will be important here. Optimally, a media in which all (spiked and cultured) bacteria grow should be used. This may not be possible and a couple of different media might be needed. Also, incubating multiple plates should guarantee that individual colonies for each type of bacteria are represented, and this is recommended.

Exercise 4: This exercise is simply a busy work application of what has been used before. Have the class pick individual colonies from plates and prepare gram stains for each pure colony. Once all of the colonies from the mixed culture have been accounted for, inoculate liquid media so that each distinct bacteria is cultured in its own media.

To simplify this process, multiple gram stains can be prepared on a single slide so long as the students keep track of which stain is from which colony. In the case that individual types require different media, inoculate many of each and group the class into media types.

Exercise 5: CONCLUSION – Identify which media contains the glowing bacteria, and referring back to which strain was used to inoculate it, the glowing bacteria. For a concluding discussion, discuss how a process of narrowing down was used to identify the bacteria. Relate this to how many aspects of science operate.

Reference Key

BR	-	*Robert Koch : A Life in Medicine and Bacteriology*
EK	-	*Essays of Robert Koch*
ID	-	"Robert Koch and the white death: from tuberculosis to tuberculin."
LC	-	"Linking Cause and Disease in the Laboratory: Robert Koch's Method of Superimposing Visual and 'Functional' Representations of Bacteria."
MI	-	"Historical perspectives on the etiology of tuberculosis."
MM	-	"Money and Microbes: Robert Koch, Tuberculin and the Foundation of the Institute for Infectious Diseases in Berlin in 1891."
PK	-	""Like All That Lives': Biology, Medicine and Bacteria in the Age of Pasteur and Koch."
RK	-	"Methods for the study of pathogenic organisms."
SO	-	"Second Opinions: Epidemics and Infections in Nineteenth-Century Britain."
TD	-	*Twelve Diseases That Changed Our World*

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